CHAPTER I
INTRODUCTION

Nicotine in tobacco product has a well-established association with physical dependent. This dependence results in a withdrawal syndrome when these products are stopped, leading to early relapse in significant number of cases (Kochak, Sun, Choi and Piraino, 1992). Nicotine replacement therapy offers an effective approach to act in smoking cessation (Ross, Chan, Piraino and John, 1991). It allows the nicotine-dependent user to focus on the behavioral and psychological components to their smoking habit before going on its nicotine withdrawal (Aungst, 1988). The partial replacement of plasma nicotine which would have otherwise been obtained from cigarettes, reduces the severity of nicotine withdrawal symptoms and so allows the smoker to abstain from smoking more easily.

The first widely used method of nicotine replacement employed nicotine containing chewing gum. It is bound to an ion-exchange resin. The drug is release from the gum by interaction with saliva and is then absorbed through the oral mucosa or after swallowing. Studies have shown that nicotine chewing gum can reduce symptoms of smoking withdrawal and improve smoking cessation. However, nicotine chewing gum have some unpleasant side effects, including bad taste, nausea, heartburn, and hiccups. Other disadvantages include that chewing gum probably be socially unacceptable to some smokers or under some social circumstances and that it is contraindicated for people with dentures or other dental appliances (Lane, et al., 1993).

An alternative method for nicotine substitution is the use of a transdermal nicotine patch. Transdermal drug delivery offers a safer and more convenient method of drug administration. In addition, transdermal drug delivery promotes good compliance, patients being encouraged by the ease with which the transdermal patch applied and removed.

The advantages of transdermal nicotine include :

(a) the convenience and increased compliance of once-a-day dosage form,

(b) a more constant plasma level to minimize the undesirable side effect of nicotine, even during period of sleep, so morning cigarette craves might be reduced,

(c) the elimination of the poor taste, irritation and hiccups associated with the nicotine-containing gum,

(d) a decrease in the gastrointestinal side effect of the gum (Berner, Mazzenga, Gargiulo and Steffen, 1992),

(e) nicotine absorbed transdermally is not transported first pass through the liver where 80-90 percent of nicotine deactivation occurs, but goes directly and rapidly into systemic circulation with rapid rises in nicotine blood level (Etscorn, 1986; Rose, et al.,1985; Rose, et al., 1990; Mulligan, et al., 1990; Christen, et al., 1991).

From the advantage of the nicotine transdermal over the other routes of nicotine replacement therapy. This research study is aimed to develop the preparation of nicotine as transdermal delivery system, study the effects of the pH values, vehicles/solvents, on nicotine release and permeation through the membrane, adhesive and skin. To avoid toxicity and to minimize skin irritation, a transdermal system designed the form of a reservoir system with a rate-limiting membrane to control the drug delivery, in which a depot of nicotine is separated from the skin by a nonporous polymeric membrane (Baker, et al, 1990). This study aimed to develop the drug reservoir with rate-limiting membrane which will deliver nicotine transdermally over an extended period of time up to 24 hours. Finally, an attempt was made to prepare transdermal therapeutic system of nicotine with the release rate as comparable to transdermal nicotine commercial product (Nicotinell®-TTS) in *in-vitro* characterization.

The objectives of this research were to :

1. Study the kinetics of the release and permeation of nicotine from the design and development TDDS dosage forms compared to commercial product (Nicotinell®-TTS) by *in-vitro* skin permeation method.
2. Study the effect of pH values on the partition of nicotine between n-octanol and buffer solutions.
3. Study the effect of pH values of nicotine aqueous solutions on the stability and permeation of nicotine through membrane, adhesive and skin.
4. Study the effect of solvents/vehicles on the stability and permeation of nicotine through membrane, adhesive and skin.
5. Design and develop the drug reservoir of nicotine using solvents/ vehicles, polymer and other additives.

REVIEW LITERATURE

1. The hazards of smoking

Cigarette smoking has been identified as one of the most significant causes of deaths and disease. In USA more than 1 in 6 deaths is associated with smoking, representing 30% of all cancer deaths, including 87% of lung cancer deaths, 21% of deaths from coronary hart disease, 18% of stroke deaths, and 82% of deaths from chronic obstructive pulmonary disease (Palmer, Buckley and Faulds, 1992).

Coronary heart disease is the major killer among the smoke related diseases. In 1980, 31% of all male deaths in England and Wales were from coronary heart disease, three times more than the number of deaths from lung cancer. Current lung cancer rates are related to the smoking habits of 20 to 30 years earlier, as well as to current smoking.

Though smoking is an important factor associated with lung cancer and bronchitis, there is an evidence consistent with the hypothesis that air pollution (from burning coal smoke and sulphur dioxide) also contributes significantly to death rates from both causes.

Smoking 20 or 30 cigarettes daily for 20 years or more can cause atherosclerosis of the peripheral arteries of the legs and intermittent claudication.

The second most important smoking induced disease is chronic obstructive lung disease. The air passages become narrowed and damaged. When much of the lung tissue is destroyed the patient becomes breathless and distressed and often unable to work. The onset of this disease during 40 or 50 years of smoking can be monitored by the slow changes in forced expiratory volume (FEV1) that occur. The FEV1 is the maximal amount of air that can be expelled during the first second of forced expiration after a full deep breath. The fall in FEV1 is largely irreversible and once it falls to about 1 litre the patient is disabled.

Tobacco smoking over several decades is one cause of cancer in the lungs, oral cavity, pharynx, larynx, oesophagus, pancreas, bladder and possibly in the kidney and liver.

Smoking is probably the largest single preventable cause of ill health in the world today. On May 31, 1989, World No Tobacco Day, the director general of the World Health Organization referred to the "Blight of tobacco induced disease which takes 25 million lives annually".

Passive Smoking

Several studies have demonstrated an increased risk of lung cancer in nonsmoking spouses of smokers, who constantly breathed in cigarette smoke-contaminated air (Myer, 1990).

2. Nicotine Replacement Therapy

Nicotine has been shown to be the drug in tobacco that causes addiction. The nicotine withdrawal syndrome is primarily characterized by craving, irritability, frustration, anger, anxiety, poor concentration, restlessness, weight gain, and decreased heart rate. Pharmacotherapeutic interventions can be classified into four groups therapy that (1) replaces nicotine (2) antagonizes nicotine (3) provides symptomatic treatment for nicotine withdrawal and (4) deters smoking.

Nicotine replacement therapy was first investigated in the late 1960s by Ferno et al (1973). Based on the assumption that nicotine is the chemical reinforcer of the smoking habit, they proposed that nicotine replacement alone may help to reduce the characteristic craving for cigarettes the develops shortly after smoking cessation (Nunn-Thompson and Simon, 1989).

Nicotine polacrilex chewing gum is currently marketed as an aid to smoking cessation but there are a number of problems associated with its use. These include adverse effects (such as gastric disturbances), transference of dependence to the gum, problems with extraction of sufficient nicotine due to improper use, absorption being adversely affected by acidic beverages, and problems for people with dentures. Therefore, the efficacy of a number of other forms of nicotine delivery has been investigated. The nicotine patch was likely to be useful. It was not inherently more effective than nicotine chewing gum but was easier to use, requiring less explanation. This might increase compliance with therapy. Further studies of long term follow-up will determine whether abtinence rates following nicotine therapy are maintained, and whether continued presence of nicotine in the body results in tolerance or

adverse effects. In the meantime, the risk of short term nicotine replacement therapy appear to be substantially outweighed by the risk of cigarette smoking, and transdermal nicotine replacement therapy must therefore be seen as a useful advance in a difficult area of patient management (Baker, et al., 1989; Lin and Chien, 1993).

A new generation of nicotine replacement products is now being developed in addition to nicotine patches, researchers are looking at nasal sprays and inhalers. The new devices deliver nicotine into the blood at different rates and it is expected that they could be used singly or in combination (Norris, 1992; Jarvis, 1992).

3. Nicotine

3.1 General Properties of Nicotine

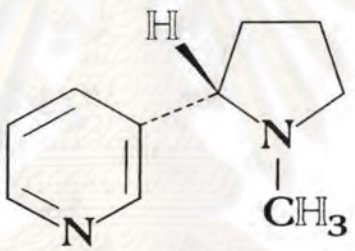

Figure 1 Molecular structure of nicotine.

Chemical name : S-3-(1-methyl-2-pyrrolidinyl) pyridine
Molecular formula : $C_{10}H_{14}N_2$
Molecular weight : 162.23
Ionization constants :
$pKa_1 = 10.96$, $pKa_2 = 6.16$ (Aungst, 1988)
$pKa_1 = 7.84$, $pKa_2 = 3.04$ (Sifton, 1994)
$pKa_1 = 8.2$, $pKa_2 = 3.4$ (Cordell, 1981)

Nicotine is a pyridine alkaloid. It is a highly purified extract obtained from the dried leaves of the tobacco plant; *Nicotiana tobacum* (Solanaceae). Tobacco leaves contain 2-8% of nicotine combined as malate or citrate. Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless to pale yellow, volatile, hygroscopic liquid, oily liquid with an unpleasant pungent odour and a sharp burning persistent taste. Weight per milliliter is about 1.01 g. It gradually becomes brown on exposure to air or

light. Of its two stereoisomers, s-(-)-nicotine is the more active and is the more prevalent form in tobacco. The free alkaloid is absorbed rapidly through the skin and respiratory tract. Nicotine free base is readily absorbed through mucous membrane and intact skin, but the salts are not.

Solubility : Soluble in water, alcohol, chloroform, ether, kerosene, light petroleum, and fixed oils.

Storage : Store in airtight containers. Protect from light.

Adverse effects : Nicotine is a highly toxic substance and is acute poisoning. Death may occur within a few minutes due to respiratory failure arising from paralysis of the muscles of respiration. The fatal dose of nicotine for an adult is from 40 to 60 mg.

Less severe poisoning causes nausea and salivation, abdominal pain, vomiting, diarrhoea, dizziness, mental confusion, disturbed hearing and vision, faintness, convulsions, sweating, and prostration. Chronic poisoning, which is usually arised from continued excessive smoking, causes local irritation of the respiratory tract, digestive and nutritional disturbances, peripheral vasoconstriction and a rise in blood pressure, and more rarely amblyopia (Reynolds, 1993).

3.2 Pharmacology

Nicotine is a ganglionic (nicotinic) cholinergic-receptor agonist. The pharmacology of nicotine is complex and includes a variety of autonomic effects, both adrenergic and cholinergic. The effects of the drug are generally dose related; large doses can produce toxic symptoms (acute toxicity). Chronic doses of nicotine may result in psychologic and physical dependence, and tolerance to some of the pharmacologic effects may occur. The action of nicotine in the body is characterized by a primary transient stimulation followed by a persistent depression of all sympathetic and parasympathetic ganglia. The actions are explained by a common mechanism, namely, that of depolarization of the postsynaptic membrane. During the onset of depolarization, nerve action potentials are generated. Once the postsynaptic membrane becomes fully depolarized postsynaptic membrane at their outset. Thus, a block of synaptic transmission results from the persisting depolarization induced by nicotine. Even after the membrane is restored, the block may persist. The synaptic stimulatory and depressant effects of nicotine cannot be overcome by atropine.

Nicotine likewise stimulates then paralyzes skeletal muscles and thus induces a curariform action, which is the major reason for the toxic effect of the alkaloid on respiration. However, nicotine is more active on ganglia than on skeletal muscles, whereas the reverse is true of curare. In addition to the above well-established action, nicotine also first stimulates then paralyzes the central nervous system. There is also evidence that the alkaloid possesses activity as a direct vasoconstrictor and that it increases intestinal motility.

Nervous System Effects

Nicotine exhibits both stimulant and depressant effect in the peripheral and central nervous systems.

A. Peripheral Nervous System

The principal pharmacologic effect of small doses of nicotine is initial, transient stimulation of all autonomic ganglia, large doses or prolonged neuronal receptor exposure to nicotine results in subsequent persistent depression of receptor activity. Although nicotine has similar dose-related effects at the myoneural junction, its rapidly developing skeletal muscle paralysis obscures the stimulant phase. Small doses of nicotine directly stimulate, sympathetic ganglia and facilitate neurotransmission; however, large doses produce initial ganglionic stimulation, which is quickly followed by inhibition of neurotransmission.

Like acetylcholine, nicotine directly stimulates a variety of peripheral sensory receptors including mechanoreceptors that respond to stretch or pressure of the skin, mesentery, tongue, lung and stomach, chemoreceptors of the aortic and carotid bodies; thermal receptors of the skin and tongue, and pain receptors.

B. Central Nervous System (CNS)

Nicotine produces marked CNS and respiratory stimulation. Nicotine seizures may subsequently develop. Delirium may also occur at toxic doses. The effect of nicotine on respiration following large doses is medicated via a direct effect on the medulla, however, small doses of the drug reflexly simulate respiration via stimulation of chemoreceptors of the aortic and carotid bodies. Nicotine-induced CNS stimulation is followed by depression, following

exposure to large doses of the drug, death may occur as a result of respiratory failure secondary to centrally mediated paralysis and peripheral blockade of the muscles of respiration.

Cardiovascular Effects

The cardiovascular effect of nicotine are dose dependent and are mediated principally via stimulation of sympathetic ganglia and the adrenal medulla and via release of catecholamines from neuronal tissue. Small doses of nicotine produce peripheral vasoconstriction and increase heart rate, myocardial contractile force, cardiac output, stroke volume, velocity of myocardial contraction, and blood pressure, resulting in an increase in cardiac work and oxygen consumption, however, large dose of the drug may cause hypotension. Nicotine may also cause tachycardia, vasospasm, and cardiac arrhythmias.

GI Effects

Unlike the cardiovascular effects, the effects of nicotine on the GI tract are mediated principally via cholinergic stimulation. Nicotine induced stimulation of parasympathetic ganglia and cholinergic nerve endings results in increased tone and motor activity of GI smooth muscle. Nausea, vomiting, and diarrhea may occur following systemic absorption of nicotine.

Other Effects

Nicotine exhibits antidiuretic activity, which is mediated by stimulating the secretion of vasopressin via a direct effect on the hypothalamic-pituitary system.

Nicotine produces an initial increase in salivary and bronchial secretion, however, the drug subsequently produces an inhibitory effect on exocrine glands. Nicotine also has a local irritant effect (Sifton, 1994; Mcevoy and Litvak, 1989; Fiore, Jorenby, Baker and Kenford, 1992).

3.3 Pharmacokinetics

3.3.1 Absorption and Plasma Concentration

The amount of nicotine released from transdermal systems has been calculated in trials, with values in the range of 43 to 85 % reported. The actual amount of nicotine absorbed has been estimated to be 36%, 68% and 96% depending on the system used. Metabolism of nicotine by the skin does not appear to occur but it is possible that some are lost from the edges of the system (Palmer, Buckley and Faulds, 1992).

Plasma nicotine concentration rose rapidly in the first 1 to 4 hours after application. Maximum plasma nicotine concentration (C_{max}) were reached 3 to 12 hours (t_{max}) after both single and repeated application of the system. Plasma nicotine concentration were maintained for the duration of patch application and despite a gradual decrease with time, were still elevated above baseline at the end of the application period. Maximum plasma nicotine concentration achieved following the use of a transdermal delivery system were lower than those achieved after smoking cigarettes. Smoking results in peak to trough oscillations in daytime plasma nicotine concentration whereas transdermal administration results in a more gradual rise in, and more constant, plasma nicotine concentrations throughout the application period. Thus transdermal nicotine systems partially replace the plasma nicotine obtained by smoking but the level and pattern of nicotine replacement appears to be sufficient to reduce withdrawal symptoms (Palmer, Buckley and Faulds, 1992; Rotenberg, 1982; Robinson, Balter and Schwartz, 1992).

3.3.2 Distribution

Distribution of nicotine into human body tissue and fluids has not been fully characterized. Following IV administration of nicotine in animals, the drug is rapidly distributed into most body tissues and fluids with highest concentrations in the cerebral cortex and adrenal medulla and lower concentration in spleen, adrenal cortex, kidney, and pancreas.

Nicotine crosses the plasma and is distributed into milk. Nicotine concentration in amniotic fluid, placental tissue, and fetal serum exceed corresponding maternal serum concentration in women who smoke cigarettes, apparently as a result of ion trapping of alkaline nicotine in these

acidic compartments. Small amounts of nicotine appear in serum and urine of infants of nursing women who smoke cigarettes (Mcevoy and Litvak, 1989).

3.3.3 Metabolism and Elimination

Nicotine undergoes extensive metabolism, primarily in the liver, but also in the lung and kidneys. Nicotine administered transdermally dose not appear be metabolised by the skin, since analysis of skin strips taken from smokers following application of transdermal systems was unable to detect cotinine in the epidermis.

The major metabolite of nicotine is cotinine, a product of oxidation of the pyrrolidine ring, while other metabolites include nicotine-N-oxide, isomethyl-nicotinium ion, nornicotine and trans-3-hydroxycotinine (Figures 2-3).

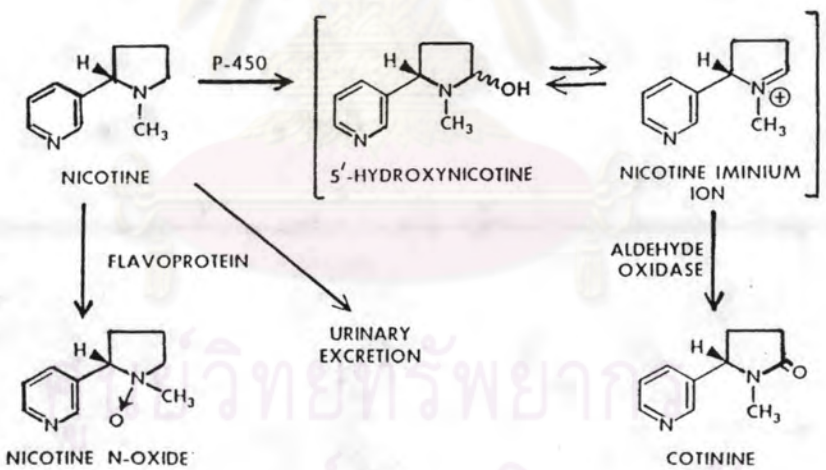

Figure 2 Major pathways of nicotine metabolism (Benowitz, 1987).

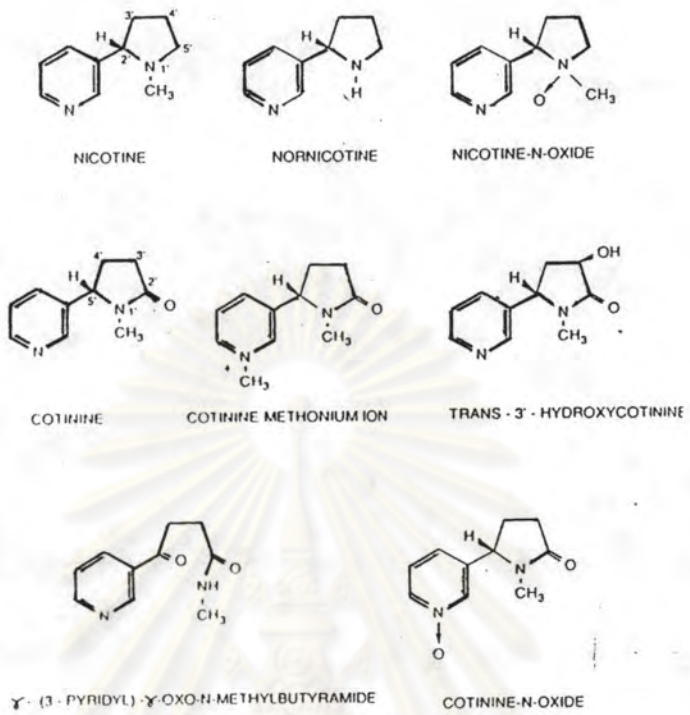

Figure 3 Chemical structures of nicotine and its major metabolites (Benowitz, 1987).

Nicotine and it metabolites are excreted in urine. Quantitative aspects of nicotine metabolism, based on pharmacokinetic studies of nicotine and cotinine, and 24 hour metabolite excretion data are summarized in Figure 4. Approximately 10-20% of an absorbed dose of nicotine is excreted unchanged. Urinary excretion of nicotine is pH dependent, excretion of the drug is increased in an acid urine and by high urine out put. Nicotine-1-N-oxide is reduced to nicotine by bacterial flora in the large intestine via an N-oxide reductase system and subsequently undergoes enterohepatic circulation and repeat metabolism in the liver (Palmer, Buckley and Faulds 1992; Silverman, 1992; Benowitz, 1987).

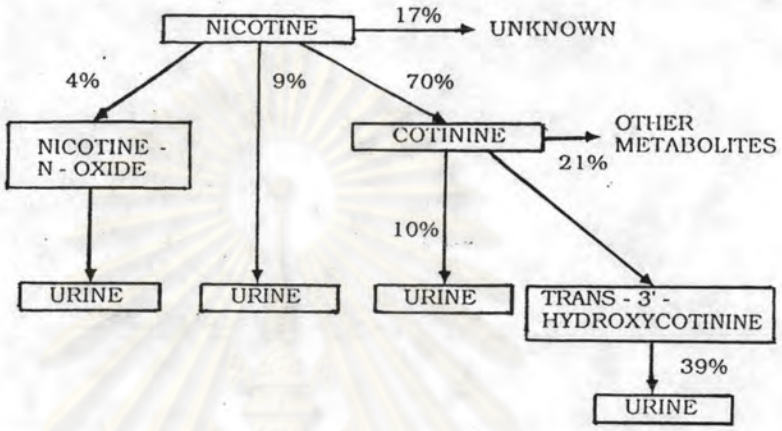

Figure 4 Quantitative disposition of nicotine based on the analysis of 24 hours urine collections in 25 habitual cigarette smokers.

3.4 Therapeutic Efficacy

The effect of transdermal nicotine as an aid to smoking cessation has been evaluated in a number of placebo-controlled trials, some of which also included concomitant behavioral counselling and therapy. Transdermal nicotine treatment has been reported to significantly reduce daily cigarette in those subjects who were unable to totally abstain from smoking, and attenuates some nicotine withdrawal symptoms, including cigarette craving, but has little effect on the body weight gain that occurs following smoking cessation (Palmer, Buckley and Faulds, 1992).

3.5 Preparations

1. Nicotine Polacrilex (Transmucosal, chewing gum)
2. Nicotine Transdermal (Tables 1-2)
   (Sifton, 1994; Cocaba and Kin, 1993)

Table 1 Current commercial nicotine dosage forms.

Trade Name	Dosage Form	Manufacturing/Distributor
Nicorette®	Chewing gum 2 mg/piece	Olic/Kabi Pharmacia
Prostep®	Transdermal Patch	Lederle Laboratories
Nicoderm®	Transdermal Patch	Alza/Marion Merrell Dow
Habitrol®	Transdermal Patch	Basel Pharmeceutical/Ciba-Geigy
Nicotrol®	Transdermal Patch	Warner-Lambert Co.,USA.
Nicotinell®	Transdermal Patch	Ciba-Geigy, USA.*

* Nicotine Transdermal which is available in Thailand

Table 2 Comparison of systemic characteristics of Nicotine-TDS.

Trade name	Delivery control method	Application period (hr)	Drug release area (cm^2)	Total nicotine content (mg)	Nicotine absorbed (mg/app)	Release rate ($\mu g/cm^2/h$)
Nicoderm®	rate controlling membrane	24	7	36	7	40
			15	78	14	
			22	114	21	
Habitrol®	polymer	24	10	17.5	7	29
			20	35.0	14	
			20	52.5	21	
Prostep®	gel metrix	24	3.5	15	11	130
			7.0	30	22	
Nicotrol®	adhesive	16	10	8.3	5	31
			20	16.6	10	
			30	24.9	15	
Nicotinell®	polymer	24	10	17.5	7	-
			20	35.0	14	
			30	52.5	21	

(Data obtained from manufacturer's prescribing information)

4. Polymeric Additive to Regulate Skin Permeation

4.1 Colloidal silicon dioxide

Chemical name : silica, amorphous silicon dioxide
Empirical structure : SiO_2
Molecular weight : 60.08
Synonyms : Aerosil®, Cab-O-Sil®, collioidal silica, flumed silica
Function : thickening and gelling of fluids and free flow of powders, anti-settling
Concentration use : 2-4% in gels, 0.5-2% as thickening agent, and 0.2-0.5% as anti-settling and free flowing agent
Solubility : soluble in strong alkalies at a pH of 10.5, not soluble in water or organics
Form Supplied : Dry powder

Colloidal silicon dioxide is widely use in pharmaceutical industry as hygroscopic materials, absorbent, dispersing agent of liquid in powder. It is used as glidant and antiadherent in tablet and capsule with a range of 0.1-0.5%. In aerosol, colloidal silicon dioxide promotes particular suspension, eliminates hard setting minimized clogging of the spray nozzle. It can be used as viscosity modifier, thixotropic thickening and suspending in suspension and gel preparation in the range of 2-10% (American Pharmaceutical Association Staff, 1986; Lochhead and William, 1993; Sherrift and Enever, 1979).

In general, colloidal silicon dioxide gel is gelled with mineral oil, a non-hydrogen bonding liquid, as anhydrous system to provide a hydrophobic transparent gel. The gel formation of colloidal silicon dioxide is due to the ability of very small silica particles to form a network structure throughout the medium by interparticle hydrogen bonding via the silanol groups on the silica surface (Schmolka, 1984).

4.2 Carbomer

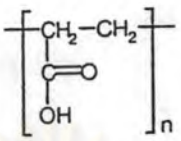

Figure 5 Structure formula of carbomer.

Chemical description	:	poly (acrylic acid) cross-linked with allyl ethers of pentaerythritol or allyl ethers of sucrose
Trade name	:	carbopol resins : 907, 910, 934, 934-P, 940, 941, 954, 980, 981, 2984, and 5984 (BF Goodrich) acritamer 934, 934-P, 940, and 941 (R.I.T.A.); Synthalen K, Synthalen M, Synthalen N (3-V)
Synonyms	:	carboxypolymethylene; carboxyvinyl polymer, acrylic acid polymer, carbopol
Function	:	thickening/gelling agent,suspension and emulsion stabilizer
Concentration use	:	0.3-1.0 % in gels, 0.2-0.6 % in cream, 0.2-0.5 % in lotions
Solubility	:	very hydrophilic, highly swellable in water, alcohol and polar solvents
Formulating	:	highly efficient thickener needs care in dispersing in liquid swells rapidly in water upon neutralization with suitable base (no heat required), effective thickeners in pH range 5-10, thickening efficiency is reduced in presence of electrolytes, incompatible with some cationic surfactants and some cationic polymers.
Form supplied	:	white, fine amorphous powder
Special comments	:	carbomers 940 and 980 give highest clarity for gels. carbomers 934, 941, 945, 981, 2984 and 5984 preferred for emulsion stabilization

Carbomer is a synthetic polyacrylic acid resin, which is copolymerized with about 0.75 to 2% polyalkylsucrose. Carbomer is a high molecular weight polymer that contains carboxylic acid groups on about two thirds of its repeat units. Gels are formed on neutralization between pH 5 and 10 with metal hydroxides or amines such as diisopropanolamine and triethanolamine. Neutralization expands the long chains of carbomer by charge repulsion to produce an entangled gel network. Because electrostatic repulsion plays a critical role in forming a gel, viscosity and gel strength depend on both pH values and salt contents (American Pharmaceutical Association Staff, 1986; Lochhead and William, 1993).

4.3 Poloxamer

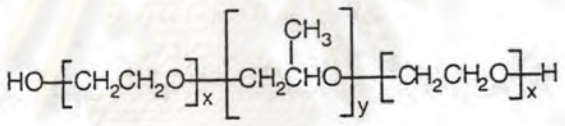

Figure 6 Structure formula of poloxamer.

Chemical name	: polyethylene glycol/polypropylene glycol block copolymer
Trade name	: pluronic F-127, Lutrol
Function	: thickener, gelling agent for aqueous systems
Concentration use	: up to 20% in water
Solubility	: soluble in cold water than hot water
Form supplied	: prills

Poloxamer is the generic name for a series of block copolymers which are composed of one polypropylene oxide block sandwiched between polyethylene oxide blocks (Figure 6). When the value of Y is at least 15, X is varied from 20 to 90% by weight. Its molecular weight ranges from 1,000

to greater than 16,000. Polyoxypropylene segment is hydrophobic while the polyoxyethylene segment is hydrophilic. The alteration of both hydrophobic and hydrophilic may change in surfactant functions and physical properties.

Pluronic F is a series of poloxamer that is manufactured by BASF Wyandotte, USA. All of them are very soluble in cold water and form gel at high temperature. Pluronic F series consist of F-38, F-68, F-77, F-87, F-88, F-98, F-108 and F-127. Pluronic F-127 is the most efficient gellant in the pluronic F series (American Pharmaceutical Association Staff, 1986; Lochhead and William, 1993; Fox, 1984).

4.4 Ethylene/vinyl/acetate copolymer (EVAco)

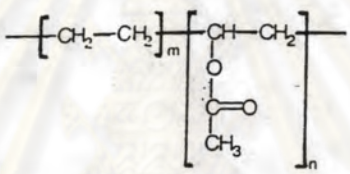

Figure 7 Structure formula of EVAco.

Chemical name : poly (ethylene-co-vinyl acetate)
Trade name : A.C. copolymer 400, 430
Function : Gellant for antiperpirants and gels
Concentration use : 5-10% in solvent
Solubility : insoluble in water, insoluble in alcohol, insoluble at room temperature in all solvents, forms a flocculated suspension when heated with solvent above the cloud-point and allowed to cool.
Form Supplied : powder or prill

Copolymer of ethylene and vinyl acetate have some advantages over other polymers in controlled-release applications because they can be processed more easily and are less expensive. A wide range of EVA polymers is commercially available with a range of vinyl acetate content (4 to 60%) although non of these are supplied as a medical-grade polymer. The stiffness, tensile strength, and softening point decrease with increasing vinyl acetate content, while the permeability and toughness increase. EVA has been shown to be chemically stable, nontoxic, and biocompatible. EVA can be processed by extrusion, film casting and injection molding. This ease of processing is a major advantage in the development of commercial drug delivery system. The devices manufactured from EVA can be sterilized either chemically or by radiation.

The polyethylene regions of EVA are crystalline in nature. Thus, crystallinity is reduced with increasing vinyl acetate content. The solubility parameter also increases with the proportion of vinyl acetate. These factors affect the increasing rate of permeation of drug molecules across polymer membranes, the comonomer ratio can be used to tailor the properties of EVA for a variety of applications (Swarbrick and Baylan, 1990; Lochhead and William, 1993).

5. Brief Description of Controlled Release Devices

Table 3 categorizes the various controlled release technologies including physical as well as chemical systems. The chemical systems do not appear to be useful for the delivery of drugs transdermally. The four major classes of physical systems are :

5.1 Reservoir Devices with Rate-controlling Membrane

These include microcapsules, macrocapsules, and membrane systems. Membrane systems are most applicable in transdermal delivery and are composed of a liquid containing the drug encapsulated by a solid or microporous polymeric membrane.

5.2 Reservoir Devices without Rate-controlling Membrane

These systems include hollow fibers, impregnation in porous plastics. The simplest example is perhaps the hollow fibers which hold the active agent in their bore and release it by diffusion through the air layer above the agent. Systems utilizing impregnated porous plastics are more complex, but in all cases, the active agent is retained by capillary action physically embedded in the pores. Release also occurs by diffusion through the air layer above the liquid that fills the pores.

5.3 Monolithic Systems

Probably the simplest and the least expensive way to control the release of a drug is to disperse it in an inert polymeric matrix. In monolitic systems, the active agent is physically blended with the polymer powder and then fused together by compression molding, injection molding screw extrusion, calendering, or casting, all of which are common processes in the plastics industry. The active agent dissolves in the polymeric or elastomeric matrix until saturation is reached.

5.4 Laminated Structures

In this system, at least two and usually three polymeric films are adhered or laminated together. The center layer of a three-layer laminate is the reservoir layer. It contains a large amount of the active agent and may be

made of porous or nonporous polymeric material. The outer layers control the rate of release of the agent and are usually fabricated from a more rigid polymer than that of the reservoir (Kydonieus and Berner,1987).

Table 3 Categorization of polymer for controlled release systems.

Physical system

Reservoir systems with rate-control
membranes systems
adhesive membrane systems
microreservoir systems
(microencapsulation or macroencapsulation)
Reservoir systems without rate-control
hollow fibers
porous films
Monolithic systems
physically dissolved in nonporous, polymeric,or elastomeric matrix (nonerodible, erodible, environmental agent, or degradable)
physically dispersed in nonporous, polymeric, or elastomeric matrix
Laminated structure
Other physical methods (osmotic pumps, adsorption onto ion-exchanger resins)

Chemical systems

Chemical erosion of polymer matrix
heterogeneous, homogeneous
Biological erosion of polymer matrix
heterogenous, homogenous

---

6. Release Characteristics of Controlled Release Devices

The active agent passes through the polymer or polymeric barrier in the absence of pores or holes by a process of absorption, solution, and diffusion down a gradient of thermodynamic activity until desorbed or removed. The transport of the active agent is governed by Fick's first law:

$$J = dM_t/Adt = -DdC_m/dx \quad \text{.....(1)}$$

J is the flux in $g/cm^2/sec$, C_m is the concentration of active agent in the polymeric membrane in g/cm^3, dC_m/dx is the concentration gradient, D is the diffusion coefficient of the active agent in the polymeric membrane in cm^2/sec, A is the surface area through which diffusion takes place in cm^2, M_t is the mass of agent released, and dM_t/dt is the steady-state release rate at time t.

6.1 Reservoir Systems with Rate-controlling Membrane

When applied to these systems, Fick's law predicts that a steady state will be established with the release rate being constant and independent of time if an active agent is enclosed within an inert polymer membrane and concentration of the agent is maintained constant within the enclosure. The amount of active agent released per day is therefore constant for the life of the device.

$$M_t = Kt \quad \text{.....(2)}$$

Where K is a constant. This type of release is "Zero order."

6.2 Reservoir Systems Without Rate-controlling Membrane

It can be shown that these devices should follow a rate of release proportional to $t^{-1/2}$. The amount of agent released is then proportional to $t^{+1/2}$ ($t^{+1/2}$ order), and given by the following equation :

$$M_t = Kt^{+1/2} \quad \text{.....(3)}$$

With this system, a large amount of the agent is released initially, and substantially smaller and decreasing amounts are released using the last half of the life of the device.

6.3 Monolithic Systems

6.3.1 Physically Dissolved, Nonerodible Polymeric, or Elastomeric Matrix

Release rate in this system is proportional to $t^{-1/2}$, (same as Equation 3) until about 60% of the active agent is released. The release rate thereafter is related exponentially to time,

$$dM_t/dt = K_1 e^{-k_2 t} \quad \text{.....(4)}$$

where K_1 and k_2 are propational constants

Thus, the rate of release above 60% drops exponentially. This type of release, which is called "first order", is also observed in reservoir systems in which the solution of active agent within the enclosure is less than saturated.

6.3.2 Physically Dispersed, Nonerodible, Polymeric, or Elastomeric Matrix

The amount released in this systems is proportional to the $t^{+1/2}$ as long as the concentration of the active agent present (dispersed and dissolved) is higher than solubility of the agent in the matrix. Thus, the dispersed systems are similar to the dissolved systems, instead of a decreased release rate after 60% of the chemical has been emitted, the relationship holds almost our the complete release curve.

6.4 Laminated Structures

Two cases are easily discernible; first, if the distribution coefficient of the active agent between the reservoir layer and the barrier membrane is much smaller than unity, the system could approximates to be "Zero order" release (reservoir system with rate-controlling membrane), and the amount released per day is independent of time. If the distribution coefficient is close to unity, then the system could approximates to be the $t^{+1/2}$ order release (monolithic, physically dispersed system) (Kydonieus and Berner,1987).

7. Diffusion in Nonporous Polymers

Permeation of drug in polymers with molecular pore size occurs by molecular diffusion in the space available the macromolecular chains of the carrier. For cross-linked polymers this space is equivalent to the mesh size of the network, usually characterized by a linear correlation length. The drug diffusion through these membranes and polymeric films may be expressed by Fick's law in its two forms or Equation 5 and 6

$$J = -D_{sm}\, dc/dx \quad \text{.....(5)}$$

$$\partial c/\partial t = D_{sm}\, \partial^2 c/\partial x^2 \quad \text{.....(6)}$$

Where, J is the solute flux, c is solute concentration, t is release time, and x is position normal to the effective area of diffusion for one-mensional diffusional processes, D_{sm} is the drug diffusion coefficient through the polymeric membranes which depends on the molecular characteristics of the polymer carrier. This parameter depends on temperature and the concentration of drug as well.

For membrane (reservoir)-type devices where the concentration difference across the polymer is quite large and almost constant for a long period of release time, Equation 5 may be integrated over the thickness δ assuming constant J and D_{sm} to give Equation 7

$$J = D_{sm}K/\delta\Delta C \quad \text{.....(7)}$$

Where ΔC refers to the solute concentration difference across the membrane and K is a solubility-type coefficient which is included to account for sometimes significant changes of the drug solubility in the external (solution) phase and in the polymer membrane. The parameter K is know as the solute partition coefficient, it is dimensionless, and it is defined according to Equation 8

$$K = C_{\text{in membrane}}/C_{\text{in solution}} \quad \text{.....(8)}$$

The permeability coefficient of the solute, P, defined according to Equation 9 and expressed in units of cm/sec, is preferred by membranologists to describe the overall permeation of a solute through a polymer.

$$P = D_{sm}K/\delta \quad \text{.....(9)}$$

Clearly solute permeation, in addition to reasonable values of the diffusion coefficient, D_{sm}, requires that the partition coefficient be high. This requirement translates into important thermodynamic considerations for solute permeation. A bioactive agent will not diffuse through microporous or gel-type membranes or films unless it is thermodynamically compatible with the polymer. Indeed, polar drugs may readily transport through hydrophilic polymers, whereas hydrophobic drugs have very low (commercially unacceptable) permeation rates through the same systems.

8. Permeability Mechanisms

The transport behavior of biological membranes differs in many respects from the more familiar processes in synthetic macroscopic membranes. Studies of the permeability of excised human skin *in-vitro* to a large number of substances, they were able to show conclusively that the principle barrier to permeation is provided by the stratum corneum. In a typical *in-vitro* skin permeation experiment, a sample of skin of essentially uniform thickness is contacted on its external (stratum corneum) surface with a solution of penetrant of known concentration on its internal (dermis) surface with water, physiological saline or Ringer's solution, and the steady-state rate of transport of penetrant across the tissue is measured by appropriated means.

In this manner, the transdermal flux of penetrant J, in for example, $\mu g/cm^2/hr$, can be computed with little ambiguity. If one assumes the tissue layer to be homogeneous and that the penetrant permeates by simple molecular diffusion, then the flux J can be represented by Fick's equation:

$$J = -D_M(dC_M/x) \sim D_M(C_M/t) \quad \text{.....(10)}$$

D_M is the penetrant diffusibility in the membrane, C_M is the penetrant concentration decrement across the membrane, and t is the membrane thickness.

In most cases, the penetrant concentration at the downstream boundary is maintained at or close to zero, where upon

$$J = D_M(C_{M(1)}/t) \quad \text{.....(11)}$$

$C_{M(1)}$ is the concentration of penetrant in the tissue contacting the source of the penetrant. Since the direct determination of $C_{M(1)}$ is usually difficult, it is common practice to express Equation (11) in the form

$$J = P(C_1 / t) \quad \text{.....(12)}$$

P is the specific permeability of the membrane to the penetrant, and, C_1 is the penetrant concentration in the solution contacting the membrane (Kydonieus and Berner, 1987; Martin,1993).

9. Transdermal Drug Delivery Systems

Delivery of drug by the transdermal route has been known to be theoretically possible for many years. The earliest developed transdermal patches were medicated bandages, usually with the drug mixed into the adhesive, designed to bring a known quantity of drug to a known area of skin for a known time. Such devices do not control the rate at which the drug is released. Controlled release transdermal patches rely for their effects on delivery of a known flux of drug to the skin for a prolonged period of time, measured in hours, days or weeks. Two mechanisms are used to control the drug flux from the patch: either the drug is contained within a drug reservoir, separated from the skin of the wearer by a synthetic membrane, through which the drug diffuses; or the drug is held dissolved or suspended in a polymer matrix, through which the drug diffuses to the skin. Patches incorporating a reservoir and membrane will deliver a steady drug flux across the membrane as long as excess undissolved drug remains in the reservoir; matrix or monolithic devices are typically characterized by a falling drug flux with time, as the matrix layers closer to the skin are depleted of drug. To date limited commercial exploitation of transdermal administration route has been achieved, because of the many practical problems to be overcome with real systems. The skin is an effective barrier against the majority of drugs. Unless the delivery device is made unacceptably large, or the natural skin permeation rate of the drug is increased, then the drug flux across the skin is inadequate for useful therapy. Thus although in theory any drug might be delivered by this route, serious investigation of candidate drugs has been limited to a few where there are strong indications for transdermal use; small molecular size, short half life, rapid metabolization by the liver, rapid degradation in the gastointestinal tract, other problems with oral administration,

high *in-vivo* skin permeability, and high potency, ie. small effective therapeutic dose (Baker, et al., 1990; Rose, et al.,1990, Langer, 1990).

In response to this new idea, several transdermal drug delivery systems (TDDS) have been recently developed, aiming to achieve the objective of systemic medication through topical application of the drug on the intact skin surface. It is exemplified first with the development of the scopolamine releasing TDDS (Transderm-Scop® by Ciba Geigy) for 72 hours prophylaxis or treatment of motion induced sickness and nausea (Chandrasekaran, 1983) and then by the successful marketing of several nitroglycerin releasing transdermal therapeutic (Deponit® by Pharma Schwarz/Lohmann, Nitrodisc® by Searle, Nitro-Dur® by Key, and Transderm-Nitro® by Ciba Geigy), as well as an isosorbide dinitrate releasing transdermal therapeutic system (Frandol® by Toaeiyo, Yomanouchi) for once-a-day medication of angina pectoris, Clonidine-releasing transdermal therapeutic system (Catapress®-TTS by Boehringer Ingelheim) for weekly treatment of hypertension. Oestradiol releasing transdermal therapeutic system (Estraderm® by Ciba-Geigy) containing 17-β-oestradiol for the treatment of symptoms associated with the female menopause, and most recently by the regulatory approval of a nicotine releasing transdermal therapeutic system (Habitrol® by Basel Pharmaceutical, Nicoderm® by Marion-Merrell dow, Nicotrol® by Warner-Lambert Co., Prostep® by Lederle and Nicotinell® by Ciba-Geigy) as an aid in reducing the craving for cigarettes. Current commercial transdermal drug delivery is shown in Table 4 (Sifton, 1994; Cooaba and Kin, 1993; Berba and Banakar, 1990; Bidout, Santusand Cuy, 1988; Sugibayashi and Morimoto, 1994).

Table 4 Representative of commercial transdermal products.

Active agent (indication) Product name	Company	Type of device	Polymer
Scoparamine (motion sickness)			
Transderm-Scop	Alza/Ciba	Reservoir	PIB, EVA
Kimete Patch	Myun Moon	Reservoir	
Nitroglycerin (angina)			
Transderm-Nitro (Nitriderm TTS, Nitroderm TTS)	Alza/Ciba	Reservoir	EVA, Silicone
Nitro-Dur II (Diafusor)	Key/Schering	Matrix	Acrylic type PSA
Nitrodisc	G.D. Searle	Microsealed	Silicone, PEG
Deponit	Lohman/Schwarz /Wyeth	PSA adhesive	
Minitran	3M Riker	PSA	
NTS Patch (Nitrocine)	Hercon/Bolar	Matrix	PVC
Nitrol	Paco/Adria	Matrix	
Herzer (Myrisrol)	Nichiban/Taiho /Nihon Kayaku	PSA	Acrylic type PSA
Isosorbide dinitrate (angina)			
Frandol Tape-S	Toaeiyo /Yamanouchi	PSA	Acrylic type PSA
Apatya Tape	Teikoku	PSA	Acrylic type PSA
Antup Tape	Tisan/Teijin	PSA	Hollow fiber
Isopit Tape	Toko/Mitsui	PSA	Rubber type PSA
Sawadol Tape	Sawai	PSA	Acrylic type PSA
Nitrous Tape	Taikyo	PSA	
Penety ISDN Tape	Sekisui	PSA	Acrylic type PSA
Rifatac	Meiji	PSA	Acrylic type PSA
Clonidine (hypertension)			
Catapres TTS	Alza/Boehringer Ingelheim	Reservoir	PIB, PP
Estradiol (hormone treatment)			
Estradiol	Ciba	Reservoir	HPC, EVA, PIB
Nicotin (aid to smoking cessation)			
Nicotinell TTS	Lohman/Ciba	Woven pad	
Niconil (ProStep, Nicolan, Nicotrans)	Elan		
Nicoderm*	Alza		
Habitrol	Ciba		
Nicotrol	Cygnus		
Fentanil (opioid analgesic)			
Duragesic	Alza/Ivers Lee Reservoir /Janssen		
Mepindodol (Hypertension)			
Pharmed*		Bio-TSD	

*FDA or related organization approved.

Transdermal rate-controlled drug delivery offers the following potential advantages over classical drug delivery systems administrated via other routes (oral, parenteral)

1. Ease of self-administration
2. Good patient compliance
3. Avoidance of variation in gastrointestinal absorption
4. Bypass of the hepatic first-pass metabolism
5. Production of sustained and constant plasma concentrations of durgs
6. Reduction in repeat dosing intervals
7. Reduction of potential adverse side effects
8. Removal of TTS provokes an immediate decrease of drug plasma levels
9. Substitute for oral or parenteral administration in certain clinical situations (pediatrics, geriatrics, nausea, etc.)
10. Adaptability to drugs with a short half-life
11. Suitability for drugs producing a therapeutic response at very low plasma concentrations

An ideal TTS should provide a constant plasma level of drugs so as to ensure a consistent pharmacodynamic response. Most of these systems can deliver the drug to the skin for prolonged periods with zero-order kinetics. Drug candidates for transdermal delivery, as represented in Figure 8, following controlled release from the TTS will have to partition into the lipophilic stratum corneum, then into the more hydrophilic viable epidermis and dermis where it will gain access to the systemic circulation (Rolland, 1993).

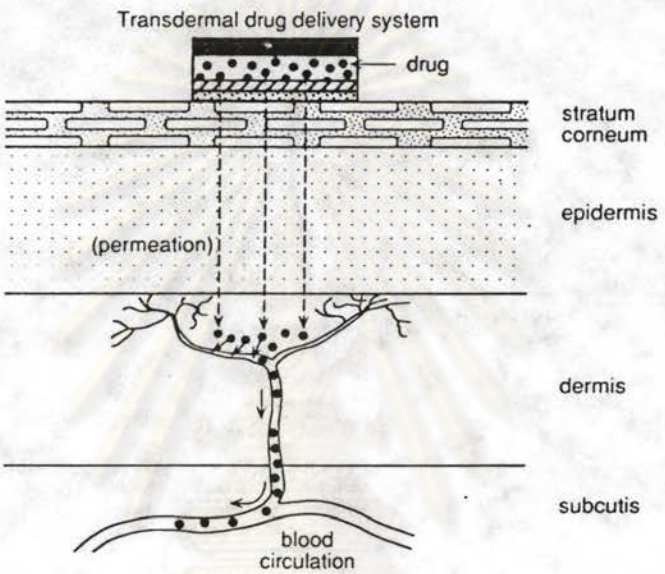

Figure 8 Diagram of transdermal drug delivery and percutaneous absorption.

Technologies for TDS Development

Several technologies have been successfully developed to provide rate control over the release of drugs and their subsequent permeation across the skin. These technologies can be classified into the following 5 basic approaches :

1. Pressure-sensitive Adhesive (PSA) Matrix Devices

The PSA can be positioned on the face or the back of the device and extended peripherally. Either way, it must fulfill the following requirements : cause no irritation and no sensitization during its period of contract with skin, provide sufficient adhesion to skin during the dosing interval, and be easily removed without leaving an unwashable residue. The most typical PSAs are acrylic, rubber or silicone adhesive.

One of the simplest TDS is a PSA matrix devices; Figure 9a shows a common type. The drug reservoir itself is the adhesive. The rate of drug release is defined by the equation of either W.I. Higuchi or T. Higuchi, 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®.

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 9b shows a cross-section of a typical device. In the drug reservoir compartment, the drug solids are either dispersed homogeneously in a solid polymer matrix or suspend in an unbleachable, viscous liquid medium to form a paste-like suspension, or dissolved in a releasable solvent to form a drug solution. The rate-controlling membrane can be either a microporous or a non-porous polymeric membrane (eg., ethylene-vinyl acetate copolymer). Surface of the polymeric membrane 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 are best examplified by Transderm-Scop®, Transderm-Nitro®, Estraderm® and Catapres®-TTS.

3. 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. In monolithic systems, the drug is physically blended with polymeric powder (hydrophilic or lipophilic nonadhesive), and the medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. This drug reservoir containing polymer disc is then glued onto an occlusive baseplate in a compartment fabricated with a drug-impermeable plastic backing. This type of TDS is exemplified by the Nitro-Dur®, a cross section of which is shown in Figure 9e. The adhesive polymer is usually applied around the circumference to form an adhesive rim around the medicated disc.

4. Adhesive Membrane System

An adhesive layer can be used instead of polymeric membrane or rate-control in reservoir devices. Figure 9c shows a typical type of adhesive diffusion-controlled system. The drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or heating molding onto a flat sheet of drug-impermeable backing to form a thin drug reservoir layer. On top of this, a layer of nonmedicated, 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 composed of several PSA layers is controlled by different diffusivities of the layers.

5. Microreservoir System

Microcapsules and macrocapsules prepared by polymers and polymeric membranes can be used in types of reservoir devices, such as hollow fibers, porous polymer sheet or filter, and foam as the wall of a capsule. Microencapsulation agents are one of the most important components in this system, and several hydrophilic and hydrophobic polymers are avilable for this purpose. A microreservoir type TDS is actually a hybrid of reservoir and matrix dispersion-type TDS. In this approach, the drug reservoir is formed

by suspending the drug solids in an aqueous solution of water-soluble liquid polymer. The drug suspension is then dispersed homogeneously in a lipophilic polymer by high-shear mechanical force, to form thousands of unleachable, microscopic spheres of drug reservoirs. A cross-section of this type TDS is shown in Figure 9d. This technology has been utilized in the development of Nitrodisc®. Release of a drug from microreservoir-type TDS can follow either a partition-control or a matrix diffusion-control depending upon the relative magnitude of solubility of the drug in the liquid compartment and in the polymer matrix (Sugibayashi and Morimoto, 1994; Chien, 1987).

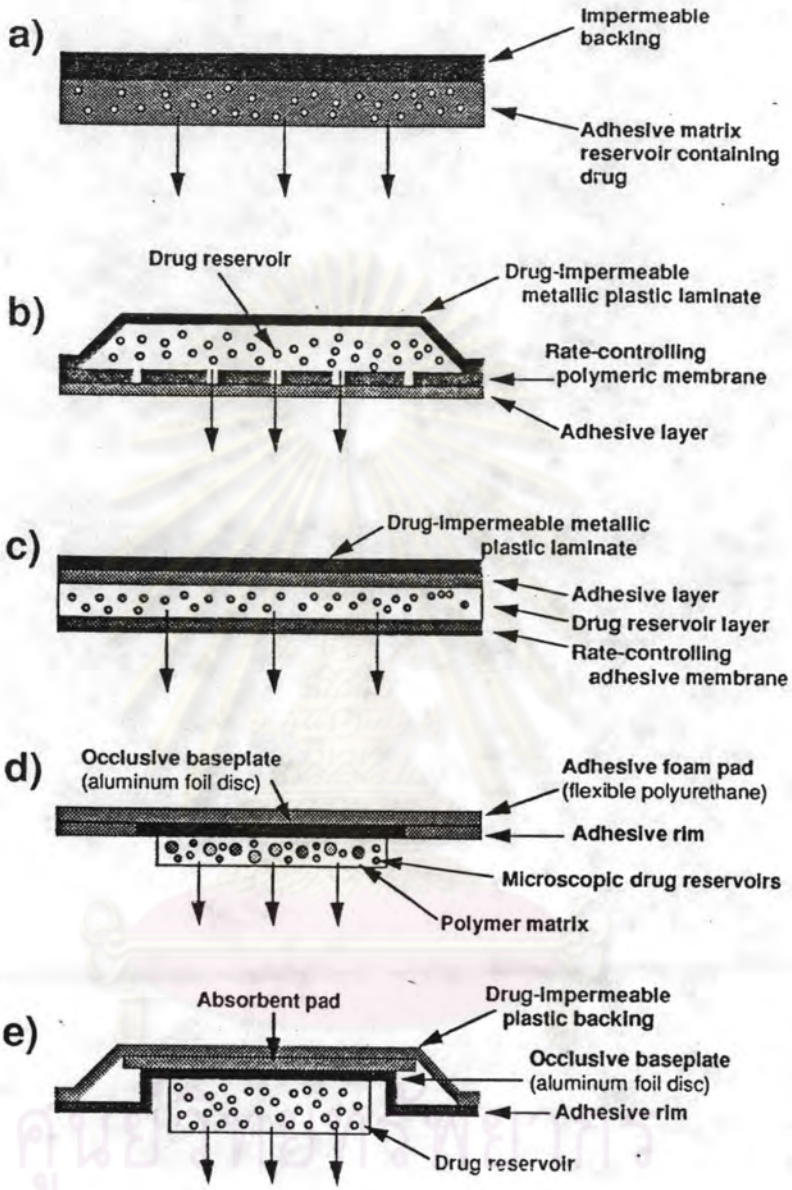

Figure 9 Cross-sectional view of several TDS : (a) PSA matrix device; (b) membrane-moderated TDS; (c) adhesive-controlled TDS; (d) microreservoir-type TDS; (e) matrix dispersion-type TDS (Sugibayashi and Morimoto, 1994).

In-vitro Study of TDS

The evaluation of all topical dosage forms may investigate on permeation of active compound through the skin. During the development TDS, *in-vitro* experiments is more useful method for evaluation dosage form. It is low cost and high ability to test large number of formulation in a relative short time. In addition, *in-vitro* studies are possible to screen candidate formulations as well as test the effect of various ingredients on skin permeation.

Diffusion cell

An early model of *in - vitro* diffusion cell has been desinged to study the routes of skin penetration since 1965 by Scheuline (Chien and Valia, 1984). Later, several *in-vitro* diffusion cells have been desinged to achieve both objectives, ease of operation and quantitative improvement.

Franz-diffusion cell, a finite-dosing upright type, one of the most frequently used *in-vitro* techniques for skin permeation studies, was designed and developed by Franz (1975). Franz diffusion cell, a commercial model, has been marketed and extensively used for skin permeation studies, over the years, to assist the development and the evaluation of a controlled-release transdermal therapeutic system. Schematic illustration of the commercially available finite-dosing Franz diffusion cell assembly is shown in Figure 10. Each of the difffusion cells consist of two compartments; a donor compartment, which is exposed to an ambient condition, and a receptor compartment which is maintained at $37 \pm 1^{\circ}C$ by circulating a thermostated water jacket. The solution hydrodynamics in the receptor compartment is kept at constant by a tiny rod-shaped magnetic rotating at 600 rpm by a synchronous motor mounted underneath the cell mouting block (Keshary and Chien, 1984).

Chien and Valia (1984) have designed the horizontal arrange diffusion cell with aiming to minimize the potential deficiencies which observed in the Franz diffusion cell (Figure 11). It is composed of a skin permeation cell and a magnetic driving unit, where consists of two half-cells in mirror image. Each of the half-cells contains a solution chamber within a stirring platform to rotate at a synchronous speed. A sample port on solution chamber could be tighly close with glass stopper. Chien and Valia suggested that their diffusion cell showed consistently superior than the Franz diffusion cell, by comparative

studies, in terms of the control of skin surface temperature and the efficiency of solution mixing .

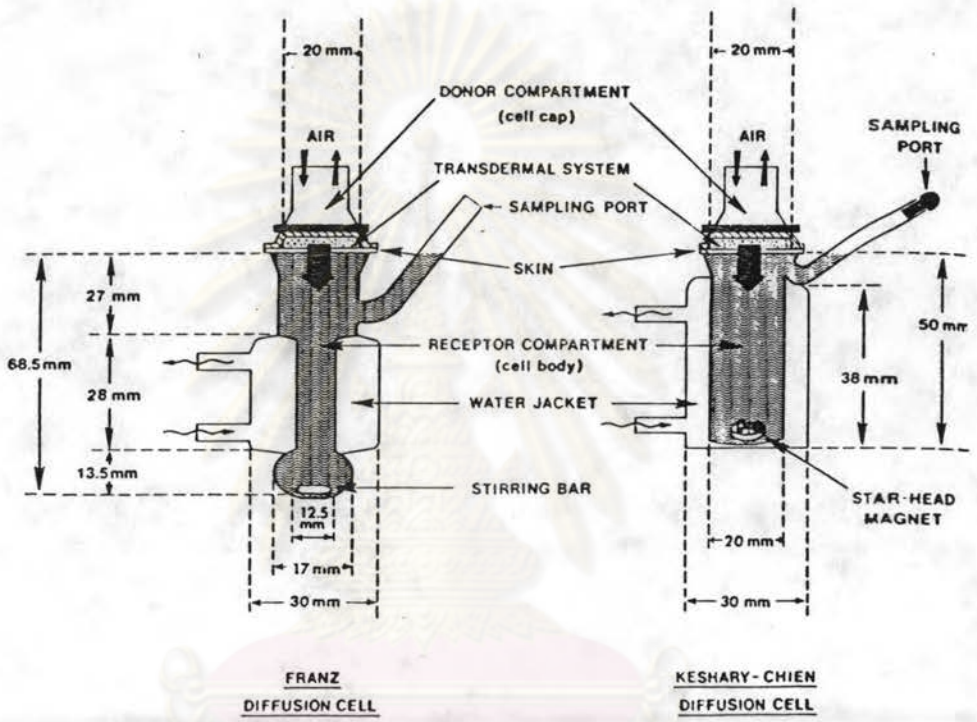

Figure 10 Diagrammatic illustration and comparison of Franz and Keshary-Chien diffusion cells.

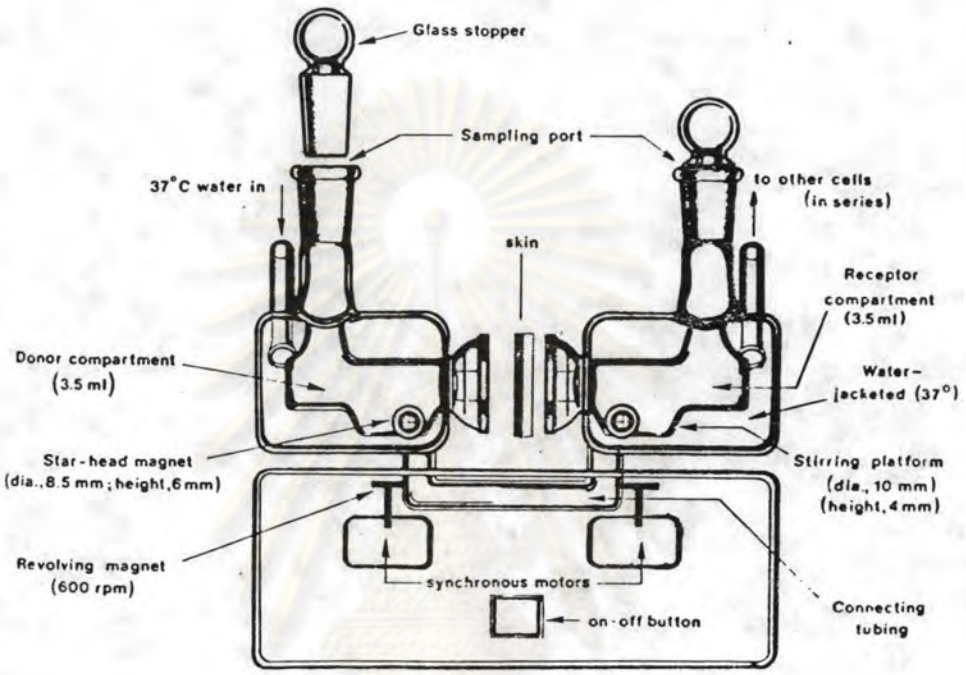

Figure 11 Schematic illustration of Valia-Chien horizontal diffusion cell.

Keshary and Chien (1984) have desinged a new finite-dosing diffusion cell for *in-vitro* skin permeation studies, which is illustrated side-by-side with a unit of the commercially available Franz diffusion cell in Figure 10. To improve the temperature control on the skin surface and in the receptor solution as well as to enhance the efficiency of solution mixing and the distribution of drug solute following skin permeation, and could be attributed to the combine effect of the reducing thickness of hydrodynamic boundary layer and the better control of the temperature in the diffusion path, so the skin permeation rate profiles could be realized with minimal of effect from the mass transfer process.

Mueller, Robert and Scott (1990) has designed an *in-vitro* diffusion cell that is large enough to accommodate drugs delivery systems up to 20 cm^2,

approaches sink conditions for large devices when tested through skin, and will maintain limited sink conditions for the same device when test directly into water, similar to a dissolution bath. The patch cell (Figure 12), is constructed from glass, teflon and stainless steel. The patch cell consists of a large receiver compartment, with a volume of approximately 200 ml, completely surrounded by a glass water jacket containing inlet and outlet ports for connection to a water bath. The patch cell can accommodate a large variety of device size for studying *in-vitro* percutaneous absorption. When using large patches, the skin is mounted directly on the teflon template with the dermal side in contact with the receiver fluid. When using smaller device sizes, an aperture, smaller than that in the teflon templated, can be punched into the polyester. The polyester can then be cemented to the teflon template. The skin is then cemented to the polyester. The delivery system can now be placed over the skin and the cell assembly completed as above .

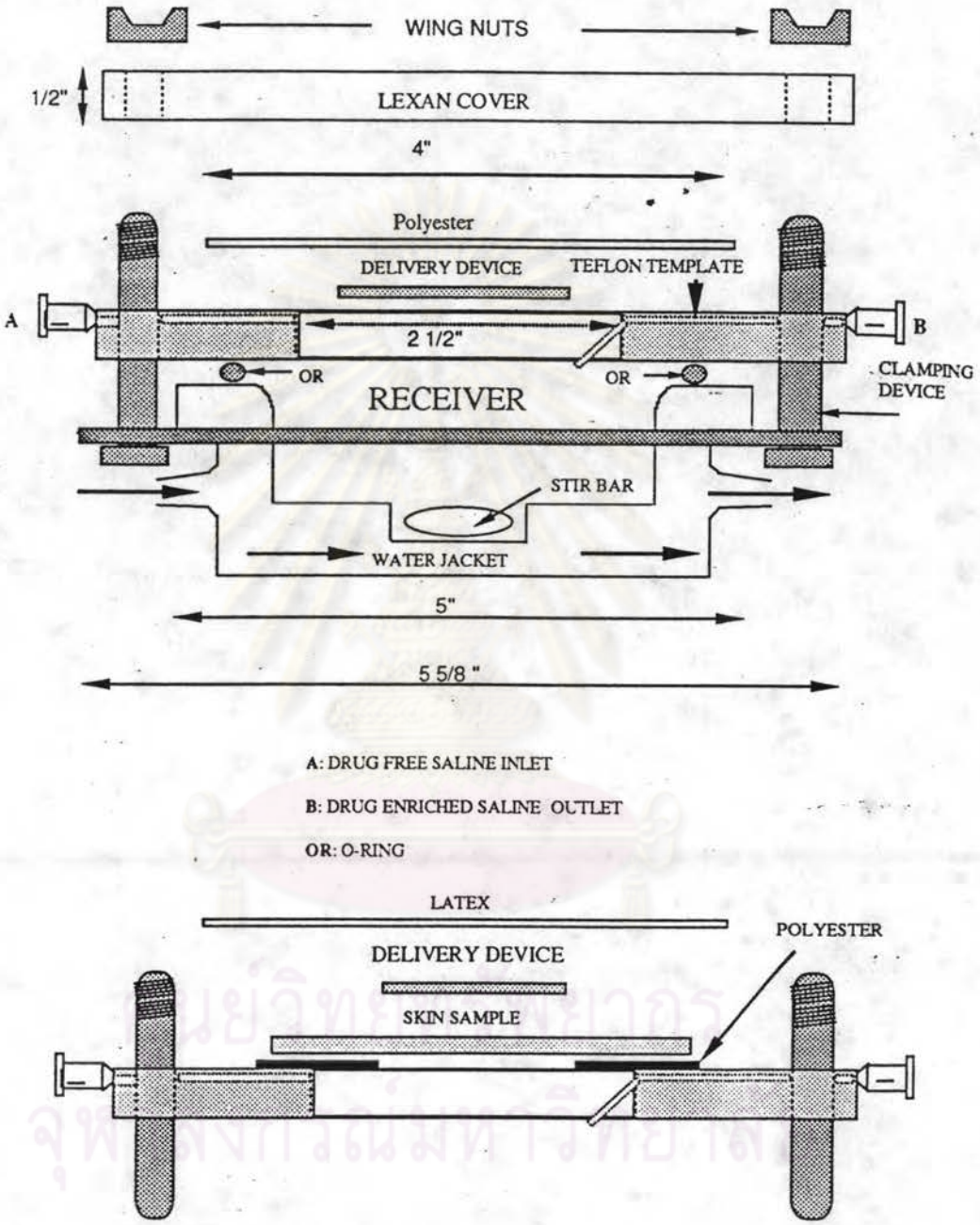

Figure 12 Schematic illustration of patch cell assembly.