CHAPTER II

REVIEW OF LITERATURE

The potentials of using the intact skin as the post of administration of systematically active drugs have been increasingly recognized. Several transdermal therapeutic systems have successfully been developed and recently commercialized to accomplish the goals of systemic medication. Intensive research and development efforts over more than a decade have succeeded in the development and commercialization of several rate-controlled transdermal drug delivery systems.

Transdermal rate-controlled drug delivery offers the following potential advantages [Barry, 1985];

1. Avoidance of the risks and inconveniences of intravenous therapy, and of the varied condition of absorption and metabolism associated with oral therapy.

2. Continuity of drug administration, permitting the use of a drug with short biological half-life.

3. Achievement of efficacy with lower total daily dosage of drug by continuous drugs input and bypassing hepatic first-pass elimination.

4. Less chance of over or under dosing as the result of prolonged preprogrammed delivery of drug at the required therapeutic rate.

5. Provision of a simplified therapeutic regimen, leading to better patient compliance.

6. Ability to easily terminate the medication as needed by simply removing the drug delivery device from the skin surface.

Transdermal drug delivery systems (TDDS) were classified, according to the technological basis of their approach, into the following categories [Chien, 1987];

1. Membrane permeation controlled transdermal therapeutic systems.

Transderm-Scop delivers scopolamine for the prophylactics of motion sickness.

Transderm-Nitro delivers nitroglycerine for the medication of angina pectoris.

Clonidine-TTS delivers clonidine for the treatment of hypertension.

Estraderm-TTS delivers clonidine for the relief of post menopausal syndromes.

2. Adhesive dispersion type transdermal therapeutic systems.

Deponit delivers nitroglycerin for the treatment of angina pectoris.

Frandol delivers isosorbide dinitrate for the medication of angina pectoris.

3. Matrix diffusion controlled transdermal therapeutic systems.

Nitro-Dur delivers nitroglycerin for the medication of angina pectoris.

NTS delivers nitroglycerin for the medication of angina pectoris.

4. Microreservoir dissolution controlled transdermal therapeutic system.

Nitrodisc delivers nitroglycerin for the medication of angina pectoris.

The basic composition of TDDS is shown in Figure 1. TDDS consists of five compositions as [Parich, Babar, Palkogiannis, 1985];

1. Backing membrane :

It is an impermeable membrane as backing support of the system.

2. Drug reservoir :

This may be a single or poly layer where the required amount of drug is stored in a stable form.

3. Rate controlling polymeric membrane :

This can establish and maintain the prescribed rate of drug administration through the operational life of the system.

4. Contact adhesive layer :

This component is applied to provide an intimate contact with the skin surface. It should not be irritant to the skin.

5. Protective pool strip :

It protects the TDDS from the environment until the system is used.

From the compositions of TDDS, it is considered that the important composition which affected the control release rate is either drug reservoir or rate controlling polymeric membrane. Therefore, controlled release system can be divided into two systems. One is a membrane permeation-controlled TDDS and other is monolithic-controlled TDDS.

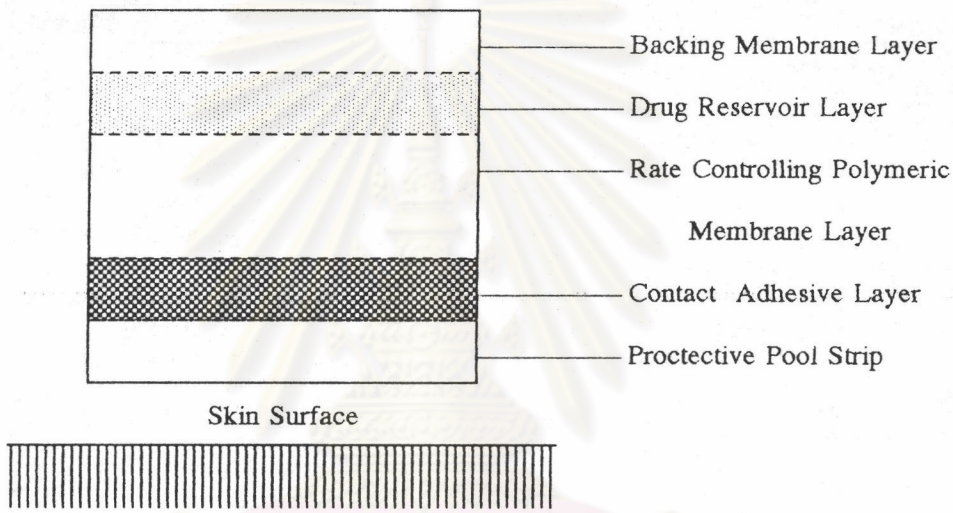

Figure 1 Schematic Illustration of Basis Composition of Transdermal Drug Delivery System

For the membrane permeation-controlled TDDS, the drug reservior is prepared by dispersing the drug homogeneously in a solid polymer. The drug in reservior is migrated through a rate-controlling membrane to the skin. The rate of drug release from this system is followed :

$$(dQ)/(dt) = [K_r K_m D_r D_m/(K_r D_m h_a + K_m D_r h_m)]C_R \quad \ldots\ldots \quad (1)$$

where $(dQ)/(dt)$ = rate of drug release

C_R = drug concentration in the reservior compartment

K_r, K_m = partion coefficients for the interfacials partioning of drug from the reservoir to membrane and from membrane to the adhesive, respectively

D_m, D_r = diffusion coefficients in the rate-controlling membrane and in the adhesive layers, respectively

h_m, h_a = thickness of the rate-controlling membrane and the adhesive layers, respectively

For the monolithic-controlled TDDS, the system control the release rate of drug by drug reservoir. It can be subdived to be drug reservoir gradient-, matrix diffusion- and microreservoir dissolution-controlled TDDS.

For the drug reservoir-controlled TDDS, the drug reservoir is formulated by proportionally increasing the drug loading level to form a

gradient of drug reservoir in order to compensate the increasing in diffusional path of drug during the ralease time. the rate of drug release can be express by :

$$(dQ)/(dt) = K_a D_a A_{(ha)} / h_{a(t)} \quad \text{.....} \quad (2)$$

where $(dQ)/(dt)$ = rate of drug release

K_a = adhesive reservoir partition coefficient

D_a = diffusion coefficient in the adhesive layer

$A_{(ha)}$ = drug loading level which is increasing proportionally

$h_{a(t)}$ = the increased thickness of diffusional path to adhesive layer

In the case of matrix diffusion-controlled TDDS, drug reservoir is formed by homogeneously dispersing the drug in a hydrophillic or lipophillic polymeric matrix. The medicated polymeric disc is mold with a defined surface area and thickness. The rate of drug release from matrix diffusion-controlled TDDS is defined as :

$$(dQ)/(dt) = [(AC_pD_p) / 2t\ ]^{1/2} \quad \text{.....} \quad (3)$$

where $(dQ)/(dt)$ = rate of drug release

A = initial drug loading dose

C_p = solbility of drug in polymer

D_p = diffusivity of drug in polymer

t = time

The drug reservoir of microreservoir dissolution-controlled TDDS is complicated formulated. The drug is suspended in an aqueous solution of a water-soluble polymer. This suspend is dispersed homogeneously in a lipophillic polymer by high shear mechanical force to form thousands of microscopic drug reservoir. These microscopic drug are unstable so the are quickly stabilized by cross-linking the polymer chains in situ. Release of drug from this system can follow either a partition or matrix diffusion controlled process. So, a Quantity versus Time or Quantity versus $Time^{1/2}$ release profile is resulted [Chien, 1987].

Polymers play a very important role in pharmaceutical formulation. Both natural and synthetic polymers are widely used in pharmaceutical system as adjuvants, suspending agent, emulsifying agent, and coating agent. In novel drug delivery system, polymers are frequently used to achieve rate controlled release of drug because they act as the barrier for drug movement [Chien, 1985].

Nifedipine is not soluble in water, as the hydrophobic particle so the drug may release from the hydrophilic polymer more than from the hydrophobic polymer according to the poor affinity between the hydrophobic drug and the hydrophilic polymeric matrix. The hydrophilic polymers have reasonably polyhydroxyl groups in their molecules which could form hydrogen bonding with water molecules. When the drug has been dispersed or entrapped into these polymers, the solubility of drug is likely to be increased according to the surrounding water molecules attached to these polymers. Therefore, more drugs are dissolved and likely to diffuse through the polymers into the medium or the skin.

Criteria in Selection of Polymers for Matrix Development. [Pillai, Babar and Plakogiannis, 1988]

1. The physico-chemical properties of the polymer such as ; molecular weight, glass-transition temperature, and chemical functionality must be appropriate enough in allowing the proper diffusion and release of the specific active agent.

2. Polymer functional group should not react chemically with the active agent.

3. The polymer and its degradation product must be non-toxic.

4. The polymer must not decompose during the entire shelf-life.

5. The polymer must be easily manufactured or fabricated into a desired product.

6. The cost of polymer should not be expensive as to make the sustained drug release devices very expensive.

7. The polymer should be readily available.

Pluronic F-127.

Pluronic F-127 (Poloxamers 407) are the series of nonionic polyoxyethylene-polyoxypropylene copolymers with the following chemical structure; where a and c is statistically equivalent [Reynolds, 1989].

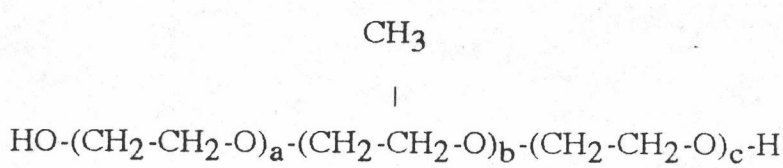

Figure 2 Structural Formula of Poloxamers

The other names of poloxamers are Pluronic(R), Lutrol(R) [BASF Waydotte, 1987a, 1987b], available grades of the poloxamers vary from liquids through pastes to solid waxy flakes. The solution of poloxamers can be sterilized by autoclaving. It is incompatible with phenol, resorcinol, and betanaphthol in certain concentrations. It has low toxicity and low potential to cause irritation or sensitization. Poloxamers can be used as a dispersing agent, emulsifying agent, solubilizer, thickening agent, gel former, and dissolution controlling agent [BASF Waydotte, 1987b, 1987c].

Poloxamers can be liquefied by merely lowering their temperature without concomittant loss of product integrity. Also, they can be reversed to their original consistency. Therefore they are called as " reversible gel " [BASF Waydotte, 1987b]. One of the advantages of the reversible gel product is it can eliminate any air bubbles which may have been accidentally incorporated during the process. Pluronic(R) F-127 (Poloxamer 407) is one of the poloxamer series that have molecular weight of 12,500. The polymer consists by weight of approximately 70% ethylene oxide and 30% propylene oxide. It is almost odourless and tasteless. It can be used as a thickener for aqueous and aqueous/alcoholic systems. It is the most efficient gelling agent in the poloxamer series [BASF Waydotte, 1987c].

Reverse thermal gelation is one of the characteristics of aqueous solution of this compound, about 20-30% of poloxamer 407 gels are fluid at refrigerator temperature (4-5^{o}C), but are highly viscous gels at room temperature and body temperature. The gelation at elevated temperatures is

reversible upon cooling. The gels consist of the large populations of micelles, forming an apparently viscous isotropic liquid crystal. The aqueous, crystal clear, and colorless gels have potential as topical drug delivery systems[Chen-Chow and Frank, 1981].

Pluronic F-127 had been investigated as sustained release depot preparation for barbiturates. It was found that the linear relationships between the amount of barbiturate released and the squared root of time excisted [Kohri, 1987]. The release of lidocaine from Pluronic F-127 gel in the *in vitro* release model without a membrane barrier had been studied. The drug was released by diffusion through the extramicellar aqueous channels of the gel matrix [Chen-Chow and Frank, 1981].

Nifedipine

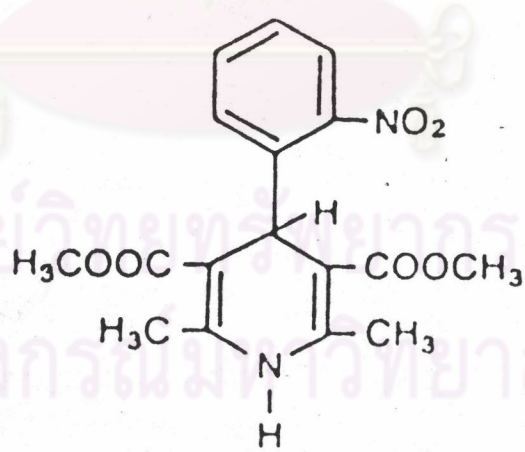

Figure 3 Structural Formula of Nifedipine.

Nifedipine, $C_{17}H_{16}N_2O_6$, is a yellow crystalline powder, odourless and tasteless. Its melting point is between 171-175°C. It is soluble in alcohol, acetone and chloroform. It must be stored in tight,

light-resistant container at temperature of 15-25°C. It is a photo-decomposition chemical. nifedipine is used for treatment and prophylaxis of angina pectoris and hypertension [Reynolds, 1989].

The sustained release dosage forms of nifedipine had also been developed. Nifedipine sustained release granules were prepared by using polymer " ethylcellulose ". It was found that the release rate of the drug was decreased with an increment of ethycellulose. The release pattern of the drug from ethylcellulose matrix granules *in vitro* study was first order kinetics. Clinical study in healthy subjects with oral administration, the plasma drug concentration was detected over 2-12 hours [Kohri, 1987]. Nasal absorption of nifedipine gel preparation was developed from polyethylene glycol 400 (PEG 400) and carbopol 941. The gel preparation with a combination of 50% w/v PEG 400 and 0.05% w/v carbopol 941 showed plasma drug concentration of rat model in the range of 0.4-0.2 mcg./ml. and prolonged action of 6 hours [Morimoto, Tabata and Morisaka, 1987].

Cellulose acetate phthalate (CAP) - Polyethylene glycol 4000 (PEG 4000) matrix was prepared for a solid dispersion suppository base with CAP as a poorly water-soluble carrier and PEG as a water-soluble carrier. *In-vivo* study using a rabbit as a model, the matrix suppository enhanced the bioavailability of nifedipine and gave a sustained release characteristic without causing an excessively high peak level in plasma [Umeda et al., 1983]. The pharmacokinetics of rectal administration of this matrix suppository to healthy volunteers follow a one compartment model with first order kinetics [Umeda et al., 1985].

Presently, the available nifedipine preparations in Thailand are in form of soft gelatin capsules in the dosage of 5 and 10 mg. Under the following names; Adalat, Apo-nifed, Avenol, Calcegard, Femanon, Nelapine, Nifecard, Nificard, Nifelat, Servidipine and in the form of retard tablets in the dosage of 10 to 20 mg. as Adalat, Calcegard, Coracten, Femanon SR, Nifecard.

Surfactants

A surfactant is a compound that can reduce the interfacial tension between two immiscible phases and this is due to the molecule containing two localised regions, one being hydrophilic in nature and the other hydrophobic. Surfactants are major components of pharmaceutical, cosmetic, and food formulations [Attwood and Florence, 1983]. The hydrophobic portion of surfactants usually consists of flexible alkyl or aryl chains. The classification of these compounds is based on the charge carried by the hydrophilic group. Thus, they can be anionic (e.g., sodium dodecyl sulfate), cationic (e.g., cetyltrimethyl ammonium bromide), or nonionic (e.g., polyoxyethylene sorbitan monopalmitate).

These substances are characterised by the presence of both polar and non-polar groups on the same molecule. It is the unique solution properties of surfactants that result in their widespread use as emulsion and suspension stabilizers, wetting agents, solubilizers, and detergents. In biological systems the effect of surfactant is complex, particularly their effect on cell membranes which can lead to alterations in permeability patterns [Attwood and Florence, 1983].

Benzalkonium Chloride

Benzalkonium chloride, $[C_6H_5CH_2N(CH_3)_2R]Cl$, cationic quaternary ammonium compound, is a white or yellowish-white, thick gel or gelatinous flakes with a mild aromatic odour. It has a very bitter taste. It forms a clear molten mass on heating. It is hygroscopic and affected by light and air. It is very soluble in water, alcohol, and acetone but insoluble in ether. A solution in water is usually alkaline and foams strongly when shaken[Boyland, Cooper and Chowhan, 1986].

Benzalkonium chloride has bactericidal activity against Gram-positive and, at a higher concentration, against some Gram-negative organisms. It is relatively inactive against spores and molds, but active against some viruses, fungi and protozoa. It may lose antimicrobial activity when the dilute solutions are stored in poly vinyl chloride and polyurethane foam containers. It has been employed as aqueous solution or creams for cleansing skin and wounds. Its solution is stable at room temperature for prolonged periods, and may be autoclaved without loss of effectiveness. It is incompatible with anionic surfactants, nonionic surfactants in high concentration, some rubber mixes, some plastics, cotton and protein [Reynolds, 1989; Boylan et al., 1986].

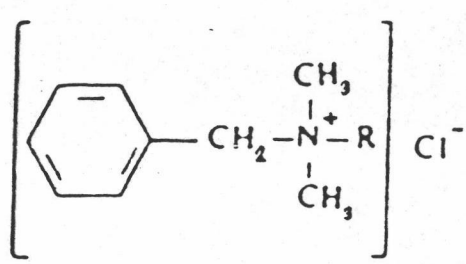

Figure 4 Structural Formula of Benzalkonium Chloride.

Brij 35

Brij is one of trade names of polyoxyethylene alkyl ether series, e.g., Cetomacrogal, Collone, Crodex, Texafor, and Emiplan etc., the nonionic surfactants. Its general formula is $CH_3(CH_2)_X(O\text{-}CH_2\text{-}CH_2)_YOH$; where (X+1) is the number of carbon atoms in the alkyl chain, and Y is the number of ethylene oxide groups in the hydrophilic chain, typically 10-60. The products tend to be mixtures of polymers of slightly varying moleculer weight, and the numbers quoted are average.

Brijs are used as; emulsifying agents for w/o or o/w emulsions; solubilizing agents for essential oils and drugs of low water solubility; and detergents, especially in shampoos and similar cosmetic cleaning preparations. They are stable in strongly acidic and alkaline conditions. They can undergo autooxidation on storage, resulting in the formation of peroxides and a contiual increase in acidity. Brij 35 is soluble in water, ethanol, and propylene glycol but insoluble in fixed oils [Reynolds, 1989; Boylan et al., 1986].

$$CH_3 - (CH_2)_X - (O - CH_2 - CH_2)_Y - OH$$

Figure 5 Structural Formula of Brij series.

Chlorhexidine Diacetate

Chlorhexidine diacetate, $C_{22}H_{30}Cl_2N_{10},2C_2H_4O_2$, is white to pale; odourless or almost odourless microcrystalline powder. It is soluble in water and alcohol; very slightly soluble in glycerol and propylene glycol. Chlorhexidine and its salts are stable at normal temperatures. Heating to 150°C will cause decomposition, yielding trace amount of parachloroaniline. Aqueous solutions of chlorhexidine salts may slowly undergo hydrolysis to from parachloroaniline.

Chlorhexidine salts and their solutions should be stored in tightly sealed containers, protected from light and controlled temperatures (15-30°C). Cork-based closures or liners should not be used. It is incompatible with soaps and other anionic materials. As a precaution against contamination with *Pseudomonas* species resistant to chlorhexidine, stock solutions may be further protected by inclusion of at least 7%W/V ethanol or 4%W/V isopropanol.

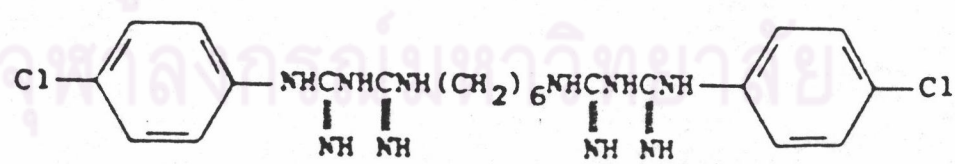

Figure 6 Structural Formula of Chlorhexidine Diacetate.

Dioctyl Sodium Sulfosuccinate

Dioctyl sodium sulfosuccinate, the nonproprietary name in USP is Docusate sodium, $C_{20}H_{37}NaO_7S$, is a white or almost white, plastic solid, hygroscopic waxy masses or flakes. It has bitter taste and a characteristic octanol-like odour. At room temperature, It is stable in acid solution, but hydrolyzes slowly in weak alkaline solutions above pH 10. The addition of aqueous solution may cause turbidity.

Dioctyl sodium sulfosuccinate is used in capsule and direct compression tablet formulation to assist in wetting and dissolution. It is used as a fecal softening agent in the management of constipation. It is also used for softening wax in the ear.

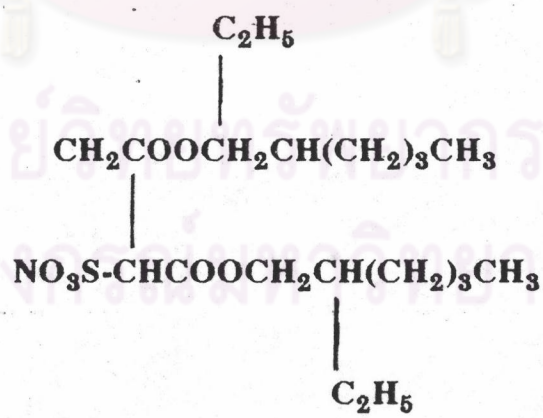

Figure 7 Structural Formula of Dioctyl Sodium Sulfosuccinate.

· Sodium Lauryl Sulfate

Sodium lauryl sulfate is a mixture of sodium alkyl sulfates, consisting mainly of sodium dodecyl sulfate, $C_{12}H_{25}O.SO_2.ONa$. It is a white or pale yellow powder or crystals with a slight characteristic, soapy, bitter taste and a faint odour. It is partly soluble in alcohol, practically insoluble in chloroform, ether and light petroleum. Its 1 in 10 water solution gives an opalescent solution [Reynolds, 1989].

It is an anionic emulsifying agent. It is a detergent and wetting agent, effective in both acid and alkaline solutions and in hard water. It is used in medicated shampoos and as a skin cleanser. It has a bacteriostatic action against Gram-positive bacteria, but is ineffective against many Gram-negative organisms. It is incompatible with some alkaloidal salts, cationic materials and acid below pH 2.5. It precipitates with lead and potassium salts [Attwood and Florences, 1983; Boylan et al.1986].

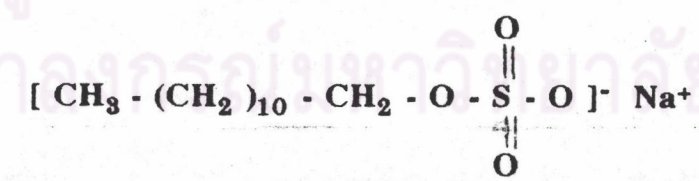

Figure 8 Structural Formula of Sodium Lauryl Sulfate.

Tween 80

Tween 80, polyoxyethylene 20 sorbitan monooleate, is a mixture of partial oleic ester of sorbitol and its mono- and di-anhydrides with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. It is a hydrophilic nonionic surfactant which is used as emulsifying agents for the preparation of stable oil-in-water emulsions in pharmaceutical products, cosmetics, insecticides and other products. It is also used as emulsifiers in the food industry. It has been used to promote increased absorption of dietary fat in certain conditions [Reynolds, 1989].

Tween 80 is a clear yellowish or brownish-yellow oily liquid with a faint characteristic odour. It is miscible with water, alcohol, ethyl acetate and methanol; practically insoluble in liquid paraffin and fixed oils. It may increase the absorption of fat soluble substances. It is stable to electrolytes as well as to weak acids and bases. Precipitation and/or discoloration occur with various substances, especially with phenols, tannins, tars or tar-like compounds. It is well tolerated, practically non-irritating, and very low toxicity.

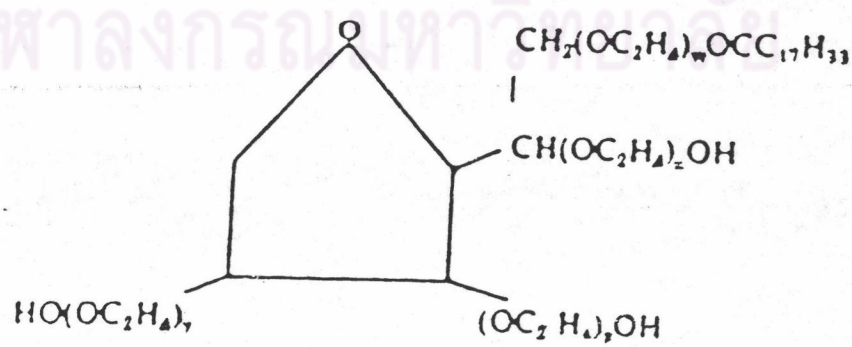

Figure 9 Structural Formula of Tween Series.

Diffusion Cell

The aim of *in vitro* experimentation in transdermal delivery is to understand and/or predict the delivery and penetration of a molecule from the skin surface into the body via the skin of a living animal. The ultimate goal is to produce, *in vitro*, an experimental design that will predict, exactly, the penetration of the drug into the human body *in vivo*. Theoretically, the *in vitro* experiment is easy to control. The diffusion cells may be designed with two factors; easy of operation and quantifiable improvement [Bronaugh and maibach, 1985].

In vitro transdermal delivery experiments are conducted on either vertically or horizontally arranged diffusion cells. In either horizontal or vertical cells it is easily stirred and temperature controlled. Thus, the receptor cell compartment is made as small as possible while maintaining infinite sink conditions. Temperature control of the receptor compartment, as with the donor compartment, is essential in order to avoid changes in ambient conditions. Typically, diffusion experiments are conducted at 35-37°C in order to mimic *in vivo* core temperatures. The whole of the receptor compartment should be controlled, utilizing of a flow-through water jacket [Gummer, Hinz and Maibach, 1987].

The recommendations of diffusion cell design are as follow [Gummer et al. 1987];

1. All materials should be assessed for their ability to absorb or adsorb the test penetrant.

2. Donor compartment.

2.1 Easy access to deliver the penetrant to the skin.

2.2 Stirred where possible.

2.3 Control of evaporation for volatile vehicles and penetrants.

3. Membrane.

3.1 Study of penetration kinetics on human skin should be used.

3.2 For vehicle or device release studies other barriers may be used.

3.3 The skin sample should contain both stratum corneum and viable epidermis.

3.4 A molecule of known penetration kinetics should be used prior to the test molecule to assess barrier function.

3.5 Where applicable, metabolic viable of the epidermis must be assessed.

4. Receptor compartment.

4.1 Either flow-through or static.

4.2 Temperature controlled.

4.3 Sufficient volume to maintain infinite sink conditions.

4.4 Stirred without obvious formation of boundary layers.

5. Receptor fluids.

5.1 Should not compromise barrier function.

5.2 Of favorable partitioning charcteristics to receive the penetrant.

5.3 Capable of maintaining epidermal viability where necessary.

5.4 Must be contained once collected.

Usually, the system of diffusion study consists of the following compositions;

1. Skin or membrane as a barrier of the drug diffusion,
2. Diffusion cell with two compartments; donor and receptor
3. Water circulating system for controlling the temperature of the whole system to be 37°C
4. Stirring system for ensuring homogeneity of drug concentration in the medium solution.

Diffusion cell is the only composition that has been modified to achieve the convenient and suitable pattern for each diffusion system proposed. An upright-type diffusion cell was designed by T. J. Franz in 1975. The feature of this diffusion cell was that it could provide the finite-dosing. This led the diffusion cell as one of the most frequently used for the *in vitro* study of the release of the drug or the mechanism of TDDS. However, several deficiencies from Franz 's model were noticed. The model could not achieve the solution hydrodynamics, the mixing efficiency, and the controlled temperature which were required in the quantitative evaluation of skin permeation kinetics.

The other improved diffusion cell called as Keshary-Chien diffusion cell [Keshary and Chien, 1984]. It was indicated as the fulfill diffusion cell commonly used until now. It could achieve and maintain the temperature on the membrane and in the receptor solution. Solution mixing efficiency was substantially improved, so the drug distribution and concentration could be homogenized within a duration four times shorter than that in the Franz diffusion cell. A 3-fold reduction in the thickness of

the hydrodynamic boundary layer reduced the mass transfer rate profile on the skin permeation.

In this study, Keshary-Chien diffusion cell was modified and selected to be used. Modification was done to solve the problems. First, the volume of sample needed for further drug analysis was much greater than the volume drawn from the diffusion cell. The Keshary-Chien diffusion cell could provide only less than 1.0 ml. per sampling while the volume needed should be 1 to 5 ml. Thus, the diameter and the height of the receptor compartment were enlarged from the former Keshary-Chien diffusion cell.

Secondly, due to the bending of the sampling port, the way to pipette the sample was inconvinient and the air bubbles often entered into the receptor compartment during pipetting. The sampling port was modified to be straight at the end of the receptor compartment. The other external features of the Keshary-Chien diffusion cell were still retained. This modified diffusion cell in this study was shown in Figure 10.

Synthetic membrane model have been proposed to be used in studying drug diffusion kinetics [Barry and Brace, 1977]. Durapore membrane is the synthetic membrane consisted of polyvinylidene difluoride [Millipore, 1987]. It is low protein binding and compatible with many chemicals with the exception of concentrated ketones, amines, and esters. Usually, its utility is a membrane filter for HPLC sample, antibiotic, virus, sterilizing filtration for insulin, DNA solution, etc. In this study, Durapore is selected to be used as a support for gel matrix in *in vitro* release study. The reasons are, it is designed to provide the

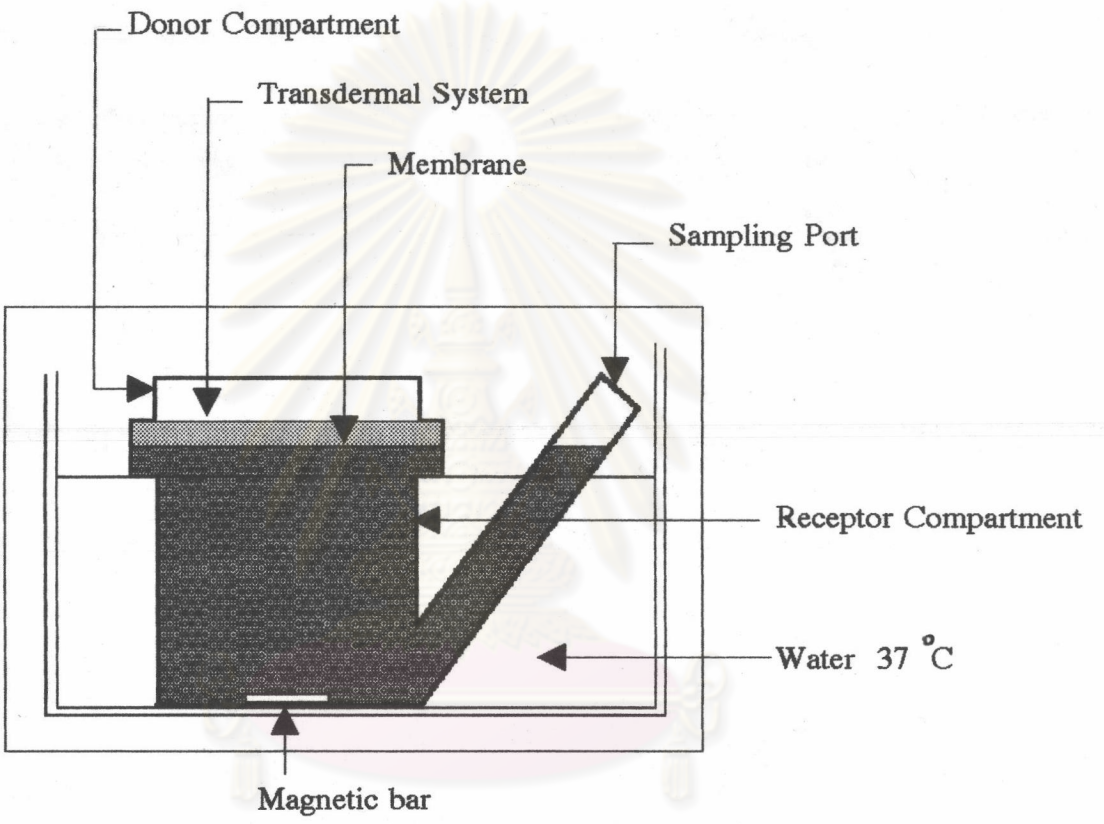

Figure 10 Schematic Illustration of the Modified Diffusion Cell

maximum purity and strength, and compatible with most of the organic reagent. It contains the uniform pore size of 0.45 micron. It is not soluble in dissolution medium used in this study. The other benefit of Durapore is that it can be fitted to the diffusion cell with 4 cm diameter.

It is important to ensure that the release profile of drug from the preparation is not limited by the solubility of drug in the receptor medium. Therefore, the receptor medium in diffusion cell must essentially act as a perfect sink condition [Gummer et al., 1987]. In diffusion study of nifedipine, a poor water-soluble drug, a volume of diffusion cell used in this study is limited to 60 ml so it is neccessary to find out a solvent vehicle dissolves nifedipine completely.

Nifedipine is soluble in ethanol, methanol, chloroform and acetone [Reynolds, 1989]. These solvents are carcinogenic agents. The evaporation of them affects the drug concentration. It is considered that co-solvent can be used to increase the solubility of the drug. The intravenous preparation of nifedipine was reported that it could be prepared by using either 30%W/W polyethylene glycol 400 [Umeda et al.1983] or the co-solvent of polyethylene glycol 400, ethanol and water in the ratio of 15:15:17 as a vehicle [Morimoto et al., 1987].

However, neither of them could not dissolve 50 mg of nifedipine completely. From the preliminary trials, it was found that the cosolvent of polyethylene glycol 400 and ethanol in the ratio of 1:1 could dissolved 50 mg of nifedipine in the volume of 4.5 ml. Therefore, this co-solvent was used in this study as a medium in diffusion cell.