CHAPTER I

INTRODUCTION

Transdermal drug delivery system can deliver certain medication to systemic circulation in a more convenient and effective way than is possible with conventional dosage forms. It can offer many advantages such as avoidance of the variables in the absorption and metabolism associated with oral administration, avoidance of first-pass metabolism in the liver, ease of administration and allowance of rapid termination of medication, if required, by removing the device from the skin surface. The potential of skin as a part of drug administration has been amply demonstrated by the acceptability of marketed transdermal therapeutic systems of scopolamine, nitroglycerin, nicotine, clonidine, isosorbide dinitrate, estradiol and indomethacin (Chien, 1987).

Terbutaline sulfate acts selectively on β_2-adrenoreceptors and is employed in the treatment of bronchial asthma. It is reported that terbutaline sulfate is incompletely absorbed from the gastrointestinal tract and also subjected to extensive hepatic first-pass metabolism following sulfate conjugation in the liver and possibly in the gut wall (Davies et al., 1974 cited in Jain, Vyas and Dixit, 1992). A 5 mg conventional terbutaline sulfate tablet provides bronchodilation for approximately 6 hours, which seems to be too short to protect patients against nocturnal wheezing. Recently, a slow release preparation of terbutaline sulfate has been formulated in order to extend the duration of its effect and to permit a change to a twice daily dosage regimen.

Terbutaline sulfate has been identified to have appreciable transdermal skin permeation and demands a controlled supply of drug to skin for systemic delivery via this route (Jain, Vyas and Dixit, 1992; Murthy, Hamsa and Bhaskaran, 1995). Therefore, the present work was aimed at developing and evaluation of a controlled release transdermal formulation of terbutaline sulfate.

Several technologies have been successfully developed to provide a rate-control over the release and skin permeation of drugs. Adhesive dispersion-type transdermal drug delivery systems are, however, advantageous by virtue of their simple construction. Moreover, the adhesive is a major component of a transdermal drug delivery system and plays an important role in maintaining intimate contact of the delivery system with the skin. The basic compositions of this type of transdermal drug delivery system compose of backing material, drug-loaded adhesive and release liner. This system is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive, by solvent casting, onto a drug-impermeable backing support (Chien, 1987; Pai et al., 1994).

Chitosan has been reported to be useful for pharmaceutical preparations (Miyazaki, Ishii and Nadai, 1981; Sawayanagi, Nambu and Nagai, 1982a, 1982b; Miyazaki et al., 1988; Shiraishi, Imai and Otagiri, 1993). Chitosan is a natural, non-toxic, biodegradable, high molecular weight polymer. The polymeric cationic character together with its potential reactive groups give chitosan unique chemical and biological properties for utilization in controlled release technologies and make it a water soluble polymer at acidic pH. In addition, the adhesiveness of chitosan to natural polymers such as hair and skin, which are composed of negatively charged mucopolysaccharides and proteins has been reported (Lower, 1984).

The usefulness of chitosan as a rate controlling membrane has been reported (Hasegawa et al., 1992; Qurashi, Blair and Allen, 1992a, 1992b; Thacharodi and Rao, 1995). Besides, the use of chitosan blended with polyvinyl alcohol has been investigated (Kim et al., 1992; Nakatsuka and Andrady, 1992; Warunee Leesajakul, 1995; Jarupa Viyoch, 1996). Studies of polyvinylpyrrolidone as a polymer matrix were subjected to a number of investigations (Baichwal et al., 1987; Thassu and Vyas, 1991; Dehghan, Parakh and Deshpande, 1993; Kanikkannan, Jayaswal and Singh, 1993; Mandal, Bhattacharyya and Ghosal, 1994; Misra et al., 1996). It provides suitable lattice structure and satisfactory *in-vitro* permeation study. The study of effect of blending with polyvinyl derivatives (polyvinyl alcohol and polyvinylpyrrolidone) is of interest. Polyvinyl derivatives were employed to improve adhesiveness and physicochemical properties of transdermal patch. Since these polymers are non-ionic polymer and miscible readily with chitosan. The present study investigated a combination of chitosan with polyvinyl derivatives as the drug loaded adhesive matrices for delivery of terbutaline sulfate. The use of plasticizers to improve the adhesiveness of drug-free Eudragit E-100 films was examined (Lin, Lee and Lin, 1995). Then, glycerol and propylene glycol were used as plasticizer to improve adhesiveness for good contact with skin.

Therefore, the purposes of this study are to point out the effects of molecular weight and amount of chitosan; amount and type of polymer blended with chitosan on the physicochemical properties of transdermal patch. The effect of amount of plasticizer on adhesiveness of transdermal patch. In addition, terbutaline sulfate transdermal patch is examined for *in-vitro* skin permeation study.

OBJECTIVES

On the basis of the rationale mentioned above, the objectives of this research are

1. To design and develop terbutaline sulfate transdermal patches by using chitosan combine with polyvinyl derivatives as adhesive matrices.

2. To study the effects of molecular weight of chitosan and amount of chitosan, polyvinyl alcohol and polyvinylpyrrolidone on adhesiveness and physicochemical properties of transdermal patches.

3. To study the effect of plasticizer on adhesiveness of transdermal patches.

4. To study and compare the amount of terbutaline sulfate permeation from transdermal patch by *in-vitro* skin permeation study using shed snake skin of *Elaphe obsoleta* as a model membrane.

LITERATURE REVIEWS

Transdermal Drug Delivery Systems

Transdermal drug delivery systems (TDDs) are self-contained, discrete dosage form, which deliver the drug through the skin at a controlled rate to the systemic circulation. The basic compositions of TDDs consist of five components as outlined below :

1. Backing material : It is an impermeable membrane or film, acts as a backing support for the system.

2. Drug reservoir : This may be a single or multilayered part 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. Adhesive layer : It is a thin layer of drug compatible, hypoallergenic, pressure sensitive polymer and is applied to provide an intimate contact with the skin surface.

5. Protective peel strip : This component prevents lost of drug that has migrated into the adhesive layer during storage, and protects TDDs from the environment before administration.

The advantages of controlled transdermal drug administration include :

- Avoids the risk and inconveniences of intravenous therapy.
- Avoids the variable absorption and metabolism sometimes associated with oral therapy.
- Permits use of pharmacologically active agents with short biological half-life.

- Permits lower daily dosage of drug, because of reduced liver metabolism and continuous drug input.
- Reduces in repeated dosing intervals.
- Diminishes chance of over or underdosing, because of prolonged, preprogrammed delivery of drug at the required therapeutic need.
- Provides for a simplified medication regimen.
- Allows rapid termination of drug input by removal of the system from the surface of the skin.

The transdermal route, however, is not suitable for drugs that irritate or sensitize the skin and is restricted by the surface area of the delivery system to potent drugs that need to be administered on a chronic basis.

Mechanism of Rate-controlled Transdermal Drug Delivery (Chien, 1987)

For a systemically-active drug to reach a target tissue, which is remote from the site of drug administration on the skin surface, it has to possess some physicochemical properties which facilitate the sorption of drug by the stratum corneum, the penetration of drug through the viable epidermis, and also the uptake of the drug by microcirculation in the dermal papillary layer (Figure1). The rate of permeation, dQ/dt, across various layers of skin tissue can be expressed in mathematical form as follow :

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

where

P_s = the permeability coefficient of the skin tissues to the penetrant

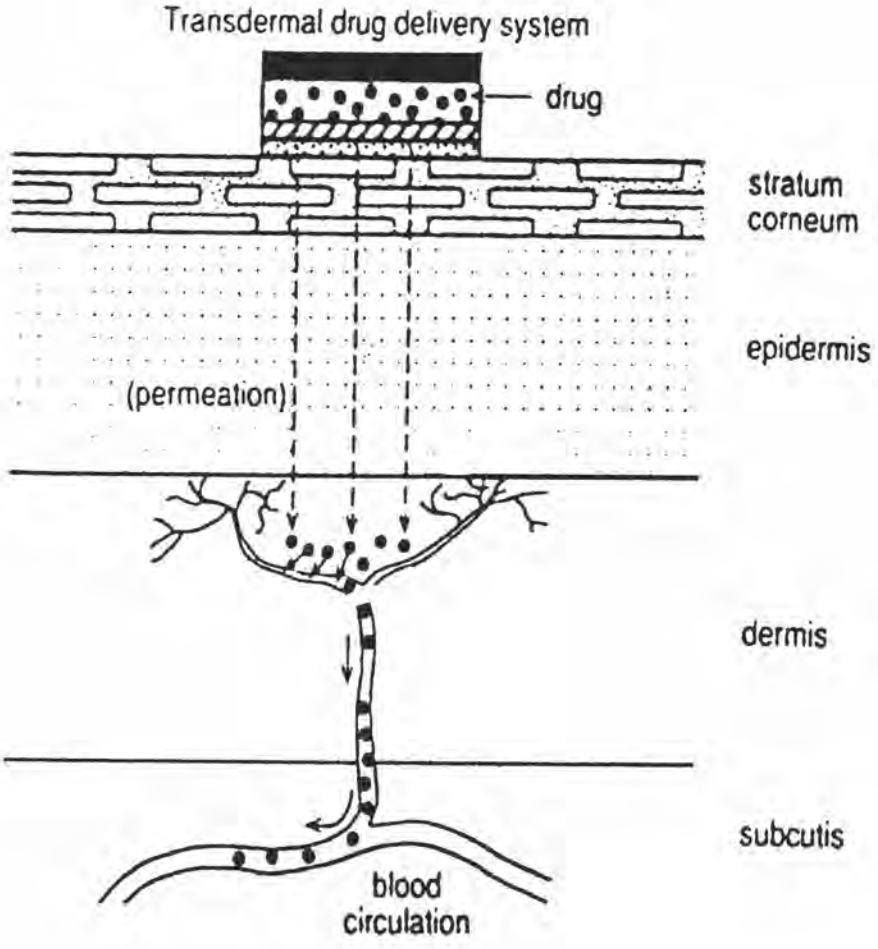

Figure 1 A multilayer skin model showing the sequence of transdermal permeation of drug: sorption by stratum corneum, permeation across viable epidermis and then uptake by the capillary network in the dermal papillary layer for systemic distribution

C_d = the concentrations of a skin penetrant in the donor phase, e.g., stratum corneum surface

C_r = the concentrations of a skin penetrant in the receptor phase, e.g., systemic circulation

The overall permeability coefficient of the skin tissues to the penetrant is defined in equation 2.

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

where

K_s = the partition coefficient for the interfacial partitioning of the penetrant molecule from a transdermal drug delivery system onto the stratum corneum

D_{ss} = the apparent diffusivity for the steady-state diffusion of the penetrant molecule through skin tissues

h_s = the thickness of the skin tissues for penetration

Technologies for Transdermal Drug Delivery System (TDDs) Development (Chien, 1987; Sugibayashi and Morimoto, 1994)

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. Membrane-Moderated TDDs

In this system, the drug reservoir is encapsulated in a shallow compartment molded from a drug impermeable metallic plastic laminate and a rate-controlling polymeric membrane. Figure 2a 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 suspended in an unleachable, viscous liquid medium to form a paste-like suspension. The rate-controlling membrane can be either a microporous or a non-porous polymeric membrane (e.g. ethylene-vinyl acetate copolymer). Surface of the polymeric membrane is coated with a thin layer of a drug-compatible, hypoallergenic, pressure sensitive adhesive polymer. The rate of drug release from this type of TDDs can be tailored by varying the composition of drug reservoir formulation, the permeability coefficient and/or the thickness of the rate-controlling membrane and adhesive. Several TDDs have been successfully developed from this technology such as Transderm-Scop®, Transderm-Nitro®, Estraderm® and Catapres-TTS®.

2. Adhesive-Controlled TDDs

An adhesive layer can be used instead of polymeric membrane or rate-control in reservoir devices. Figure 2b 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 heat 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 pressure-sensitive adhesive (PSA) layers is controlled by different diffusivities of the layers.

3. Matrix Dispersion-Type TDDs

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 reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix, 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 mounted onto an occlusive baseplate in a compartment fabricated from a drug-impermeable plastic backing. This type of TDDs is exemplified by the Nitro-Dur®, a cross section of which is shown in Figure 2c. The adhesive polymer is usually applied around the circumference to form an adhesive rim around the medicated disc.

4. Microreservoir-Type TDDs

A microreservoir type TDDs is actually a combination of reservoir and matrix dispersion-type TDDs. In this approach, the drug reservoir is formed by suspending the drug solids in an aqueous solution of water-soluble 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. This thermodynamically unstable dispersion is stabilized by immediately crosslinking the polymer chain *in situ*, which produces a medicated polymer disc with a constant surface area and a fixed thickness. A cross-section of this type TDDs is shown in Figure 2d. This technology has been utilized in the development of Nitrodisc®.

Release of a drug from microreservoir-type TDDs 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.

5. Pressure-Sensitive Adhesive (PSA) Matrix TDDs

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 contact 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 TDDs is a PSA matrix devices; Figure 2e 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 (1962) or T. Higuchi (1963), which can be used for drug in solution or suspension formulation respectively, like a matrix device. The examples of monolithic PSA, are Frandol® and Nitro-Dur II®.

***In-vitro* Study of Transdermal Drug Delivery System** (Chien, 1987; Hadgraft and Guy, 1989)

The aim of *in-vitro* experiment in transdermal delivery is to understand and predict the delivery of drug from the skin surface into the body via the skin of a living animal. Ideally, an *in-vitro* system for transdermal drug delivery studies should be designed in such a way that the intrinsic rate of release or permeation, which is theoretically independent of the *in-vitro* design, can be accurately determined. During the development of transdermal delivery system, *in-vitro* experiment is more useful

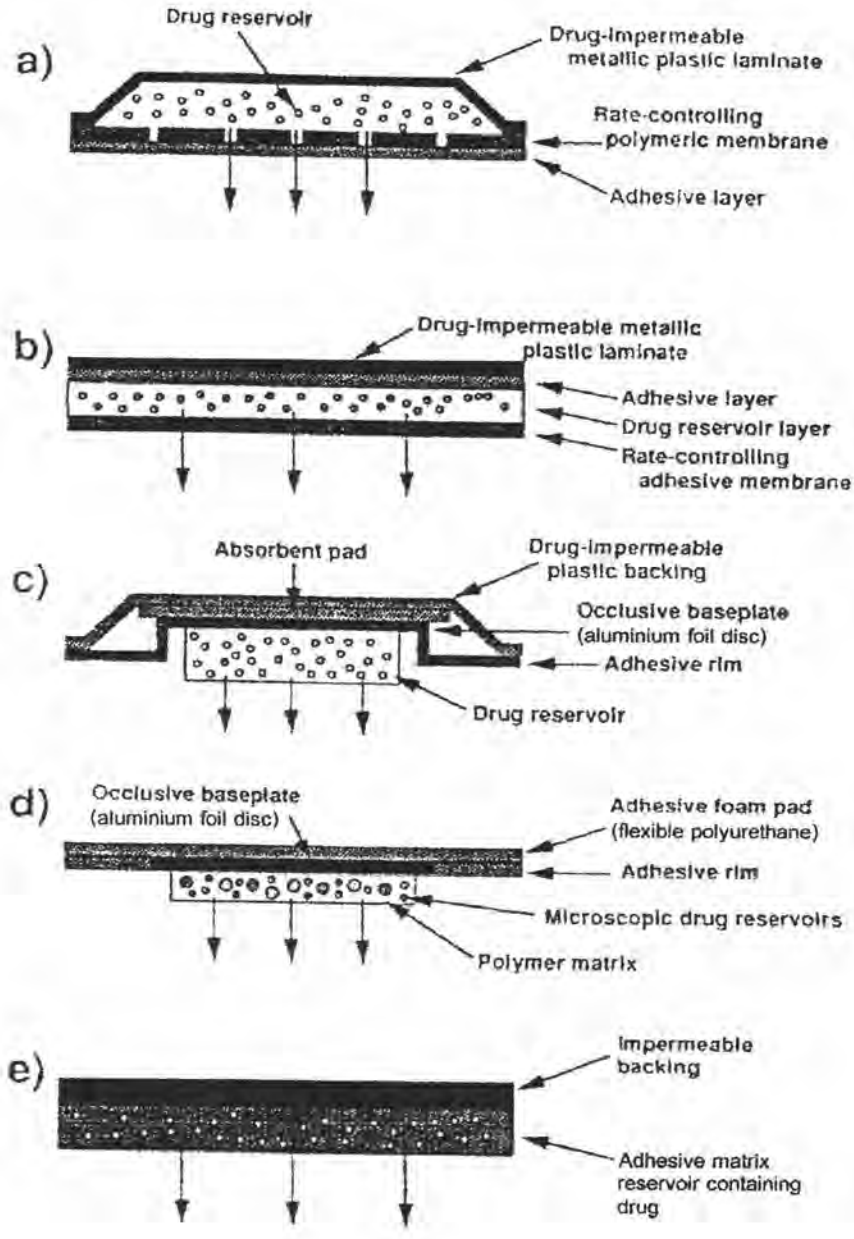

Figure 2 The cross-sectional view of several transdermal drug delivery systems: (a) Membrane-Moderated TDDs, (b) Adhesive-Controlled TDDs, (c) Matrix Dispersion-Type TDDs, (d) Microreservoir-Type TDDs and (e) Pressure-Sensitive Adhesive Matrix TDDs

method for the evaluation of dosage form. It is low cost and ability to test large number of formulations 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. The release and skin permeation kinetics of drug from transdermal drug delivery system can be evaluated using a two compartment diffusion cell assembly under identical conditions. This is carried out by individually mounting a skin specimen on a vertical or horizontal diffusion cell. Each unit of transdermal drug delivery system is then applied with its drug-releasing surface in intimate contact with the skin specimen. The skin permeation profile of drug is followed by sampling the receptor solution and assaying drug concentrations in the samples by a sensitive analytical method, such as high performance liquid chromatography. The release profiles of drug from these transdermal drug delivery systems can also be investigated in the same diffusion cell assembly without a skin specimen. Hence, the important elements for *in-vitro* evaluation of transdermal delivery are diffusion cell apparatus and skin model.

1. Diffusion Cell

For transdermal drug delivery, it is well known that the main resistance to drug transport resides in the skin, that is, diffusion through the stratum corneum. If an *in-vitro* apparatus has poor mixing condition, the release rate from transdermal drug delivery system, which is usually much greater than the skin permeation rate, may be strongly distorted by the diffusion boundary layer. In this case, the *in-vitro* release rate may become relatively close to the *in-vivo* permeation rate, and it will be believed erroneously that the rate of drug delivery is controlled by the transdermal drug delivery system, not by the skin permeation. On the other hand, a well-designed

in-vitro apparatus can assure that the mechanism of drug delivery is truly from the transdermal drug delivery system.

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

Franz diffusion cell, a finite dosing vertical-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 3. Each of the diffusion cells consists of two compartments; a donor compartment, which is exposed to an ambient condition, and a receptor compartment which is maintained at 37 ± 1 °C by a circulating thermostated water through the water jacket surrounding the receptor compartment. The solution hydrodynamics in the receptor compartment is kept at constant by a tiny rod-shaped magnetic stirrer rotating at 600 rpm by a synchronous motor mounted directly underneath the cell mounting block.

Keshary and Chien (1984) have designed a new finite-dosing diffusion cell for *in-vitro* skin permeation studies, which is illustrated along with a unit of the commercially available Franz diffusion cell in Figure 3. To improve the temperature control on the skin surface and in the receptor solution as well as to enhance the

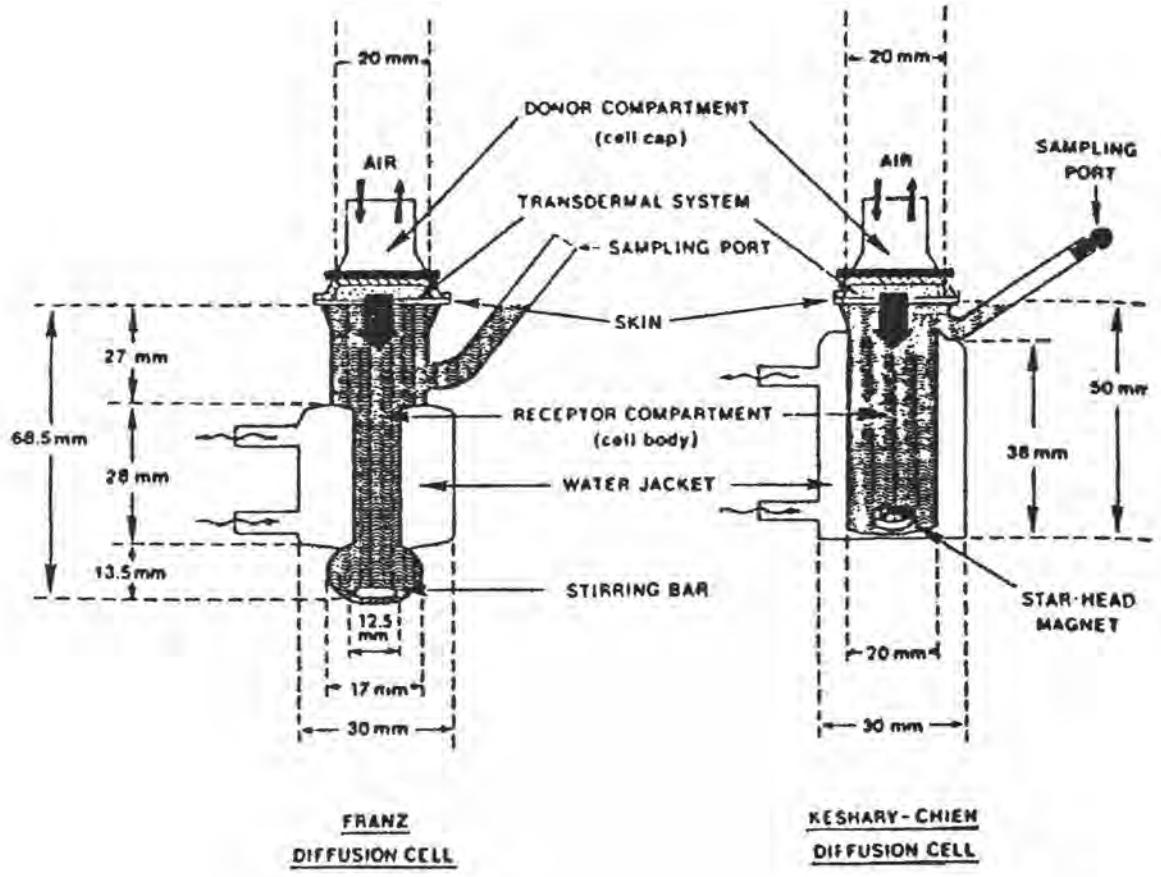

Figure 3 Diagrammatic illustration and comparison of the vertical-type Franz and Keshary-Chien diffusion cells

efficiency of fluid 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.

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 4). It is composed of a skin permeation cell and a magnetic driving unit, where consists of two half-cells in mirror image. This cell design has a solution compartment of relatively small volume (3.5 ml) in each half-cell for maximal analytical sensitivity. 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 tightly closed 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.

Mueller, Roberts and Scott (1990) have designed an *in-vitro* diffusion cell that is large enough to accommodate drug 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 5), 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

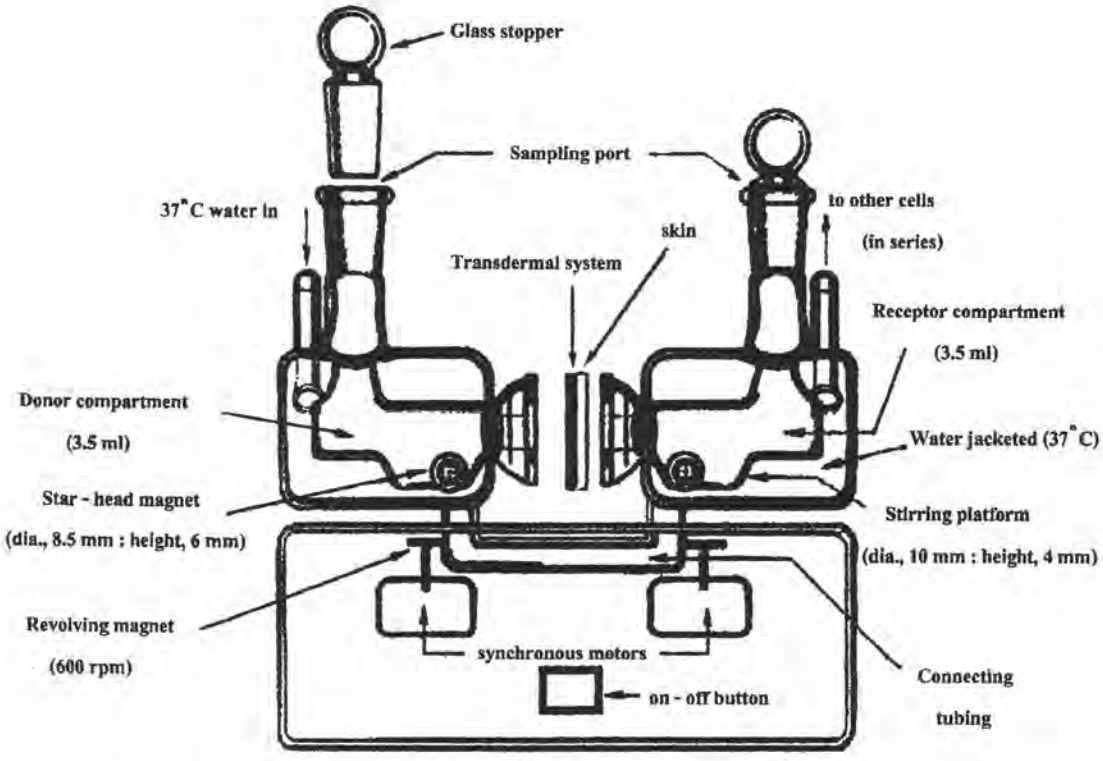

Figure 4 Schematic illustration of Valia-Chien horizontal diffusion cell

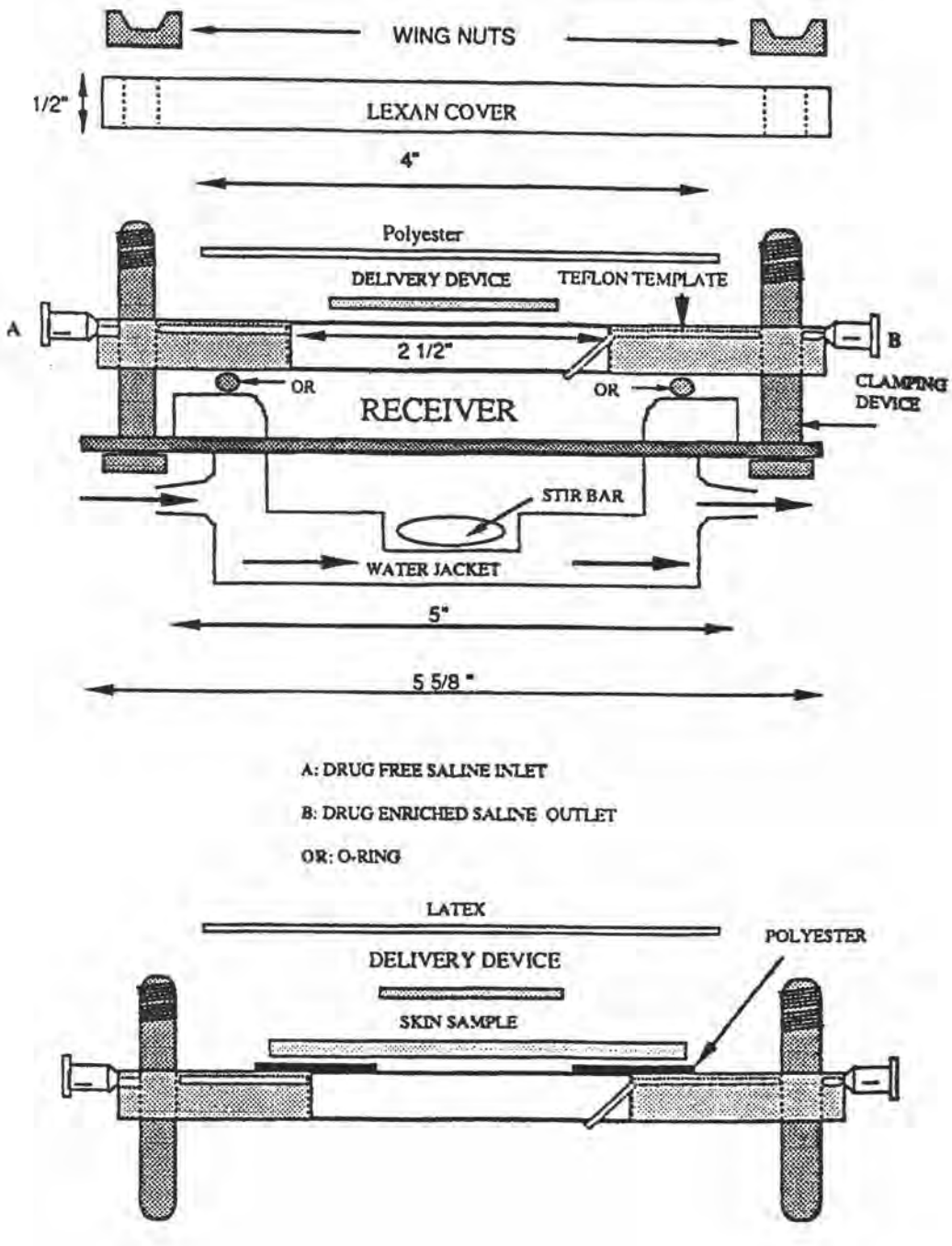

Figure 5 Schematic illustration of patch cell assembly

large patches, the skin is mounted directly on the teflon template with the dermal side in contact with the reciever fluid. When using smaller device sizes, an aperture, smaller than that in the teflon template, 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.

Thereby, in selection of diffusion cell apparatus, not only available dissolution equipment in laboratory is applied to reduce cost of experiment, but solution hydrodynamic, mixing efficiency, and temperature control are also considered to highest efficiency in *in-vitro* permeation study.

2. Skin Model

A variety of model membranes has been used for transdermal research, such as human cadaver skin, animal skin and synthetic membranes. Although human skin is the best model membrane, the use of human skin for *in-vitro* permeation studies is limited because human skin is often difficult to obtain, expensive, difficult to store and variable in permeation properties depending on the body site (Hadgraft and Guy, 1989; Itoh, Magavi et al., 1990).

A number of animal models have been investigated for their usefulness in *in-vitro* permeation studies. Excised animal skins also have variable properties depending on preparation method, skin area and animal species. Moreover, most animal skins such as hairless mouse, rat, rabbit and guinea pig skins are usually more permeable than human skin, partly because of the greater number of hair follicles (Kligman, 1983).

The artificial membranes may be possible to adequately simulate the *in-vitro* permeation of drug. However, a suitable synthetic membrane presents no significant diffusion barrier effects on the transport of a compound from a formulation into the receptor fluid. Therefore, the use of synthetic membranes in transdermal research is limited because they lack keratinized proteins and lipids which are primary components in the stratum corneum of mammalian skins. So, certain synthetic membranes may be unsatisfactory for the permeation studies (Wu et al., 1992)

Recently, many investigations have placed attention to use shed snake skin of *Elaphe obsoleta* (black rat snake) as a model membrane of transdermal research. There are many studies reported the potential of shed snake skin as a model membrane (Itoh, Xia et al., 1990; Itoh, Magavi et al., 1990; Bhattachar et al., 1992; Itoh, Wasinger et al., 1992).

Shed snake skin is a nonliving, pure stratum corneum with no hair follicles. Itoh, Xia et al. (1990) reported that there were similarities between human skin and shed snake skin of this species in terms of structure composition, permeability of several compounds and the functional group contribution to the permeability.

The similarities between human stratum corneum and shed snake skin in terms of thickness, lipid content and water evaporation rate are summarized in Table 1 (Itoh, Xia et al., 1990).

Shed snake skin appears to be a useful alternative to animal skin in measure the potential for transdermal drug delivery that it has many properties similar to those of the human stratum corneum, and is comparable to some other animal skins that have been used for *in-vitro* evaluation. Shed snake skin is not a living tissue, can be stored

at a refrigerated temperature for a relatively long periods and easily transported.

Table 1 Comparison of thickness, lipid content and water evaporation rate between human stratum corneum and shed snake skin

	Human stratum corneum	Shed snake skin (*Elaphe obsoleta*)
Thickness	13-15 μm	10-20 μm
Lipid content	2.0-6.5 %	6 %
Water evaporation rate	0.1-0.8 mg/cm^{2}hr	0.15-0.22 mg/cm^{2}hr

Material Information

1. Terbutaline Sulfate (Ahuja and Ashman, 1990)

Terbutaline sulfate is a synthetic β_2-adrenoceptor bronchodilator that is widely used in the treatment of bronchial asthma.

1.1 **Description**

The structural formula of terbutaline sulfate is given in Figure 6. Its empirical formular and molecular weight are $C_{24}H_{40}N_2O_{10}S$ and 548.658 respectively.

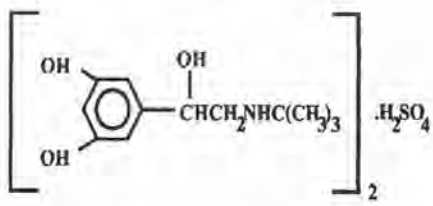

Figure 6 Chemical structure of terbutaline sulfate

Terbutaline sulfate is a white to gray-white crystalline powder, odourless or with a faint odour of acetic acid.

1.2 Pharmacology

Terbutaline sulfate is a direct-acting sympathomimetic agent with predominantly beta-adrenergic activity and a selective action on β_2-receptors. It is used as a bronchodilator.

1.3 **Pharmacokinetic** (Reynolds et al., 1989)

Terbutaline sulfate is incompletely absorbed from the gastro-intestinal tract and is also subject to extensive first pass metabolism by sulfate conjugation in the liver and possibly the gut wall. It is accordingly excreted in the urine partly as the inactive conjugates and partly as unchanged terbutaline, the ratio depending upon whether it was given orally or parenterally. The biological half-life is 3.6 hours. Although absorption from the gastro-intestinal tract is incomplete, peak plasma levels of unchanged terbutaline reach approximately 5 ng/ml, which apparently is sufficient to produce effective changes in pulmonary function.

1.4 Preparations

There are many dosage forms of terbutaline sulfate formulations in Thailand such as Tablet (2.5 mg), Durule (5 mg), Syrup (1.5 mg/5 ml), Injection (0.5 mg/ml), Inhaler (0.25 mg/metered inhalation), Turbuhaler (0.5 mg/metered inhalation) and Nebulising solution (5 mg/2 ml).

2.Polymers Used in this Experiment

2.1 Chitosan

Chitosan was first prepared by Hoppe Seyler and is a macromolecular material, obtained by the substantial or complete deacetylation of chitin, which is one of the main constituents in the outer shell of crustaceans such as crab and shrimp, but without the destruction of its polymeric chain (Lower, 1984). Chitosan is a linear biopolymer, specifically a polysaccharide, which consists of two monosaccharides: N-acetyl-D-glucosamine and D-glucosamine linked together by β(1-4) glycosidic bonds. Chemical structure for chitosan is shown below.

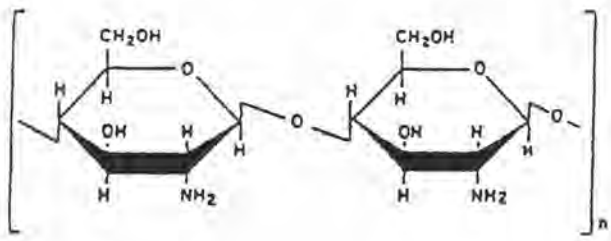

Figure 7 Chemical structure of chitosan

The molecular weight of chitosan will, for commercial products, depend on the processing conditions. Three commercial grades, different in viscosity, of chitosan were used in this experiment. The viscosity is dependent on the molecular weight, the higher the viscosity the higher molecular weight (long chain length). The viscosities of 1 % solution are shown as follows:

SEACURE 143 : viscosity < 20 mPa.s Deacetylation > 80 %

SEACURE 243 : viscosity 20-200 mPa.s Deacetylation > 80 %

SEACURE 343 : viscosity 200-800 mPa.s Deacetylation > 80 %

Standard grade of chitosan requires the addition of acid for solubilization in water. At acidic pH, the free amine groups ($-NH_2$) become protonated to form cationic amine groups ($-NH_3^+$). Acetic acid is commonly used as a reference, but other organic acids such as citric acid, formic acid, lactic acid, tartaric acid , as well as mineral acids, can also be used successfully. For practical purpose chitosan is regarded as insoluble in sulphuric acid and phosphoric acid, while a certain solubility exists for other mineral acids like hydrochloric, nitric and perchloric acid (Sandford, 1989).

The advantage of using chitosan in such products is firstly based on its ability to form tough, clear and very flexible film, more stable at high humidity and non-toxic (Blair et al., 1987). Increasingly over the last few years, chitosan has been used in the pharmaceutical industries for its potential use in controlled drug delivery systems (Hou et al., 1985; Miyazaki et al., 1988; Nigalaye, Adusumilli and Bolton, 1990; Skaugrud, 1991; Thanoo, Sunny and Jayakrishnan, 1992; Berthod, Cremer and Kreuter, 1996; Oungbho and Muller, 1997).

Chitosan is useful for the preparation of gels for sustained release of drugs. Miyazaki et al. (1981) investigated the sustained release of indomethacin and papaverine hydrochloride by using chitosan gel as a vehicle. Drugs from dried gel were released at a constant rate.

The compressing aspirin agglomerated by massing with an acetic acid solution of chitosan as a prolonged release tablet was prepared by Kawashima et al. (1985). The parameters controlling drug release rate were chitosan content, the physical stage of chitosan used for granulation i.e. liquid solution or gel and pH of the

dissolution medium. The drug release became more prolonged with increasing chitosan content in the tablet or with decreasing pH of medium.

Moreover, the development of chitosan membranes with different permeability characteristics by crosslinking with different concentrations of glutaraldehyde and its utilization in controlled drug delivery systems were investigated. With increasing degree of crosslinking a definite decrease in the diffusion coefficient, partition coefficient and permeability coefficient was observed (Thacharodi and Rao, 1993).

The influence of excipients on drug release from chitosan matrix tablets using diltiazem HCl as model drug was studied by Kristmundsdottir, Ingvarsdottir and Saemundsdottir (1995). Sustained release of directly compressed tablets was obtained in all cases but the results indicated that both the type and the amount of excipients used influenced drug release rate.

This study was focused towards the development of chitosan as an adhesive matrix by blending with polyvinyl derivatives (polyvinyl alcohol and polyvinylpyrrolidone) and its utilization in controlled drug delivery systems.

2.2 **Polyvinyl Alcohol** (Hickok, 1994)

Polyvinyl alcohol (PVA) is prepared from polyvinyl acetate by replacement of the acetate groups with hydroxyl groups. It is represented structurally as follows:

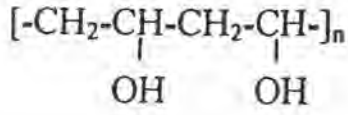

Figure 8 Chemical structure of polyvinyl alcohol

Various grades of polyvinyl alcohol with different viscosities and molecular weights are commercially available. Two main parameters determine their physical properties, the degree of polymerization and degree of hydrolysis. Polyvinyl alcohol is soluble in hot or cold water, solubility in water increases as the molecular weight decreases.

The viscosity of water solution of polyvinyl alcohol varies with the grade, molecular weight, concentration and temperature. The average molecular weight of polyvinyl alcohol are shown below.

Grade	Molecular weight
High viscosity	200,000
Medium viscosity	130,000
Low viscosity	30,000

Polyvinyl alcohol has potential for use in transdermal drug delivery systems. Polyvinyl alcohol films are easily prepared by evaporating to dry an aqueous solution of the polymer. As polyvinyl alcohol is water soluble, polyvinyl alcohol films can be formed without the use of noxious solvents. The resultant films are resistant to tear, have a high degree of clarity and gloss, and do not irritate the skin.

Bhalla and Toddywala (1988) have reported a system formulated with polyvinyl alcohol and polyvinylpyrrolidone. In addition, a combination of polyvinyl alcohol with Eugragit NE 30D was investigated as a matrix for delivery of ephedrine and its hydrochloride salt (Bhalla and Bhate, 1994). This films provided a suitable lattice structure and satisfactory *in-vitro* drug release and diffusion.

2.3 Polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP), an odorless, hygroscopic, white to creamy white powder, is soluble in water giving a colloidal solution. It is produced as a series of products having mean molecular weight ranging from about 10,000 to about 700,000. Structure formula is shown in Figure 9.

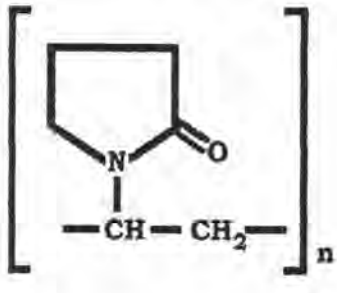

Figure 9 Chemical structure of polyvinylpyrrolidone

Polyvinylpyrrolidone is an inert and non-toxic polymer. It has no irritant effect on the skin and causes no sensitization. Polyvinylpyrrolidone is a well known material commonly used for film coating and for other pharmaceutical and non pharmaceutical applications. The film of polyvinylpyrrolidone when dry is clear, glossy and hard. It is extremely tacky while drying. Excellent adhesive qualities warrant combining it with other film-formers to keep the film from flaking and rubbing off during coating (Lachman, Lieberman and Kanig, 1986; Walkling, 1994).

The usefulness of polyvinylpyrrolidone as a polymer for transdermal drug delivery system was investigated (Koteshwar, Udupa and Kumar, 1992; Rao and Diwan, 1996). A matrix-dispersion type TDDs of pentazocine was fabricated, using combinations of ethylcellulose and polyvinylpyrrolidone (Mandal et al.,1994).

3. Plasticizer

3.1 Glycerin (Price, 1994)

Glycerin is a clear, colourless, odourless, viscous, hygroscopic liquid. Glycerin is miscible with ethanol, methanol and water while it is insoluble in acetone. It is also practically insoluble in benzene, chloroform and oils. The molecular weight of glycerin is 92.09. Its structural formula is shown in Figure 10.

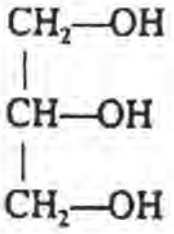

Figure 10 Chemical structure of glycerin

Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions, but decomposes on heating, with the evolution of toxic acrolein. Mixtures of glycerin with water and propylene glycol are chemically stable. Glycerin may crystallize if stored at low temperatures; the crystals do not melt until raised to 20 °C. It should be stored in an airtight container, in a cool and dry place.

Glycerin is used in a wide variety of pharmaceutical formulations including oral, topical and parenteral preparation. In topical pharmaceutical formulations and cosmetics, glycerin is used primarily for its humectant and emollient properties. Glycerin is also used as a plasticizer.

3.2 **Propylene glycol** (Worthington, 1994)

Propylene glycol is a clear, colourless, viscous, practically odourless liquid. The molecular weight of propylene glycol is 76.09. Its structural formula is presented in Figure 11. Propylene glycol has become widely used as a solvents, preservative in a variety of pharmaceutical formulations. In addition, it is used as a humectant and plasticizer.

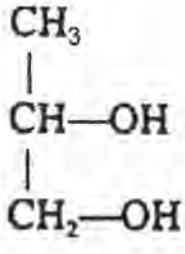

Figure 11 Chemical structure of propylene glycol

Propylene glycol is generally regarded as a nontoxic material and its metabolism and excretion is less toxic than other glycols. In topical preparations, propylene glycol is more irritate than glycerin. Parenteral administration may cause pain and irritation when used in high concentration.