CHAPTER II

LITERATURE REVIEW

1. Zidovudine (AZT)

1.1 General properties of AZT (Merk index, 1996)

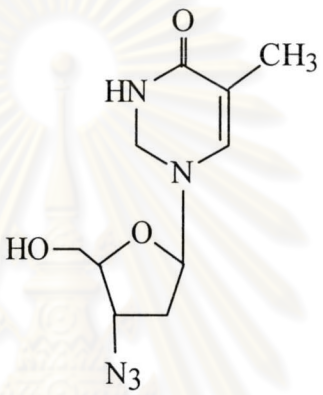

Figure 1 Chemical structure of AZT

Chemical name	:	3′-azido-3′-deoxythymidine
Generic name	:	Zidovudine, Azidothymidine (AZT)
Molecular formula	:	$C_{10}H_{13}N_5O_4$
Molecular weight	:	267.24 g/mole
Appearance	:	A white or brownish powder, odorless
Solubility	:	Soluble in water is 25 mg/ml at 25^0C
		soluble in ethanol (BP 1998)
Ultraviolet absorption		Absorption maximum at 266.5 in water (ε 11,650)
Melting point	:	120-122 ^{0}C
Therapeutic category	:	Antiviral agent

1.2 Mechanism of action

AZT is a synthetic thymidine analog that exerts the activity against HIV-1, HIV-2 and human T-cell lymphotrophic virus (HTLV) ((McLeod and Hammer, 1996).

After entering the host cell, AZT is phosphorylated by thymidine kinase to a monophosphate, that being biotrasformed into diphosphase by thymidylate kinase before become active AZT 5-triphosphate by nucleoside diphosphate kinase (Furman *et al.*, 1986). AZT 5-triphosphate inhibits reverse transcriptase of HIV by competing with thymidine triphosphate. Therefore, the regeneration of HIV was inhibited by AZT-5-triphosphate. In the other hand, the phosphorylation of AZT may reduce levels of thymidine triphosphate in host cell. These latter effects may contribute to the drug's cytotoxicity and adverse effects.

1.3 Pharmacokinetic and side effect

The pharmacokinetic parameters of AZT were summarized in Table 1. Although orally administered AZT is rapidly absorbed from intestinal mucosa, it loses considerable potency during its first pass and then is rapidly eliminated from the body with a half-life of 1 h. Serious side effect following oral administered AZT is contributed to bone marrow (Dudley *et al.*, 1992).

For other ccommon adverse effect of AZT, anorexia, fatigue, malaise, myalgia, nausea, and insomnia are included. Anemia may develop as early as four weeks treatment (Walker *et al.*, 1988).

Table 1 Pharmacokinetics parameter of AZT (MIMS Annual Thailand, 2002)

Parameter	AZT
Oral bioavailability,%	60-70
Plasma $t_{1/2\ elim}$, hours	1.1
Plasma protein binding, %	34-38
Clearance (Cl), mL/min/kg	27.1
Volume of distribution (V_d), L/Kg	1.6

$t_{1/2\ elim}$, half-life of elimination

1.4 Therapeutic uses

AZT was the first antiretroviral agent that was approved by FDA for HIV infection treatment in adults and children as monotherapy or in combination with other antiretroviral agents. It also is approved for preventing prenatal transmission of virus in pregnant women with HIV infection and is recommended for postexposure chemoprophylaxis in HIV exposed health-care workers.

Since its release in 1987, the effectiveness of AZT has been established in numerous clinical trails. An early monotherapy trial in patients with advanced disease showed that AZT improved survival over 24 weeks (Fischl *et al.*, 1987). AZT plus other nucleoside reverse transcritase inhibitors provides greater clinical benefits than AZT alone. AZT combined with lamivudine produced a 66% reduction in disease progression.

Various dosage forms of AZT are manufactured. They are 300 mg tablet or 100 mg capsule. AZT is also in the dosage form of syrup that contain 50 mg AZT per 5 ml and in the dosage form of injection solution that contain 10 mg per ml (Drug fact, 2001).

1.5 Administration

The recommended oral starting dose in adults is two 100 mg capsule or four teaspoonful (20 ml) syrup given every 4 hours around the clock. With the appearance of toxic symptom, daily dose can be reduced to 100 mg every 4 hours. For intravenous infusion, the dose used is 1 to 2 mg/kg infused over 1 hour six times daily (Drug fact, 2001).

By administered AZT orally every 4h, serious side effects, especially on the bone marrow has been reported. Its already been recognized that, non -oral zero-order delivery systems, would be benefit in reducing the high daily dose of AZT (5-10 mg/Kg. every 4h), but still maintain the anti-viral effect, leading to reduce the strong side effects, and improve patient compliance (Raffanti and Haar, 2001).

2. Transdermal drug delivery system

Transdermal drug delivery is defined as the controlled release of drug through intact skin (Kydonieus, 1987; Shah, 1992; Chien, 1992). It is designed to deliver a specific drug through various skin layers and finally into the circulatory system to exert a pharmacological action (Shah, 1992; Rolland, 1993). Transdermal delivery systems present a number of advantages over classical drug delivery

systems administered via other routes (Chien, 1983; Kydonieus, 1987; Chien, 1992; Rolland, 1993). These are

- ease of self-administration
- good patient compliance
- avoidance of variation in gastro-intestinal absorption
- bypass of the hepatic first-pass metabolism
- provision of sustained and constant plasma concentration of drugs
- reduction in repeating dosing intervals
- reduction of potential adverse side effects
- a decrease of drug plasma levels immediately removing of the delivery system
- substitution for oral or parenteral administration in certain clinical situations (pediatrics, geriatrics, nausea, etc.).

2.1 Feasibility selection of drug as transdermal delivery system

The criteria for determining the feasibility of drug as transdermal delivery can be considered in two categories (Guy and Hadgraft, 1987; 1989).

2.1.1 Biological properties of the drug

A drug subject to GI degradation or hepatic first pass metabolism would be suitable for transdermal delivery. A drug with a half-life of 3 h has been shown to reach steady-state levels rapidly and is a good candidate for transdermal delivery (Guy and Hadgraft, 1989).

2.1.2 Physicochemical properties of the drug

The skin permeation of the drug delivered from the transdermal device is presented in Figure 1, and can be described as follows:

- Drug transport within the delivery system to the device-skin surface interface.
- Partitioning of drug from the delivery system into the stratum corneum.
- Diffusion of drug across the stratum corneum.
- Drug partitioning from the stratum corneum.
- Transport of drug through the viable tissue.
- Drug uptake by the cutaneous microcapillary network and subsequent systemic distribut

The diffusion and partition of the drug are crucial properties of drug permeation. The drug must diffuse from the device to the skin surface. The diffusivity coefficient of drug in the polymer is a function of the nature of the polymer and the molecular size of the drug. For skin permeation, the diffusivity coefficient of drug through the skin is sensitive to the degree of interaction between the drug molecule and the tissue as well as the drug molecular size which should be below 800-1000 dalton (Abdou, 1989).

A drug which has a log P (log of octanol-water partition coefficient) of less than −1 would mean that the drug is in the aqueous phase and permeate poorly through the skin ; when log p equals to one or zero, it means that drug can diffuse into the stratum corneum and then partition reasonably well into the underlying tissue.

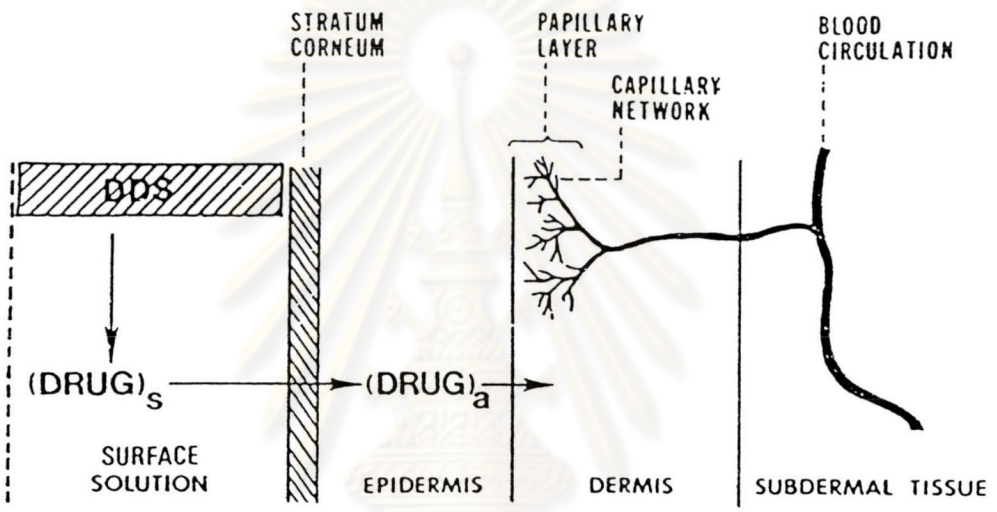

Figure 2 Diagram of drug delivered from transdermal device and permeated through skin (Chien,1987a: 81-100, 1987b : 523-552.).

However, a drug with log P value more than two, would not reach its steady plasma concentration since it deposits in the stratum corneum which behaves as a drug reservoir (Chien, 1992).

3. Reports on AZT transdermal study

The reports on AZT transdermal study were summarized in Table 2. Since 1989, AZT permeation through skin was using chemical enhancers or physical enhancers for evaluating the possibility of transdermal AZT development.

The use of chemical enhancers were reported as following:

As show in Table 2, Seki *et al.,* was the first group who investigated percutaneous absorption of AZT in rats. They suggested that the permeability of AZT through the

skin which should affect the plasma level of AZT after percutaneous applications, could be improved by the use of penetration enhancer such as oleic acid. The ester derivative of AZT were synthesized and assessed as prodrug of AZT. The skin delivery characteristics of AZT via controlled release of penetration enhancer was studied (Seki *et al.*, 1989; Seki *et al.*, 1990; Seki, Kawaquchi and Juni, 1990; Seki *et al.*, 1991).

Many novel chemical enhancers such as t-anethol, carvacrol, thymol and linolool were tried for enhancing the transdermal delivery of AZT by Karali *et al* (1995).

Kim and Chien (1996) have investigated skin permeation of three drug compounds, AZT, ddC, and ddI using hairless rat skin and a cosolvent system of

ethanol/water or ethanol/tricapylin. They found that the skin permeability of these drugs could be enhanced.

Table 2 Reported AZT transdermal studies using chemical enhancers

Year	AZT preparation in donor	Vehicle and enhancer	Animal skin		Reference
			In vitro	*In vivo*	
1989	solution	water, IPM, NMP, oleic acid		rat	Seki *et al.*
1990	solution, gel	oleic acid +S-318 +LM+ NMP+ PG	rat	rat	Seki *et al.*
	solution of AZT esters	IPM, water	rat, cadaver skin	-	Seki *et al.*
1991	solution, patch	IPM + NMP	rat	rat	Seki *et al.*
1995	solution, gel	t-anethol, carvacrol, thymol, linalool, each enhancer combined in IPA/water, PG/water	mouse, rat	rat	Karali *et al.*
1996	saturated solution	ethanol/water, ethanol/tricaprylin	hairless rat	-	Kim and Chien
	solution, suspension	IPM, simethicone, ethanol/IPM	rat	rat	Jin *et al.*

Table 2 (cont.) Reported AZT transdermal studies using chemical enhancers

Year	AZT preparation in donor	Vehicle and enhancer	Animal skin		Reference
			In vitro	*In vivo*	
2000	solution	ethanol/IPM	rat	-	Jin *et al.*
2003	saturated solution	water, ethanol, PG, and their binary combination	rat	-	Thomas and Ponchgnula

Table 3 Reported AZT transdermal studies using physical enhancers (iontophoresis).

Year	AZT preparation in donor	Vehicle and enhancer	Animal skin		Reference
			In vitro	*In vivo*	
1990	solution	*N*-decylmethyl sulfoxide	hairless rat	-	Wearley and Chien
1998	solution	PG, oleic acid	hairless mouse	-	Oh *et al.*

Thomas and Ponchagnula, (2003) observed the effects of various solvent systems containing water, ethanol, propylene glycol, and their binary combination on the ex vivo permeation of AZT across Spraque Dawley rat skin. It was concluded that the lag times of AZT from this experiment were too long that did not appropriate for developing AZT transdermal delivery system (20-50 h).

The physical enhancers, were experimented as follows:

Wearley and Chien (1990) study the effect of AZT iontophoresis on the skin permeation. In addition, Oh *et al.*, (1998) observed the effect of current, its magnitude and penetration enhancers on the transdermal flux of AZT across hairless mouse skin (Table 3).

According to these reports, the feasibility of AZT development to transdermal delivery system (TDS) would possibly be manageable. However, the use of iontophoresis for enhancing AZT permeation through skin contains limited information. Hence, this study would emphasize on the use of chemical enhancer in developing AZT transdermal delivery system.

4. Permeation studies

An ideal determination of transdermal delivery potential of a compound in human, an actual study in human is necessary. But with many limitations and other associated problems, preclinical studies that involve either animal study *in vivo* or *in vitro* studies using animal skins are substituted.

4.1 *In vitro* percutaneous absorption studies.

Kligman (1983) stated that *in vitro* data are more credible than *in vivo* data and that if differences do exist, the *in vivo* data are considered suspect. Percutaneous absorption can be studied by the *in vitro* technique since a sheet of skin could be excised without loss of its essential membrane qualities. This *in vitro* technique is usually performed by placing a skin section between a donor and a receptor phase of a kind of diffusion cell. The permeation of a drug from the donor phase to the receptor is followed carefully and the permeation rate (flux) is determined either from the depletion of drug concentration in the donor phase or from the accumulating drug concentration in the receptor phase.

There have been wide varieties of diffusion cell designed for *in vitro* measurement of skin permeation. These cells have generally been designed in one of the following two types: side-by-side (bichambers) and vertical *in vivo* mimic diffusion cells.

The side-by-side diffusion cells are useful in delineating mechanisms of permeation under controlled condition but it is limited in predicting skin permeation *in vivo*. The vertical cells are more versatile because a wide variety of experiment condition can be set to gain information useful for the evaluation of formulation ultimately destined for clinical use (Friend,1992).

An upright-type diffusion cell was first designed by Franz (Franz, 1975). The Franz diffusion cell (Figure 3) is one of the most widely used systems for *in vitro* skin permeation studies. It consists of a small upper (donor) compartment which has a wide opening at the top exposed to the air without any temperature control and a lower (receptor) compartment. The receptor solution in the inner

chamber is kept at a desired temperature by circulating water in the outer jacket and maintained at a constant hydrodynamic condition by a tiny magnetic bar rotating at a specific stirring rate. A skin sample is also sandwiched between the donor and the receptor compartments. The drug permeation through skin is followed by sampling the receptor solution via an open sampling port at a scheduled time interval.

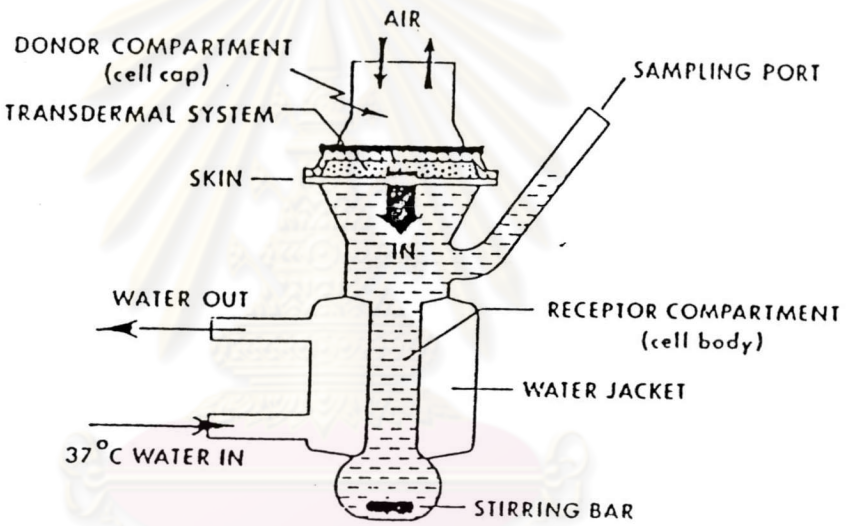

Figure 3 Franz diffusion cell (Chien,1987a).

4.2 Skins used in the *in vitro* permeation studies

Human skin provides an excellent barrier between the external environments and the body. The human skin may be subdivided into three mutually dependent layers. The epidermis which is the outermost layer of the skin, the underlying dermis and the subcutaneous fatty layer (hypodermis).

The stratum corneum, which is the outermost layer of the epidermis, typically comprises 10 to 15 cell layers and is approximately 10 mcm thick when it is dry. This layer, which consists of dead, anucleate and keratinized cells embedded in a lipid matrix, is essential for controlling the percutaneous absorption of most drugs and other chemicals. The stratum corneum is the major rate limiting barrier to molecular diffusion through the epidermis (Baetex, Budde, and Maibach, 1972). The architecture of the horny layer may be modeled as a brick and mortar structure. In this model, the keratinized corneocytes function as a protein " brick" embedded in a lipid "mortar".

Any molecule may use two diffusion routes to penetrate normal intact skin: the skin appendages (sweat glands and follicles) and the intact epidermis. However, the appendages provide a small fraction of surface area which is approximately 0.1% of total skin and are widely believed to constitute an insignificant pathway for most drug permeation. This route may be important for electrolytes and for large polar molecules with low diffusion coefficients such as the polar steroids and antibiotics. The appendages are also important in drug absorption just after application to the skin and prior to the establishment of steady state diffusion (Scheuplein, 1967).

The transepidermal route is the singular most important route of entry for most drugs. Figure 4 illustrates two potential routes of drug permeation between the cells (intercellular route) or through the protein filled cells and across lipid-rich regions in tandem (transcellular route). Overall, at least for polar drugs, it is likely that the transcellular route provides the main pathway during percutaneous absorption. As penetrants become more non-polar, the intercellular route probably becomes more significant.

Since tissue is dead, the diffusion is a passive process governed by physicochemical laws in which an active transport mechanism plays no part. Once molecules pass the stratum corneum, they permeate rapidly through the living tissues of the epidermis and dermis and are swept readily into the systemic circulation.

Several investigators (Mc Greesh, 1965; Tregear, 1966; Campbell *et al.*, 1976; Wester and Maibach, 1987a) have determined the permeability through

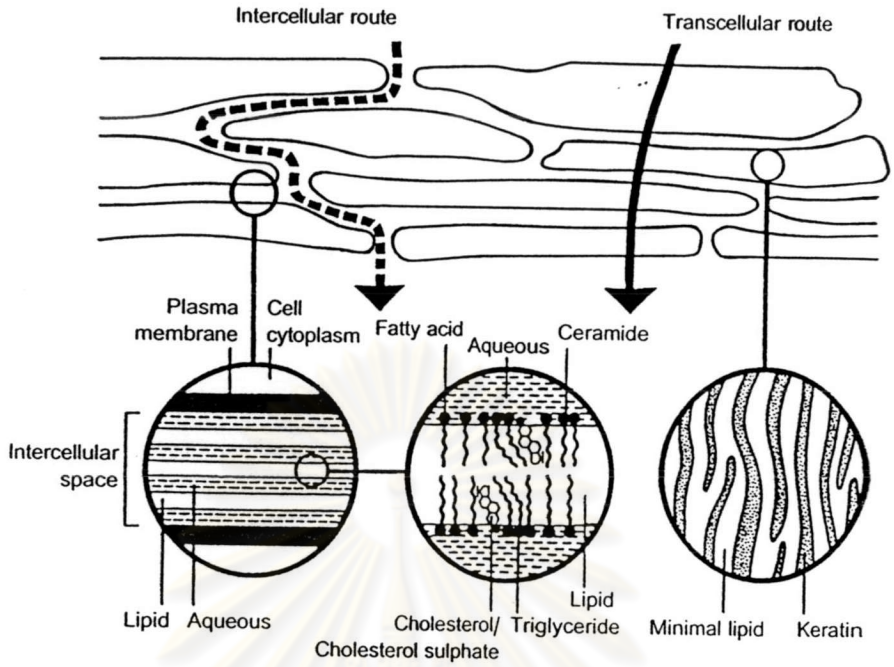

Figure 4 Permeation routes of drug molecule through stratum corneum.
(Reproduced from Hamid *rt al.,* 1996)

excised skins of different species. The studies generally showed that the skins of common laboratory animals (rabbit, rat and guinea pig) were more permeable than the skin of man. The skins of pig and monkey are more identical permeability to human skin than other animals skin (Wester and Maibatch, 1987b).

Except from the biological membranes mentioned, there have also been synthetic membranes used for percutaneous absorption studies such as Silastic® sheet which is frequently used.

Since there has been significant advances in the area of tissue culture, a reliable model of human skin using this technique may be achievable. For example, human keratinocyte cultures grown at the air-liquid interface have been found to

develop substantial barrier properties to water diffusion (Mak *et al.,* 1991). Also, constructed human epidermis has been used to examine nitroglycerine and sucrose permeability (Ponec *et al.,* 1990).

Newborn pig skin was selected to be used in this study because pig skin is more closely related to human skin than other laboratory animals (Bisset and Bride, 1983). Hawkins and Reifenrath (1986) reported that there was a good correlation between the diffusion of testosterone through pig skin *in vitro* and that through human skin *in vivo.*

Pigs and men are both backbone animals in the subphylum vertebrata of the phylum Chordata. Within the vertebrates, pigs and men belong to the same class, the mamalia, since they have a high level of metabolic activity (warm-bloodedness) to control body temperature and they nurse their young with milk secreted by mammary glands.

Pigs have a gestation period of 112 to 115 days and they are about 12 to 14 inches long at birth. The fetal pigs studied usually range from 10 to 14 inches in length (Warran, 1974).

Frandson (1986) and Warran (1974) found that the skin composition of pig and man are remarkably similar. The pig skin is divided into three major regions: the stratum corneum, the viable epidermis and the dermis. It also has skin appendages like human skin. However, the human and pig skins may have some differences in tissue thickness, hair density, gland density, lipid composition, metabolism etc.

4.3 Factors influencing *in vitro* percutaneous absorption studies

Some important factors must be considered in an *in vitro* study (Bronaugh and Collier, 1990) These factors are:

1. Maintenance of physiological temperature.
2. Provision for adequate mixing of receptor fluid.
3. Choice of receptor fluid.
4. Preparation of skin.

4.3.1 Maintenance of physiological temperature

The percutaneous absorption of a molecule is temperature dependent. The circulating water in the water jacket must be warmed.

4.3.2 Provision for adequate mixing of receptor fluid

A sufficient agitation must be controlled to prevent locally drug concentrated and to minimize static diffusion boundary layers, thereby minimizing diffusive resistance. In most diffusion systems, this step can be readily accomplished by using some kind of automatic stirring device, e.g., a magnetic stirring bar.

4.3.3 Choice of receptor fluid

The selection of receptor fluid has become an important factor. The receptor fluid is ideally isotonic saline buffered pH 7.4. Concentration of penetrant that build up in the receptor phase should not exceed 5% of its concentration in donor phase to maintain the situation of sink condition.

4.3.4 Preparation of skin

The hair on animal skins must been carefully removed by appropriate method. It was found that there was no permeation difference between the frozen human skin that stored for over one year and the fresh skin (Harrison, Berry, and Dugard., 1984). Franz (1975) also concluded that to freeze the skin up to three months did not damage the barrier properties of the excised skin. It has also been recommended to use 10 % aqueous glycerin for storing frozen skin. This can inhibit the formation of ice crystals which can disrupt cell envelope (Cooper, 1985). Pramod (1986) found that there was no difference in steady state rates between fresh and frozen rat skins.

4.4 The permeation process (James, 1995)

It is clear that the permeation process is essentially a passive diffusion. This is a phenomenon by which a diffusant moves down a concentration gradient (or more accurately, a chemical potential gradient) by a random molecular motion.

In the situation of a diffusant entering the skin, its diffusion is usually considered as a unidirectional process, i.e., the concentration gradient is directed only into the skin. This unidirectional diffusion in an isotropic medium may be explained by Fick's second law of diffusion and expressed mathematically as:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \qquad \text{.....(1)}$$

where C is the concentration of the diffusing substance in the donor solution at time t, x is a position normal to the effective area of diffusion for one-dimensional diffusive process, and D is the diffusion coefficient in membrane.

With skin permeation studies *in vitro*, investigators often use a membrane clamped between two compartments, one containing a drug formulation (the donor) and the other containing a receptor solution providing sink condition (essentially zero concentration). After a period of time, the steady state diffusion across the membrane prevails. Under these conditions eqn.1 may be simplified to eqn.2:

$$\frac{dM}{dt} = \frac{DC_0}{h} \qquad \text{.....(2)}$$

where M is the cumulative mass of permeant that passes per unit area through the membrane in time t, C_0 is the concentration of diffusant in the first layer of the membrane at the skin surface contacting the donor phase and h is the membrane thickness.

In most diffusion experiments, it is difficult to measure C_0. However, the concentration of diffusant in the donor phase bathing the membrane, C_d , may be easily determined. Also, C_0 and C_d are related as shown by eqn.3:

$$C_0 = KC_d \qquad \text{.....(3)}$$

where K is the partition coefficient of the diffusant between the membrane and the bathing solution. Substitution of eqn..3 into eqn. 2 yields eqn.4:

$$\frac{dM}{dt} = \frac{DKC_d}{h} \qquad \text{.....(4)}$$

This is the classic and most important equation used in skin permeation studies. A graph of M, the cumulative amount of drug crossing a unit area of skin against time yields a profile of drug penetrating the membrane (Figure 5). An extrapolation of the pseudo-steady state portion of the graph to the intercept on the time axis provides the lag time (L). This is the period during which the rate of diffusion across the membrane is not constant. Steady state conditions prevail after approximately 2.7 times the lag time (Barry, 1983). The lag time is related to the diffusion coefficient by eqn.5

$$L = \frac{h^2}{6D} \qquad \text{.....(5)}$$

Thus, in theory, D may be obtained measuring L, providing the membrane thickness, h, is known. In practice, however, this method for evaluating D has several disadvantages as the exact thickness of the stratum corneum is difficult to measure and may vary with penetration enhancer treatment. The measured thickness of membrane does not allow for a tortuous pathway of diffusion and the value obtained for D is therefore an apparent one. Additionally, lag times obtained from permeation experiments using human skin tend to be varied widely and include a component arising from penetrant-horny layer binding.

The permeability coefficient of a diffusant through a membrane, Kp, may be defined by eqn.6: (Michael and Kenneth, 1998)

$$Kp = \frac{KD}{h} \quad \text{.....(6)}$$

When substitute eqn (6) into eqn. (4), resulting eqn. (7).

$$\frac{dM}{dt} = KpC_d = J \quad \text{.....(7)}$$

The rate of change of cumulative mass of diffusant that passes per unit area through the membrane, dM/dt, is termed the flux of diffusant (J) and may be evaluated from the steady state portion of the drug permeation profile (Figure 5).

Thus, if the donor concentration and the flux of permeation are known, the permeability coefficient can be determined. The permeability coefficient is widely used to characterize the percutaneous absorption of drugs as it represents the flux of drug per unit skin area per unit concentration.

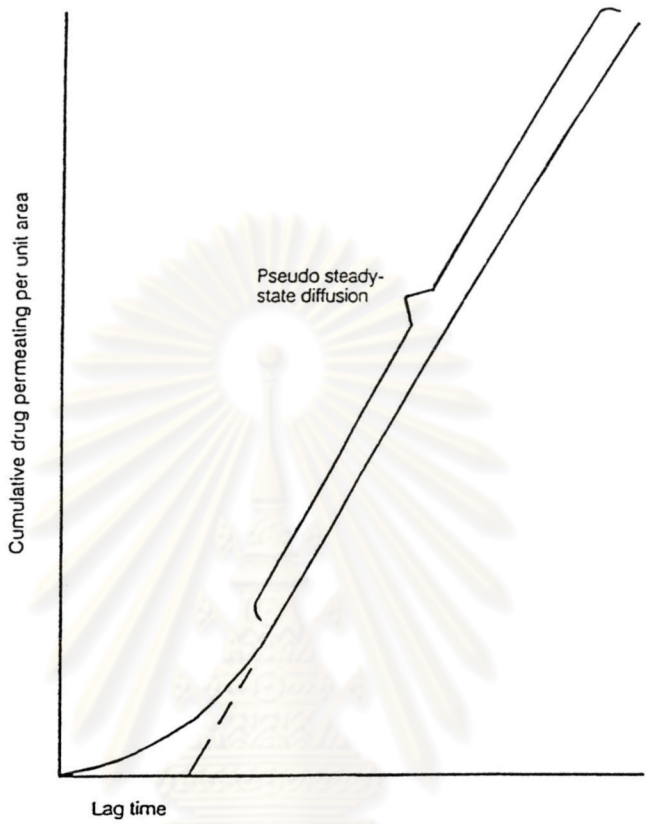

Figure 5 A typical permeation profile for a molecule diffusing across human skin. (Reproduced from James, 1995)

5. Technologies for transdermal delivery system (TDS) development

Technologies developed to provide rate control over the release of drug and their subsequent permeation across the skin can be classified into the following 5 basic approaches:

5.1 Pressure-sensitive adhesive (PSA) matrix devices

The PSA can be positioned on the face or the back of the device and extended peripherally. One of the simplest TDS is a PSA matrix devices; Figure 6a shows a common type. The drug reservoir itself is the adhesive. The rate of drug release is defined by the equation of either Higuchi ,W.I.or Hiquchi,T; which can be used for drug-in-solution or suspension formulation respectively, like a matrix device. Monolitic PSAs, for example, are Frandol®. And Nitro-Dur II®.

5.2 Membrane system

In membrane-moderated systems, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug impermeable metallic plastic laminate and a rate-controlling polymeric membrane. Figure 6b shows a cross-section of a typical device. The rate-controlling membrane can be either a micro porous or a non-porous polymeric membrane (eg., ethylene-vinyl acetate copolymer). Surface of the polymeric is coated with a thin layer of a drug-compatible, hypoallergenic, PSA polymer. The rate of drug release from this TDS can be tailored by varying the composition of drug reservoir formulation, the permeability coefficient and/or the thickness of the rate-controlling membrane. Several TDS have been successfully developed from this technology and best

examplified by Transderm-Scop®, Transderm-Nitro®, Estraderm®, and Catapres®,-TTS.

5.3 Adhesive membrane system

An adhesive layer can be used instead of polymeric membrane or rate control in reservoir devices. Figure 6c shows a typical type of adhesive diffusion-controlled system that a layer of non medicated, rate-controlling adhesive polymer of constant thickness is spread to produce an adhesive diffusion-controlled drug delivery system. The rate of drug release generally obeys Fick's law. Drug release from the Deponit® system compose of several PSA layers is controlled by different diffusivities of the layers.

5.4 Micro reservoir system

Micro capsules and macro capsules prepared by polymer and polymeric membranes can be in types of reservoir devices, such as hollow fibers, porous polymer sheet or filter, and foam as the wall of a capsule. Micro encapsulation agents are one of the most important components in this system, and several hydrophilic and hydrophobic polymers are available for this purpose. A micro reservoir type TDS is actually a hybrid of reservoir and matrix dispersion-type TDS. A cross-section of this type TDS is shown in Figure 6d. This technology has been utilized in the development of Nitrodisc®. Release of a drug from micro reservoir-type TDS can follow either a partition-control or a matrix diffusion-control.

5.5 Nonadhesive polymeric matrices

The simplest and least expensive way to control the release of a drug is to disperse it through an inert polymeric matrix. This type of TDS is examplified by the Nitro-Dur®, a cross section of which is shown in Figure 6e. The adhesive polymer is usually applied around the circumference to form an adhesive rim around the medicated disc.

Five Technologies for TDS could develop for drugs, which their log K not exceed 3. In selecting TDS, the physicochemical property of drug, the required therapeutic dose and the objective to release drug were all considered. AZT is the hydrophilic drug that required high therapeutic dose. The possible TDS of AZT would be membrane system that a large amount of AZT can be leaded in.

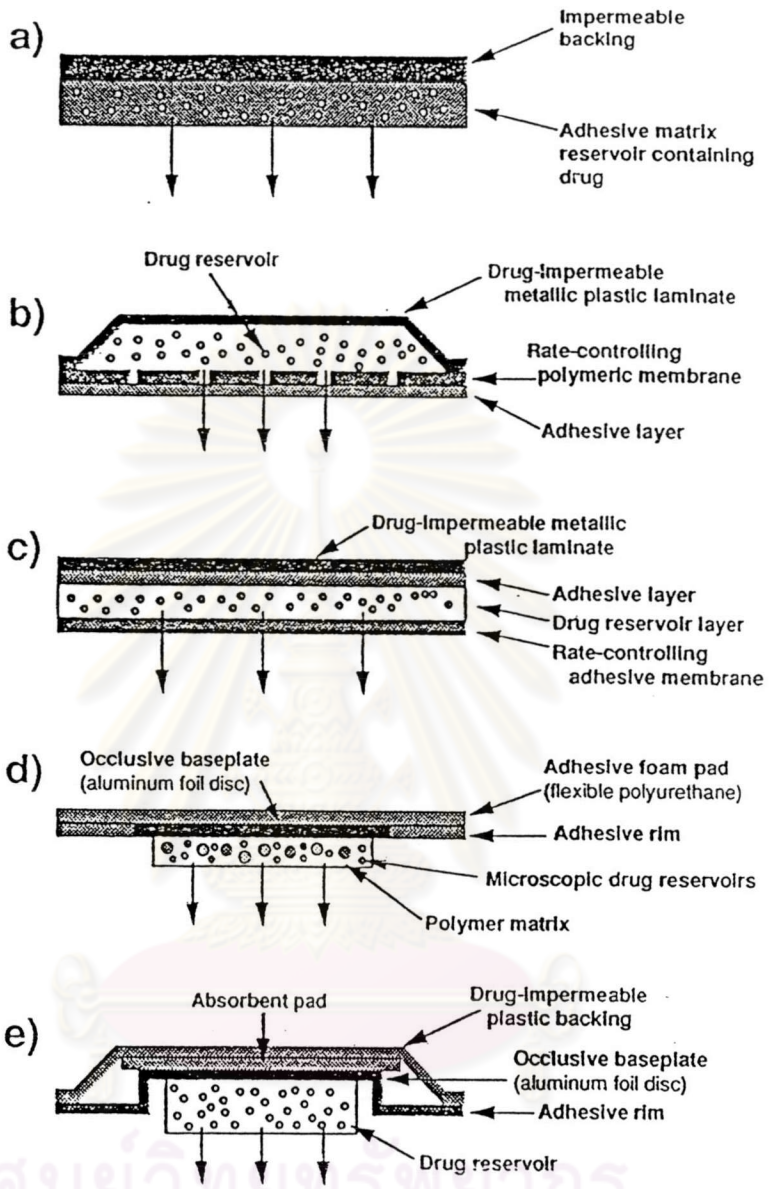

Figure 6 Cross-section views of transdermal delivery system

(a) PSA matrix device; (b) membrane-moderated TDS; (c) adhesive-controlled TDS; (d) microreservoir-type TDS; (e) matrix dispersion-type TDS (Sugibayashi and Morimoto, 1994)

6. Enhancers currently studies

Human skin is a multilayered organ, which is complex in structure and function. The outermost layer of epidermis is the stratum corneum, which is highly impermeable.

Chemicals that promote the penetration of a topically applied drug are commonly referred to as accelerates absorption promoters or penetration enhancers. An approach to increase the drug flux is to incorporate the penetration enhancer. The enhancers incorporated should be ideally safe, nontoxic, pharmacologically inert, nonirritating, and non-allergic (Barry, 1983). In addition, the tissue should revert to its normal integrity and barrier properties upon removal of the chemical. The ability of the enhancer to increase drug penetration is important but it is critical that this task be accomplished without skin irritation or sensitization. The goal is to find an enhancer that will disrupt the impermeable stratum corneum barrier membrane without destroying the fragile living tissue underneath (Cooper and Berner, 1987).

There are three pathways suggested for drug penetration through the skin: the polar, nonpolar, and polar/nonpolar parthways. The enhancers act by altering one of these pathways. A key to altering the polar pathway is to cause protein conformational change or solvent swelling. For nonpolar pathway, the rigidity of the lipid structure and fluidize the crystalline pathway that substantially increase the percutaneous absorption should be altered. Some enhancer, binary vehicles, act on both polar and nonpolar pathways by altering the multilaminate pathway (Potts, 1989).

Chemicals for enhancing the skin permeability are summarized in Table 4 (Sinha and Maninder, 2000).

Table 4 Enhancers in transdermal delivery system

Type of enhancer	enhancers
terpenes, terpenoid, essential oils	l-memthol, eucalyptus, cineole, d-limonene
pyrrolidones	*N*-methyl-2-pyrrolidone (NMP), 2-pyrrolidone, *N*-dodecyl-2-pyrrolidone, azone
fatty acids and esters	oleic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, stearic acid
sulfoxide and similar compounds	dimethyl sulfoxide (DMSO), dimethylacetamide (DMA), decylmethyl sulfoxide (DCMS)
alcohol, glycols, glycerides	ethanol, tricaprylin (TCP), l-nonanol, octyl alcohol, lauryl alcohol, medium chain glycerides
Miscellaneous - phospholipids - lipid synthesis inhibitors - cyclodextrin complexs	 Phosphatidylcholine derivatives 5-(tetradecyloxy)2-furancarboxylic acid, fluvastatin, cholesterol sulfate *β*-cyclodextrin