CHAPTER I

INTRODUCTION

Transdermal drug delivery (TDD) is an alternative route to deliver drug pass through the skin. There has been an increased interest in the drug administration via the skin for local therapeutic effect (topical application) and for systemic delivery (transdermal delivery) of drugs. Systemic drug delivery through the skin may have several advantages over conventional drug therapy, these numerous advantage are as follows: (a) avoidance of the variation in the absorption and metabolism associated with oral administration, (b) avoidance of the risks and inconveniences of injection, (c) permits continuous zero-order drug administration and the use of drugs with short biological half-lives, (d) increases the bioavailability and efficacy of drugs since hepatic first-pass elimination is bypassed and (e) provides a simple therapeutic regime, leading to good patient compliance, that can be easily terminated by a simple removal of the patch (Chien, 1987). Nevertheless, the barrier properties of the skin may prevent the entry of drug molecules from the external environment (Barry, 2001). Another disadvantage is the variability in skin permeability. Therefore, transdermal therapeutic systems have been developed to control the delivery of the drug and minimize intersubject variation.

Several technologies have been successfully developed to provide a mechanism of rate control over the release and the transdermal permeation of active drugs. These technologies can be classified into four systems (Chien, 1992) such as polymer membrane permeation-controlled, polymer matrix diffusion-controlled, drug reservoir gradient-controlled, and microreservoir dissolution-controlled transdermal drug delivery systems. The polymer matrix diffusion-controlled transdermal drug delivery system has been used in several researches (Bhalla and Toddywala, 1988; Gabiga, H., Cal, K., and Janicki, S., 2000; Amnuaikit, et al., 2005). Therefore, this basic approach is used in this study. Two types of polymeric film formers, i.e. hydroxypropyl methylcellulose and ethylcellulose, were used. Dibutyl phthalate and

diethyl phthalate were used as hydrophobic plasticizers, while triethyl citrate was used as hydrophilic plasticizers.

Diltiazem hydrochloride is a benzothiazepine calcium channel blocker with peripheral and coronary vasodilator properties. It is widely used in the management of angina pectoris and hypertension (McEvoy, 2001). It has a mean plasma half-life of 35 hr and only 40% of the orally administered drug reaches the circulation due to hepatic metabolism (Mazzo, Obetz, and Shuster, 1994). There are many groups of researcher attempted to develop and to evaluate transdermal drug delivery system for diltiazem hydrochloride (Rao and Diwan, 1998 and 1999; Gupta and Mukherjee, 2003; Jain, et al., 2003)

Several chemical substances have been shown the ability to enhance permeation across the skin. Therefore, they are commonly included in transdermal systems. These include hydrophobic permeation enhancers i.e. isopropyl myristate and isopropyl palmitate (Bhattacharya and Ghosal, 2001), N-methyl-2-pyrrolidone (Koizumi, et al., 2004), oleic acid, polyethylene glycol 400, propylene glycol (Oh, et al., 1998; Gabiga, Cal, and Janicki, 2000; Larrucea, et al., 2001; Touitou, et al., 2002; Gwak and Chun, 2002), and Tween 80 (Bennet and Barry, 1987; Hadgraft, 1999; Shokri, et al., 2001; Nokhodchi, et al., 2003).

In the presence study, the transdermal drug delivery system of diltiazem hydrochloride was developed by using hydroxypropyl methylcellulose and ethylcellulose as film formers, dibutyl phthalate, diethyl phthalate and triethyl citrate as plasticizers. Moreover, in order to enhance the skin penetration, some chemical such as isopropyl myristate, isopropyl palmitate, N-methyl-2-pyrrolidone, oleic acid, polyethylene glycol 400, propylene glycol, and Tween 80 were used as chemical enhancers.

OBJECTIVES

On the basis of the rational as was mentioned before, the objectives of this research are as follows:

1. To develop the diltiazem hydrochloride transdermal delivery system by using matrix approach.
2. To investigate the physical properties of diltiazem hydrochloride transdermal delivery system.
3. To study the *in vitro* skin permeation kinetics of diltiazem hydrochloride transdermal delivery system.

LITERATURE REVIEWS

1. Transdermal Drug Delivery

A transdermal drug delivery (TDD) is a formulation or device (for example, a transdermal patch) that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose. TDD is an alternative route for systemic drug delivery. It is a viable administration route for potent, low-molecular weight therapeutic drugs which cannot withstand the hostile environment of the GI tract and/or are subject to considerable first-pass metabolism by the liver. It offers many important advantages over an oral drug delivery, e.g., avoids gastrointestinal tract and hepatic first-pass metabolism, controls absorption rate, increases patient compliance, and enables fast termination of drug delivery if needed (Kalia and Guy, 2001; Sathyan et al., 1995).

However, transdermal therapy also has some disadvantages. The excellent barrier properties of the skin may prevent the entry of drug molecules (wanted and unwanted) from the external environment. Compounds may activate allergic responses and the drug may be metabolized by microflora on the skin surface or by enzymes in the skin (Barry, 1987; Denyer et al., 1985; Martin, Denyer, and Hadgraft, 1987). Another disadvantage is the variability in skin permeability. Therefore, transdermal therapeutic systems have been developed to control the delivery of the drug and minimize intersubject variation (Jain, Vyas, and Dixit, 1992; Thomas and Finnin, 2004).

2. Skin Permeation

The skin is a multilayered organ composed of many histological layers (Chien, 1987). It is generally described in terms of three major multilaminate layers: the epidermis, the dermis, and the hypodermis. The epidermis is further divided into five anatomical layers with the outermost layer of stratum corneum (SC) exposed to the

external environment. The SC has been identified as the principal barrier for drug penetration (Hadgraft and Guy, 2003; Hsieh, 1994; Foldvari, 2000; Barry, 2001). The outermost layer of the skin, the horny layer or SC, is approximately 10 μm thick when dry but swells to several times of this thickness when fully hydrated. It composes of 10 to 25 layers of parallel to the skin surface lying dead, keratin-rich cells, called corneocytes. It is flexible but relatively impermeable.

3. Permeation Pathways

Drug molecule may use three diffusional routes to penetrate normal intact human skin: through hair follicles with associated sebaceous glands, via sweat ducts, or across continuous SC between these appendages (Figure 1). The appendageal route comprises transport via the sweat glands and the hair follicles with their associated sebaceous glands. These routes circumvent penetration through the stratum corneum and are therefore known as shunt routes. This route is considered to be the minor importance because of their relatively small area of approximately 0.1% of the total skin area. The appendageal route may be more important for ions and large polar molecules which hardly permeate through the stratum corneum at short times prior to steady state diffusion. Additionally, polymers and colloidal particles can target the follicle (Barry, 2001).

The intact SC thus provides the main barrier; its 'brick and mortar' structure is analogous to a wall (Figure 2). The corneocytes of hydrated keratin comprise the 'bricks' embedded in a 'mortar', composed of multiple lipid bilayers of ceramides, fatty acids, cholesterol and cholesterol esters. These bilayers form regions of semicrystalline, gel and liquid crystals domains. Most molecules penetrate through skin via this intercellular microroute and therefore may enhancing techniques aim to disrupt of bypass its elegant molecular architecture (Barry, 2001). Approximately, 10% of the SC dry weight is extracellular lipid and 90% is intracellular protein (mainly keratin). The SC lack of phospholipids, but it is enriched in ceramides and neutral lipids (cholesterol, fatty acids, and cholesteryl esters) that are arranged in a bilayer format and form so-called 'lipid channels'. Interdigitated long-chain

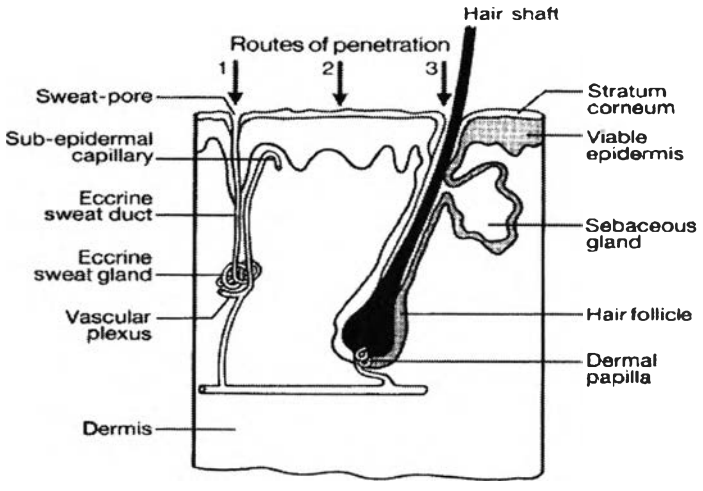


Figure 1 Simplified diagram of skin structure and macroroutes of drug penetration: (1) via the sweat ducts; (2) across the continuous stratum corneum or (3) through the hair follicles with their associated sebaceous gland (Barry, 2001).

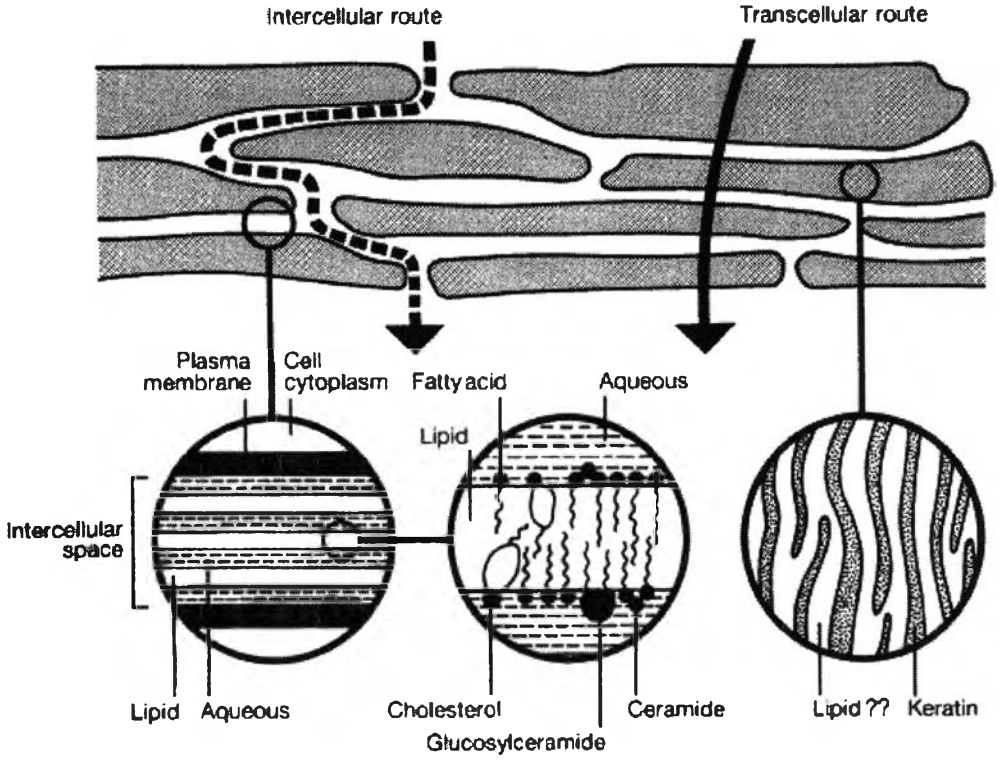


Figure 2 Simplified diagram of drug penetration across stratum corneum and the two microroutes are intracellular and transcellular routes, respectively (Barry, 2001).

ω-hydroxyceramides provide cohesion between corneocytes by forming tight lipid envelopes around the corneocyte protein component. The barrier function of the skin is created by lamellar granules, which are synthesized in the granular layer and later become organized into the intercellular lipid bilayer domain of the SC. Barrier lipids are tightly controlled and any impairment to the skin results in active synthetic processes to restore them (Foldvari, 2000).

4. Characteristics influencing Skin Permeation

Skin permeation is a complex process, with a variety of barriers to cross. Initially, a drug must first partition out of the dosing solution (vehicle) into the stratum corneum before diffusing across the viable epidermis and dermis from where most permeants are cleared by the circulation. For the majority of drugs, the main barrier is the SC. Fick's first law can be applied to describe the diffusion processes in this layer (Hadgraft and Guy, 2003). It is apparent from this equation that the flux is constant if the permeability coefficient and concentration difference are constant.

$$J = K_p \bullet \Delta C = \frac{D \bullet K \bullet \Delta C}{L} \qquad (1)$$

where:

J = steady-state flux of the permeant through the SC ($\mu g/cm^2.s$);

K_p = permeability coefficient of the permeant in the SC (cm/s);

ΔC = concentration gradient of the permeant across the SC ($\mu g/cm^3$);

D = diffusion coefficient of the permeant in the SC (cm^2/s);

K = apparent partition coefficient of the permeant between the SC and the vehicle;

L = the length of the pathway through the SC (cm).

The concentration gradient over the SC will depend primarily upon chemical characteristic of the permeant including solubility, lipophilicity, ionization and stability. To obtain high levels of permeant in the first layers of the SC, the permeant should have a high tendency to leave the vehicle and migrate into the skin, which is expressed in the value of the partition coefficient, K, of the permeant. As the barrier

within the SC is mainly lipoidal, high lipid solubility is necessary for a maximal input of the permeant into the SC. Although, the SC is the main barrier for most drugs, it should be noted that once a permeant has crossed the SC, it must partition into the underlying layers of the epidermis, dermis, and circulatory system. These tissues are more hydrophilic than the SC and can present a barrier to extremely hydrophobic permeants.

The magnitude of the partition coefficient, *K*, is affected by the composition of the vehicle, the chemical structure of the permeant and the charge of the permeant. For a given drug the partition coefficient may be increased by manipulating the composition of a vehicle in such a way that the permeant has a higher tendency to leave it.

The diffusion coefficient or diffusivity, *D*, is a rough measure of the ease with which a molecule can move about within a medium (the SC). It is dependent on molecular weight, molecular volume, and the degree of interaction between the permeant and stratum corneum. The larger the molecule is more difficult to move, as a result, it shows lower diffusivity. Up to a molecular weight of at least 500 daltons, and perhaps 5,000 daltons, the molecular size plays no crucial role. Non-specific and specific binding may occur in both the epidermis and the dermis, reducing diffusivity and thereby decreasing skin permeability.

The physicochemical properties of the permeant discussed above can be determined using literature, theoretical calculations, and experimental measurements. The chemical structure, molecular weight, and pK_a values are often available from literature.

The solubility of a permeant is best measured by allowing an excess permeant to equilibrate in the solvent while stirring at a constant temperature. After equilibration, a sample of the liquid is filtered, diluted with solvent, and analyzed. The partition coefficient, *K*, can be calculated from solubility measurements, simply as the ratio of the solubility in one solvent to that in another solvent. Alternatively,

they can be measured via liquid-liquid extraction. In this case, a fixed quantity of permeant is dissolved in one liquid, and this solution is then shaken with the other liquid at a constant temperature for at least 24 hours. The ratio of concentrations of permeant in the two liquids at equilibrium is the partition coefficient.

The diffusivity, D, can be determined *in vitro* by simply measuring the transdermal flux at early times until a steady-state flux is reached using diffusion cells. A representative plot of the cumulative amount of drug crossing the skin against time is shown in Figure 3. The time before steady state is reached is characteristic for the diffusivity of the permeant in the membrane, and can be used to calculate the diffusivity. The lag time, T_{lag}, is the time obtained from extrapolation of the steady state portion of the graph to the intercept on the time axis, and is defined by the following equation:

$$T_{lag} = \frac{L^2}{6D} \tag{2}$$

where:

L = thickness of the membrane (cm);

D = diffusivity (cm^2/s).

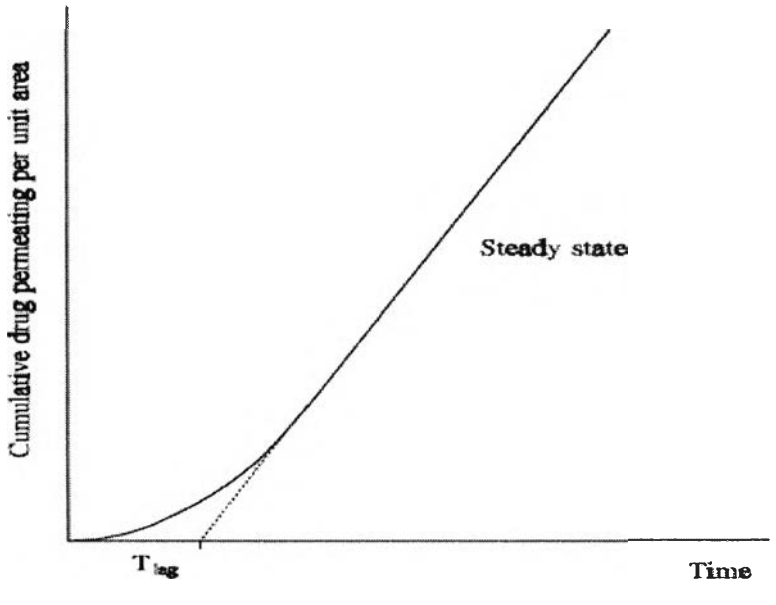


Figure 3 Typical permeation profile for a molecule diffusing across human skin.

It should be kept in mind, however, that L should represent the length of the pathway through the membrane, which most often does not correspond to the thickness of the membrane. Thus, in practice, this method for evaluating D has several disadvantages as the exact length of pathway through the membrane is difficult to measure. It also may vary with the constituents of the vehicle. Additionally, lag times obtained from permeation experiments with human skin tend to be very variable and may include a component arising from interactions between the stratum corneum and the permeant. The permeability coefficient of a permeant through a membrane, K_p, can be calculated from Fick's first law as follows:

$$K_p = \frac{J}{\Delta C} = \frac{dm/dt}{C_d \bullet A} \qquad (3)$$

where:

dm/dt = the slope of the steady-state portion of the cumulative amount versus time plot as shown in Figure 3 (μg/s);

A = skin area exposed to the dosing solution (cm^2);

C_d = the concentration of the permeant applied in the donor compartment ($\mu g/cm^3$), which equals ΔC because of low concentrations in the receptor compartment.

Thus, if the donor concentration and the flux of the permeant are known, the permeability coefficient may be determined. The permeability coefficient is constant for a given permeant under a given set of experimental conditions and depends on the diffusion coefficient, the partition coefficient and the length of the pathway through the membrane. The choice of therapeutic drug is determined by a number of factors including the physicochemical properties of the drug, its interactions with the membrane and its pharmacokinetic properties (Kalia and Guy, 2001).

For drugs which mainly cross the intact SC, two potential micro routes of entry exists, the transcellular (or intracellular) and intercellular pathways (Figure 2). The principal pathway taken by a permeant is decided mainly by the partition coefficient (log K). Hydrophilic drugs partition preferentially into the intracellular

domains, whereas lipophilic permeants (octanol/water log $K > 2$) traverse the stratum corneum via the intercellular route. Most permeants permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs. The skin's barrier function appears to depend on the specific ratio of various lipids; studies in which non-polar and relatively polar lipids were selectively extracted with petroleum ether and acetone, respectively, indicate that the relatively polar lipids are more crucial to skin barrier integrity.

5. Transdermal Drug Delivery Development

The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process (Figure 4) which involves

a. dissolution within and release from the formulation,
b. partitioning into the skin's outer most layer, the SC,
c. diffusion through the SC, principally via a lipidic intercellular pathway,
   (i.e., the rate-limiting step for most compounds),
d. partitioning from the SC into the aqueous viable epidermis,
e. diffusion through the viable epidermis and into the upper dermis, and
f. uptake into the local capillary network and eventually the systemic circulation.

A common aim in the development of new transdermal devices is the controlled delivery of drugs, so that the rate of drug input into the blood stream is predictable and reproducible. TDDS act as drug reservoirs and control the penetration rate of the drug into the skin and subsequent drug permeation into the blood circulation. When the device controls the transdermal drug flux instead of the skin, delivery of the drug is more reproducible leading to smaller inter- and intrasubject variations (Guy and Hadgraft, 1992). An ideal drug candidate would have sufficient lipophilicity to partition into the SC, but also sufficient hydrophilicity to enable the second partitioning step into the viable epidermis and eventually the systemic circulation. For most drugs, except those possessing extreme lipophilicity

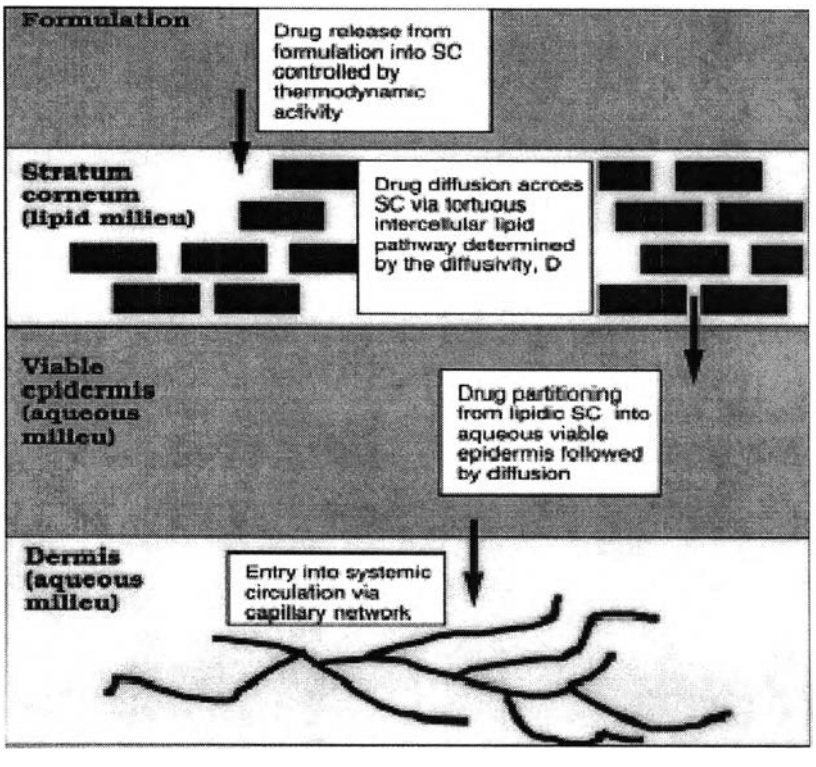


Figure 4 Schematic representation of the transport processes involved from the release of the drug from the formulation to its eventual uptake by the dermal capillaries (Kalia and Guy, 2001).

(log $K_{o/w}$ >5), the rate-determining step for drug transport across the skin is transit across the SC. However, release of the drug from the device can be controlled more exactly than the permeability of drugs across the skin. Therefore, it is better that rate control resides within the delivery device in order to attain uniform input rates and reduce inter-individual variability (Guy and Hadgraft, 1992; Kalia and Guy, 2001).

Furthermore, the flux J of a drug through the SC from Eq. (1) can be described most simply by Fick's first law:

$$J = \frac{D_m c_{s,m}}{L} \bullet \frac{c_v}{c_{s,v}} \tag{4}$$

In Eq. (4), D_m represents the diffusion coefficient of the drug in the membrane, $c_{s,m}$ its solubility in the membrane, L the diffusion path length across the membrane, c_v the

concentration of the drug dissolved in the vehicle and $c_{s,v}$ the solubility of the drug in the vehicle. Three permeation enhancement strategies may be postulated based on Fick's first law :

(i) increase D_m

(ii) increase $c_{s,m}$, i.e. increase drug partitioning into the membrane, and

(iii) increase the ratio $c_v/c_{s,v}$, i.e. the degree of saturation of the drug in the vehicle (the supersaturation approach).

The first two approaches imply an effect of the vehicle on the barrier function of the SC (for example via penetration of chemical penetration enhancer into the SC and subsequent disordering of the intercellular SC lipids, or the extraction of such lipids by a solvating component of the formulation). The latter strategy is based on interaction between the drug and the vehicle.

6. Transdermal Drug Delivery System (TDDS)

For transdermal drug delivery system, there are several technologies have been successfully developed to provide a mechanism of rate control over the release and the transdermal permeation of active drugs. These technologies can be classified into four systems (Chien, 1992),

6.1 Polymer membrane permeation-controlled TDDS

In this system, the drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate-controlling polymeric membrane. In the drug reservoir, the drug solids are dispersed in a solid polymer matrix, suspended in an unreachable viscous liquid medium, or dissolved in a releasable solvent. On the external surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic pressure-sensitive adhesive polymer may be applied to provide intimate contact of the TDDS with the skin surface.

6.2 Polymer matrix diffusion-controlled TDDS

This approach concerning about TDDS, the drug reservoir is formed by homogeneously dispersing of the drug solids in a hydrophilic or lipophilic polymer matrix. The above medicated polymer formed is then molded into medicated disks with a defined surface area and controlled thickness. This drug reservoir-containing polymer disk is then mounted onto an occlusive baseplate in a compartment fabricated from a drug-impermeable plastic backing. The adhesive polymer is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk. This system probably is the simplest and least expensive way to control the release of drug (Sugibayashi and Morimoto, 1994).

Alternatively, the polymer matrix drug dispersion-type TDDS can be fabricated by directly dispersing the drug in a pressure-sensitive adhesive polymer and then coating the drug-dispersed adhesive polymers by solvent casting or hot melt onto a flat sheet of a drug-impermeable backing laminate to form a single layer of drug reservoir. This yields a thinner and smaller TDD patch that convenience to use. This type of TDDS is best illustrated by the development and marketing of the nitroglycerin-releasing TDDS, the Minitran system and the Nitro-Dur II system, and the isosorbide dinitrate-releasing TDDS (Frandol tape) for the once-a-day medication of angina pectoris.

6.3 Drug reservoir gradient-controlled systems

In this study, polymer matrix drug dispersion-type TDDS are modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multilaminate adhesive layers.

6.4 Microreservoir dissolution-controlled systems

This type of drug delivery system can be considered by a hybrid of the reservoir- and matrix dispersion-type drug delivery systems. In this approach, the drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water-miscible drug solubilizer and then homogeneously dispersing the drug suspension, with controlled aqueous solubility, in a lipophilic polymer, by high-shear mechanical force, to form thousands of unreachable microscopic drug reservoirs. This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains *in situ*, which produces a medicated polymer disk with a constant surface area and a fixed thickness. A TDDS is then produced by mounting the medicated disk at the center of an adhesive pad.

The basic approach used in this study is the polymer matrix diffusion-controlled TDDS. The intrinsic rate of drug released from this polymer matrix drug dispersion-type TDDS is defined as (Chien, 1982)

$$\frac{dQ}{dt} = \left(\frac{L_d C_p D_p}{2t} \right)^{1/2} \qquad (5)$$

Where L_d is the drug loading dose initially dispersed in the polymer matrix; and C_p and D_p are the solubility and diffusivity of the drug in the polymer matrix, respectively. Practically, C_p is equal to C_R (the drug concentration in the receptor compartment) because only the drug species dissolved in the polymer can release.

At steady state a Q versus $T^{1/2}$ drug release is obtained as defined by (Chien, 1982)

$$\frac{Q}{t^{1/2}} = \left[(2L_d - C_p) C_p D_p \right]^{1/2} \qquad (6)$$

The Eq.(6) can be rearranged as follows,

$$D_p = \frac{(Q/t^{1/2})^2}{(2L_d - C_p) \bullet C_p} \qquad (7)$$

7. Evaluations of TDDS

The release of drug from TDDS can be evaluated using Apparatus 5 (Paddle over Disk) (USP 25, <724>) or a two-compartment diffusion cell assembly under identical conditions. The skin permeation kinetics of drug from TDDS can be also evaluated using a two-compartment diffusion cell. This is carried out by individually mounting a skin specimen on a vertical diffusion cell, such as the Franz diffusion cell and its modifications, or a horizontal diffusion cell, such as the Valia-Chien skin permeation cell. Each unit of the TDDS is then applied with its drug-releasing surface in intimate contact with the SC surface of the skin. The release profiles of drug from TDDS can also be investigated in the same diffusion cell assembly without a skin specimen.

The diffusion cell method is the standard for measuring drug permeation across the skin (Moser, et al., 2001). It consists of donor and receptor compartments separated by the skin sample. The permeation rate of drug from the donor compartment through the skin and into the receptor compartment is determined by measuring the amount of drug permeated over time with e.g. high-performance liquid chromatography (HPLC) as analytical method (Figure 5). Typically, physiological saline or a phosphate-buffered solution maintained at 37°C is used. This will keep the skin surface at approximately 32°C, which simulates the temperature of the human skin (El-Kattan, Asbill, and Haidar, 2000).

Human skin is the best and most relevant of skin source. However, its availability is sometimes limited. Therefore, an animal skin is frequently used. The most relevant animal model for human skin is the pig. It is readily available from abattoirs and its histological and biochemical properties have been shown to be similar to human skin. In addition, the permeability of drugs through pigskin has been repeatedly shown to be similar to that through human skin. Porcine ear skin is particularly well-suited for permeation studies and gives comparable results to human skin. Skin from mouse, rat, and guinea pig, which are commonly used, generally

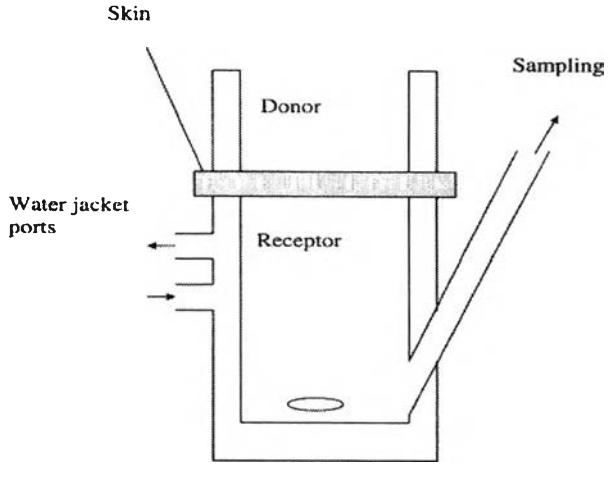


Figure 5 Schematic representation of a static diffusion cell to measure the skin permeation of a drug (Moser, et al., 2001)

show higher permeation rates (Robert and Mueller, 1990; Sato, Sugibayashi, and Morimoto, 1991; Dick and Scott, 1992).

8. Materials

8.1 Diltiazem hydrochloride (DTZ HCl)

DTZ HCl is a benzothiazepine-derivative calcium-channel blocking agent. It has been indicated for the treatment of angina pectoris and hypertension. DTZ HCl is commercial available as an oral extended-release capsules, conventional tablets, parenteral solution and powder for injection. (Mazzo et al., 1994; McEvoy, 2001)

Diltiazem (DTZ) inhibit the transmembrane influx of extracellular calcium ions across the membrane of myocardial cells and vascular smooth muscle cell, without changing serum calcium concentration, thereby dilating the main coronary and systemic arteries cause the decrease in myocardial contractility. Dilation of systemic arteries results in a decrease in total peripheral resistance, a decrease in systemic blood pressure, and a decrease in the afterload of the heart. The usual initial

dosage for management of hypertension as monotherapy is 120-240 mg daily and maintenance dosages usually range from 240-360 mg daily.

Approximately 80% of an oral dose of DTZ is rapidly absorbed from the GI tract following oral administration of conventional tablets of the drug. Only about 40% of and oral dose reaches systemic circulation as unchanged drug since DTZ undergoes extensive metabolism on first pass through the liver. Peak serum concentrations usually are reached within 2-3 or 4-11 hr after oral administration of conventional tablets or extended-release capsules, respectively. In healthy adults, direct IV injection over 3 minutes of a single 10-mg dose of DTZ results in median plasma concentration of 104 ng/ml. After continuous IV infusion at a rate of 10 mg/hr in healthy adults, steady-state plasma concentrations average approximately 160 ng/ml. Plasma concentrations of 50-200 ng/ml appear to be required for antianginal effect (McEvoy, 2001).

DTZ exhibit large volume of distribution because of its lipophilicity and is rapidly and extensively distributed into body tissues. The mean apparent volume of distribution of DTZ at steady state ranges from 260-361 L in healthy adults receiving an IV infusion of 4.8-13.2 mg/hr for 24 hr. About 70-85% of DTZ is bound to plasma proteins.

Following oral administration in healthy individuals, DTZ has plasma half-life of 2-11 hr. Half-life may be slightly prolonged after multiple oral dosing. Following a single IV injection of DTZ in healthy adults, pharmacokinetics are dose proportional over a dosage range of 10.5-21 mg with a half-life of approximately 3.4 hr and a systemic clearance of approximately 65 L/hr. After continuous infusion (10 mg/hr) in healthy adults, the plasma elimination half-life increase to 4.1-5 hr and the systemic clearance decreases to 52-68 L/hr. Plasma half-life of the drug may be increase in geriatric patients, but is unchanged or only slightly increased in patients with renal impairment. Liver cirrhosis has been shown to reduce diltiazem apparent of oral clearance and to prolong its half-life.

DTZ is rapidly metabolized in the liver via deacetylation, N-demethylation, and O-demethylation to several active metabolites. The drug and its metabolites also undergo glucuronide and/or sulphate conjugation. Plasma DTZ concentrations are higher following multiple oral doses of the drug than after single oral doses, indicating saturation of hepatic microsomal enzyme systems. Following single DTZ doses administered via direct IV injection, plasma concentrations of the principal metabolites, deacetyldiltiazem and N-monodesmethyldiltiazem, are low or undetectable; plasma concentration of active metabolites are detectable generally within 30 min of initiation of continuous IV infusion and peak at 0.25-5 h after infusion. About 10-35% of DTZ is metabolized to deacetyldiltiazem, which exhibits 25-50% of the coronary vasodilating activity of diltiazem.

Approximately 2-4% of a dose is excreted in urine unchanged. The remainder of the drug is eliminated in urine and via bile, mainly as metabolites (McEvoy, 2001).

The molecular formula and molecular weight of DTZ HCl are $C_{22}H_{26}N_2O_4S.HCl$ and 450.98 g/mole, respectively. The accepted chemical name for DTZ HCl is:

(2S-cis)-3-(acetyloxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxy-phenyl)-1,5-benzothia-zepin-4(5H)-one monohydrochloride

The CAS Registry number is 33286-22-5. Its chemical structure is shown in Figure 6.

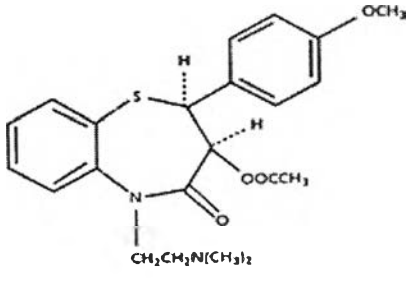


Figure 6 Chemical structure of diltiazem hydrochloride (DTZ HCl).

DTZ HCl occurs as a bitter-tasting, white to off-white crystalline powder. The melting point of DTZ HCl is about 210°C (207.5°C – 212°C) with decomposition at higher temperatures. Its solubility, indicated in terms of USP definitions, in a variety solvent is presented in Table 1. The UV absorption spectrum of DTZ HCl in 0.1 N HCl (aqueous) is characterized by maxima at approximately 205 nm and 236 nm. The pH value of saturated DTZ HCl in water is 3.0, while a 1.0% (w/w) solution has a pH of 4.2.

DTZ HCl is reported to be highly stable in the solid state. In aqueous buffer solutions (pH 1-7) it undergoes hydrolysis to deacetyldiltiazem following pseudo-first order kinetics. It is most stable at pH 5 (McEvoy, 2001; Mazzo et al., 1994).

Table 1 Solubility of diltiazem hydrochloride at 25°C.

Solvent	Solubility
Chloroform	Freely soluble
Formic acid	Freely soluble
Methanol	Freely soluble
Water	Freely soluble
Dehydrated alcohol	Sparingly soluble
Benzene	Practically insoluble
Ether	Insoluble

Okumura et al. (1989) determined DTZ HCl solubility in water at 37°C and n-octanol-water partition coefficient at room temperature. They reported that the solubility and the partition coefficient (log *K*) were 557.06 mg/ml and -2.82, respectively. In 1991, McClelland and others found that and aqueous solubility of DTZ HCl was greater than 590 mg/ml (37°C) and this high solubility was reduced in the presence of sodium chloride (1 M).

Nitsch and Banakar (1991) studied the *in vitro* release of diltiazem (1-7%) from various reservoir-type (ointment) transdermal formulations across composite skin. They found that the release rate increased with increasing drug content. The oil-in-water and water soluble systems yielded rapid drug release rates, while the

oleaginous and absorption systems exhibited slow release rates. Moreover, the release profiles supported a combination of diffusion- and dissolution-controlled mechanisms. After that, Walgren and Banakar (1994) examined the influence of drug loading, compositional characteristics, and mechanisms of drug release across composite skin membrane employing modified Franz's diffusion cell over 12 hr. They reported the time-lag effect observed for diltiazem release from oil-in-water and hydrophilic compositions, the increasing of permeability coefficients with drug load, and the adhering of drug release profiles to square-root of time dependence.

In 1998, Rao and Diwan formulated and evaluated the ethylcellulose-polyvinyl pyrrolidone film of DTZ HCl for transdermal administration. They studied the influence of film composition, initial drug concentration, and film thickness on the *in vitro* drug release rate and the drug permeation through rat abdominal skin. The release rate of drug increased linearly with increasing drug concentration and polyvinyl pyrrolidone fraction in the film. The release of drug from the film followed a diffusion-controlled model at low drug concentrations. The *in vitro* skin permeation profiles showed increased flux values with increase of initial drug concentration in the film and with the fraction of polyvinyl pyrrolidone. They concluded that the films composed of ethylcellulose:polyvinyl pyrrolidone:DTZ HCl (8:2:2) should be selected for the development of transdermal drug delivery systems. Next year, Rao and Diwan reported the comparative evaluation of DTZ HCl following oral and transdermal administration in rabbits. The films composed of ethylcellulose: polyvinyl pyrrolidone:DTZ HCl at the ratios of 8:2:2 and 8:2:3 (plasticized with dibutyl phthalate) were used. The terminal elimination half life of elimination half life of transdermal delivered DTZ was found similar to that of oral administration. A sustained therapeutic activity was observed over a study period of 24 hr after transdermal administration compared to oral administration. However, it should be noted that the time for peak serum concentration (t_{max}) of both transdermal administration (9.0 and 9.0 hr, respectively) were much higher as compared to oral administration (0.44 hr). Gupta and Mukherjee (2003) were also reported the development and evaluation of DTZ HCl using the same ingredients as Rao and Diwan. They studied the influence of different film compositions on *in vitro* drug

permeation. It was found that the cumulative amount of drug was proportional to the square root of time, i.e., Higuchi kinetics. However, they concluded that the film composed of ethylcellulose:polyvinyl pyrrolidone at the ratio of 2:1 should be selected for the development of transdermal drug-delivery system of DTZ HCl. In the same year, Jain and others reported the development of transdermal drug delivery systems for DTZ HCl to prolong and control drug delivery. They developed both the matrix diffusion controlled and membrane permeation controlled systems. The *in vitro* release studies showed the release from the matrix diffusion controlled transdermal drug delivery systems follows a nonfickian patter and that from the membrane permeation controlled transdermal drug delivery systems follow zero-order kinetics. The release from the matrix systems increased on increasing the hydrophilic polymer concentration, but the release from the membrane systems decrease on cross-linking of the rate controlling membrane and also on addition of citric acid to the chitosan drug reservoir gel. The membrane permeation controlled system achieved effective plasma concentration a little more slowly than the matrix diffusion controlled system, but it exhibited a more steady state plasma level for 24 hr.

For prediction of DTZ HCl permeation through human skin, the steady state flux can be related to steady state DTZ plasma concentration as shown below (O'Donnell and McGinity, 1997):

$$J_{ss} = \frac{C_{ss} Cl_t BW}{A} \qquad (8)$$

If the maximum surface of the transdermal patch are supposed to be 12.57 cm^2 (A), the standard human body weight (BW) is 60 Kg, the therapeutic DTZ level (C_{ss}) equals to 50 ng/ml, and DTZ HCl total clearance in human (Cl_t) is 60 L/hr. Then, the target flux (J_{ss}) in this study can be calculated and it is **238.7** $\mu g/cm^2.hr$.

8.2 Film Formers

8.2.1 Hydroxypropyl Methylcellulose, HPMC (Wade 1994)

Nonproprietary Names

Hypromellose (BP), Methylhydroxypropylcellulosum (PhEur), Hydroxypropyl methylcellulose (USP)

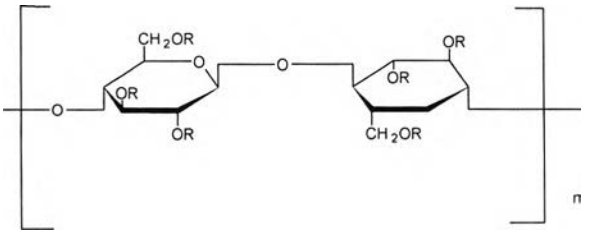
Chemical Name and CAS Registry Number

Cellulose, 2-Hydroxypropyl methyl ether [9004-65-3]

Empirical Formula Molecular Weight

The PhEur 1992 describes HPMC as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades which vary in viscosity and degree of substitution. Various grades of HPMC may be distinguished by appending a number indicative of the apparent viscosity, in mPa.s, of a 2% w/w aqueous solution at 20°C. HPMC defined in the USP XXII specifies the substitution type by appending a four digit number to the nonproprietary name. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CHOHCH_3$), calculated base on a dried basis. Molecular weight is approximately 10,000-1,500,000.

Structural formula



Where R is H, CH_3 or $[CH_3CH(OH)CH_2]$.

Figure 7 Chemical structure of hydroxypropyl methylcellulose (HPMC).

Applications in Pharmaceutical Formulation or Technology

HPMC is widely used in oral and topical pharmaceutical formulations. In oral products, it is primarily used as a tablet binder, in film-coating and as an extended release tablet matrix. High viscosity grades may be used to retard the release of water-soluble drugs from a matrix. HPMC is used as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description

HPMC is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

Typical Properties

Acidity/alkalinity: pH = 5.5-8.0 for a 1%w/w aqueous solution.

Melting point: browns at 190-200°C; chars at 225-230°C. Glass transition temperature is 170-180°C.

Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, and mixtures of methanol and dichloromethane. Certain grades of HPMC are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Stability and Storage Conditions

HPMC powder is a stable material although it is hygroscopic after drying. It should be stored in a well-closed container, in a cool, dry place.

HPMC is one of two available basic types of METHOCEL cellulose ether products. It has the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeat in structure of anhydroglucose units. HPMC is made using methyl chloride to obtain hydroxypropyl substitution ($-OCH_2CH(OH)-CH_3$) on the

anhydroglucose units. Varying ratios of hydroxypropyl and methyl substitution influences organic solubility of the products. METHOCEL K cellulose ether contains 22% methoxyl, or a methoxyl D.S. of 1.4. METHOCEL K4M Premium was used in this study. At 2% aqueous solution (20°C), It has the viscosity of 4,000 cP.

8.2.2 Ethylcellulose, EC (Wade, 1994)

Nonproprietary Names

Ethylcellulose (BP, USPNF), Ethylcellulosum (PhEur)

Chemical Names and CAS Registry Number

Cellulose ethyl ether [9004-57-3]

Empirical Formula Molecular Weight

EC is an ethyl ether of cellulose, a long-chain polymer consisting of anhydroglucose units joined together by acetal linkages. Each anhydroglucose unit has three replaceable hydroxyl groups which are substituted to the extent of 2.25-2.60 ethoxyl groups (OC_2h_5) per unit, equivalent to an ethoxyl content of 44-51%.

Structural Formula

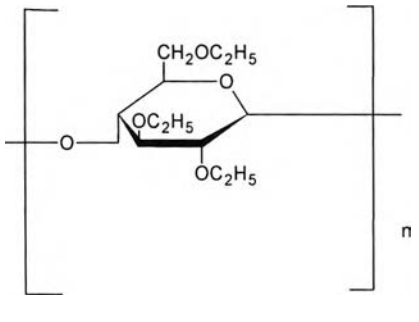


Figure 8 Chemical structure of ethylcellulose (EC), structure shown with complete ethoxyl substitution.

Applications in Pharmaceutical Formulation or Technology

EC is widely used in oral and topical pharmaceutical formulations. EC, dissolved in an organic solvent, or solvent mixture, can be used on its own to produce water-insoluble films. Higher viscosity EC grades tend to produce stronger, tougher films. EC films may be modified, to alter their solubility, by the addition of HPMC or a plasticizer. In topical formulations, EC is used as a thickening agent in creams, lotions or gels, provided an appropriate solvent is used. It is additionally used in cosmetics and food products.

Description

EC is tasteless, free-flowing, white to light tan colored powder.

Typical Properties

Glass transition temperature: 130-133°C

Solubility: practically insoluble in glycerin, propylene glycol and water.

- EC that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%).
- EC that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol and toluene.

Stability and Storage Conditions

EC is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than cellulose esters. EC is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of an antioxidant and a compound with light absorption properties between 230-240 nm. The bulk material should be stored in a dry place, in a well-closed container at a temperature between 7-32°C.

Ethylcellulose (EC or ETHOCEL) is a water-insoluble polymer that has been used as a controlled release excipient for several decades. It is derived from cellulose. Therefore, the backbone of the molecule of EC is based on repeating anhydroglucose units. Specific properties of the various EC polymers are determined by the number of anhydroglucose units in the polymer chain and the degree of ethoxyl substitution. ETHOCEL Standard 10 Premium was used in this study. From Table 2, its solution viscosity range is between 9-11 cP (5% solutions measured at 25°C; the solvent is 80% toluene and 29% alcohol). EC polymer is typically used in combination with a water-soluble polymer, HPMC. A wide variety of release rate profiles can be achieved by varying the amount of the insoluble polymer ratio.

Table 2 Degree of substitution (%w/w), number average molecular weight (M_n), polydispersity index (M_w/M_n), solubility parameter (δ) and T_g of HPMC and EC (Sakellariou and Rowe, 1995).

	Degree of substitution* (%w/w)			M_n (10^{-3}) (g/mol)	M_w/M_n	δ* ($MPa^{1/2}$)	T_g* (°C)
	Ethoxy	Methoxyl	Hydroxy propoxyl				
HPMC[a]	-	22.1	8.1	58	3.02	24.4	153.5
EC[b]	48-49.5	-	-	53	2.96	20.6	131.5

*Dow chemical, [a] Methocel K4M Premium EP, [b] Ethocel Standard10 Premium.

8.3 Plasticizers

Most polymers used alone form film formation are commonly brittle at room temperature and require plasticizer or another additive to improve their possibility and flexibility. Usually, the plasticizer behaves like a solvent when mixed into a polymer and results in alterations of the physical chemical properties of polymeric films. Basically, any plasticizer added must be compatible with the polymeric film formers to produce a good appearance and desirable physical properties of the finished film. Thus, plasticizer plays an important role in the polymeric film formation (Lin, Cheng, and Run-Chu, 2000). In this study, there are three types of plasticizers used such as dibutyl phthalate and diethyl phthalate (as hydrophobic plasticizers) and triethyl citrate (as hydrophilic plasticizer).

8.3.1 Dibutyl phthalate, DBP (Wade, 1994)

Nonproprietary Names

Diethyl phthalate (BP, USPNF)

Chemical Name and CAS Registry Number

1,2-Benzenedicarboxylic acid, dibutyl ester [84-74-2]

Empirical Formula and Molecular Weight

$C_{12}H_{22}O_4$. Molecular weight is 278.35.

Structural Formula

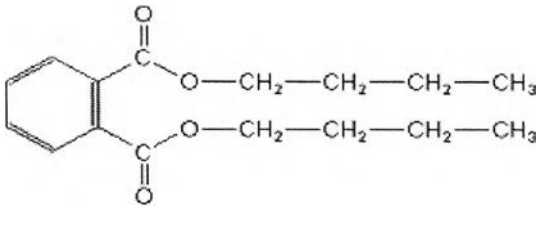


Figure 9 Chemical structure of dibutyl phthalate (DBP).

Applications in Pharmaceutical Formulation or Technology

DBP is used as a plasticizer for film coatings on tablets, beads and granules at concentrations of 10-30% by weight of polymer.

Description

DBP is a clear, colorless or faintly colored oily liquid.

Typical Properties

Boiling point: 340°C

Solubility: very soluble in acetone, benzene, ethanol (95%), and ether; soluble 1 in 2500 of water.

Stability and Storage Conditions

DBP is stable when stored in a well-closed container in a cool, dry, place.

8.3.2 Diethyl phthalate, DEP (Wade, 1994)

Nonproprietary Names

Diethyl phthalate (BP, USPNF)

Chemical Name and CAS Registry Number

1,2-Benzenedicarboxylic acid, diethyl ester [84-66-2]

Empirical Formula and Molecular Weight

$C_{12}H_{14}O_4$. Molecular weight is 222.24.

Structural Formula

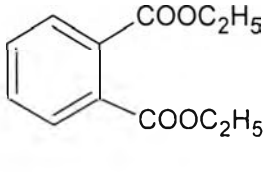


Figure 10 Chemical structure of diethyl phthalate (DEP).

Applications in Pharmaceutical Formulation or Technology

DEP is used as a plasticizer for film coatings on tablets, beads and granules at concentrations of 10-30% by weight of polymer.

Description

DEP is a clear, colorless, oily liquid. It is practically odorless, or with a very slight aromatic odor and a bitter, disagreeable taste.

Typical Properties

Boiling point: 295°C

Solubility: miscible with ethanol, ether, and many other organic solvents; practically insoluble in water.

Stability and Storage Conditions

DEP is stable when stored in a well-closed container in a cool, dry, place.

8.3.3 Triethyl citrate, TEC (Wade, 1994)

Nonproprietary Names

Triethyl citrate (USPNF)

Chemical Name and CAS Registry Number

2-Hydroxy-1,2,3-prapanetricarboxylic acid, Triethyl ester [77-93-0]

Empirical Formula and Molecular Weight

$C_{12}H_{20}O_7$. Molecular weight is 276.29.

Structural Formula

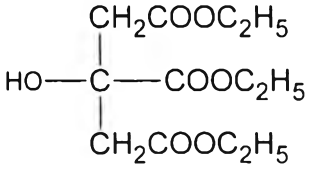


Figure 11 Chemical structure of triethyl citrate (TEC).

Applications in Pharmaceutical Formulation or Technology

TEC and other citrate esters are used as plasticizers for aqueous based coatings in oral sustained release or enteric coated capsule and tablet formulations.

Description

TEC occurs as a bitter tasting, odorless, practically odorless, oil liquid.

Typical Properties

Boiling point: 288°C

Solubility: soluble 1 in 125 of peanut oil, 1 in 15 of water. Miscible with ethanol (95%) and ether.

Stability and Storage Conditions

TEC and other citrate esters are stable if stored in a well-closed container in a cool, dry, place.

8.4 Enhancers

Penetration enhancers may be incorporated into the formulations in order to improve drug flux across the membranes. The modes of action of penetration enhancers in general are complex. William and Barry (2004) modified the scheme proposed by Menon and Lee (1998), as will be seen in Figure 12. Most enhancers interact with the intercellular lipid domain of the stratum corneum, at clinically acceptable concentrations.

Action at Intercellular Lipids

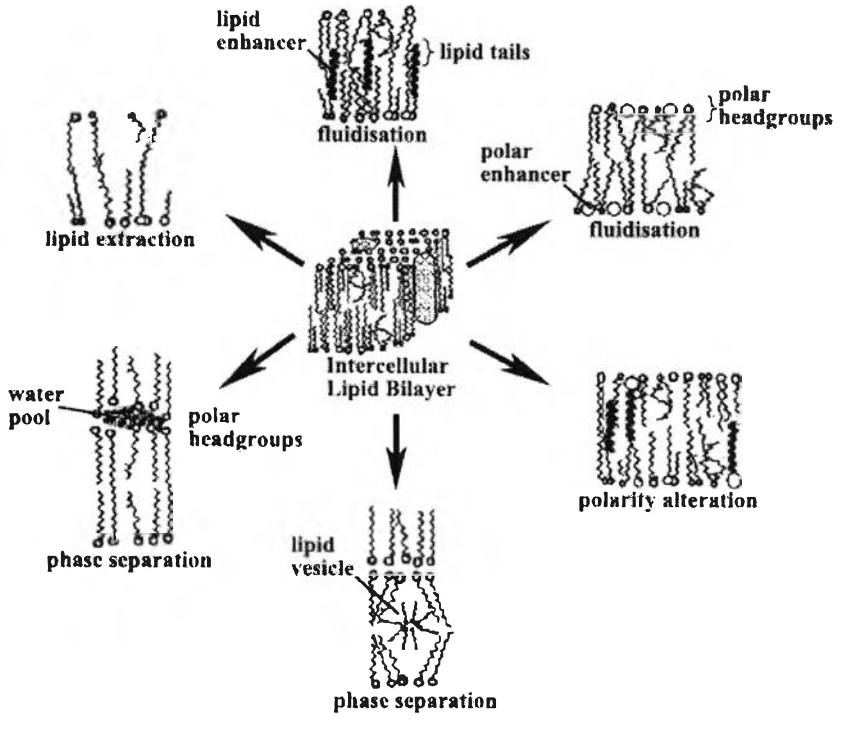


Figure 12 Actions of penetration enhancers within the intercellular lipid domain (Williams and Barry, 2004).

8.4.1 Isopropyl myristate, IPM (Wade, 1994)

Nonproprietary Names

Isopropyl myristate (BP, USPNF), Isopropylis myristas (PhEur)

Chemical Name and CAS Registry Number

1-Methylethyl tetradecanoate [110-27-0]

Empirical Formula and Molecular Weight

$C_{17}H_{34}O_2$. Molecular weight is 270.51.

Structural Formula: $CH_3(CH_2)_{12}COOCH(CH_3)_2$

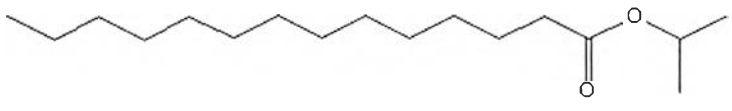


Figure 13 Chemical structure of isopropyl myristate (IPM).

Applications in Pharmaceutical Formulation or Technology

IPM is a non-oleaginous emollient that is absorbed readily by the skin. It is used as a component of semisolid bases and as a solvent for many substances applied topically. Applications in many topical pharmaceutical and cosmetic formulations.

Description

IPM is a clear, colorless, practically odorless, mobile liquid with a bland taste. It consists of esters of propan-2-ol and saturated high molecular weight fatty acids, principally myristic acid.

Typical Properties

Boiling point: 140.2°C at 266 Pa (2 mmHg)

Solubility: miscible with acetone, chloroform, ethanol, ethyl acetate, fats, fatty alcohols, fixed oils, liquid hydrocarbons, toluene and waxes. Practically insoluble in glycerin, propylene glycol and water.

Stability and Storage Conditions

IPM is resistant to oxidation and hydrolysis and does not become rancid. It should be stored in a well-closed container in a cool, dry, place and protected from light.

8.4.2 Isopropyl palmitate, IPP (Wade, 1994)

Nonproprietary Names

Isopropyl palmitate (BP, USPNF), Isopropylis palmitas (PhEur)

Chemical Name and CAS Registry Number

1-Methylethyl hexadecanoate [142-91-6]

Empirical Formula and Molecular Weight

$C_{19}H_{38}O_2$. Molecular weight is 298.51.

Structural Formula: $CH_3(CH_2)_{14}COOCH(CH_3)_2$

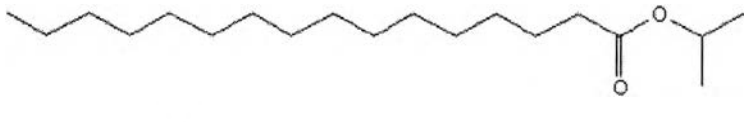


Figure 14 Chemical structure of isopropyl palmitate (IPP).

Applications in Pharmaceutical Formulation or Technology

IPP is a non-oleaginous emollient with good spreading characteristics used in topical pharmaceutical formulations and cosmetics. It has also been used in a controlled release percutaneous film.

Description

IPP is a clear, colorless to pale yellow-colored, practically odorless viscous liquid which solidifies at less than 16°C.

Typical Properties

Boiling point: 160°C at 266 Pa (2 mmHg)

Solubility: soluble in acetone, chloroform, ethanol, ethyl acetate, mineral oil, propan-2-ol, silicone oils, vegetable oils, and aliphatic and aromatic hydrocarbons. Practically insoluble in glycerin, glycols and water.

Stability and Storage Conditions

IPP is resistant to oxidation and hydrolysis and does not become rancid. It should be stored in a well-closed container, above 16°C, and protected from light.

8.4.3 N-Methyl-2-pyrrolidone, NMP

Nonproprietary Names

N-Methyl-2-pyrrolidone (BP, USPNF)

Chemical Name and CAS Registry Number

N-methyl-2-pyrrolidinone [872-50-4]

Empirical Formula and Molecular Weight

C_5H_9NO. Molecular weight is 99.1.

Structural Formula

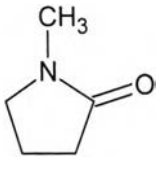


Figure 15 Chemical structure of N-methyl-2-pyrrolidone (NMP).

Applications in Pharmaceutical Formulation or Technology

NMP is used in the petrochemical industry, in the microelectronics fabrication industry, and in the manufacture of various compounds, including pigments, cosmetics, drugs, insecticides, herbicides, and fungicides. It is further used as an intermediate in the pharmaceutical industry, as a penetration enhancer for topically applied drugs, and as a vehicle in the cosmetics industry.

Description

NMP is a colorless hygroscopic liquid with a mild amine odor. It turns yellow on exposure to heat.

Typical Properties

Boiling point: 202°C at 101.3 Pa

Solubility: completely miscible with water. It is highly soluble in lower alcohols, lower ketones ether, ethyl acetate, chloroform, and benzene and moderately soluble in aliphatic hydrocarbons.

Stability and Storage Conditions

NMP is a basic and polar compound with high stability. It is only slowly oxidized by air and is easily purified by fractional distillation. NMP is hygroscopic. It should be stored in a well-closed container and protected from light, in a cool, dry, place.

8.4.4 Oleic acid, OA (Wade, 1994)

Nonproprietary Names

Oleic acid (BP, USPNF)

Chemical Name and CAS Registry Number

(Z)-9-Octadecenoic acid [112-80-1]

Empirical Formula and Molecular Weight

$C_{18}H_{34}O_2$. Molecular weight is 282.47.

Structural Formula: $CH_3(CH_2)_7CH=CH(CH_2)_7COOH$

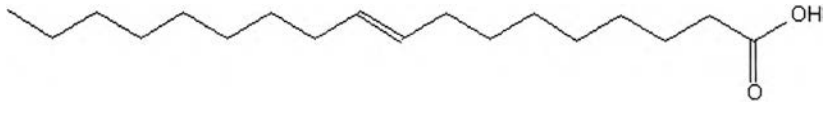


Figure 16 Chemical structure of oleic acid (OA).

Applications in Pharmaceutical Formulation or Technology

OA is as an emulsifying agent in foods and topical pharmaceutical formulations. It has also been used as penetration enhancer in transdermal formulations, to improve the bioavailability of poorly water soluble drugs in tablet formulations, and as part of a vehicle in soft gelatine capsules.

Description

A yellowish to pale brown, oily liquid with a characteristic odor.

Typical Properties

Boiling point: 286°C at 13.3 kPa (100 mmHg) (decomposition at 80-100°C)

Solubility: very soluble in benzene, chloroform, ethanol (95%), ether, hexane, and fixed and volatile oils; practically insoluble in water.

Stability and Storage Conditions

On exposure to air, OA darkens in color and its odor becomes more pronounced. It should be stored in a well-filled, well-closed container, and protected from light, in a cool, dry, place.

8.4.5 Polyethylene glycol 400, PEG (Wade, 1994)

Nonproprietary Names

Macrogol 400 (BP), Macrogolum 400 (PhEur), Polyethylene glycol (USPNF)

Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxy-poly(oxy-1,2-ethanediyl) [25322-68-3]

Empirical Formula and Molecular Weight

$HOCH_2(CH_2OCH_2)_mCH_2OH$.

Where m is 8.7 and represents the average number of oxyethylene groups. The average molecular weight of polyethylene glycol 400 is 380-420.

Structural Formula

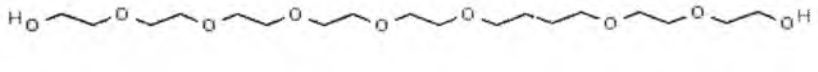


Figure 17 Chemical structure of polyethylene glycol 400 (PEG).

Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations. They are stable, hydrophilic substances that are essentially non-irritant to the skin.

Description

PEG occurs as a clear, colorless or slightly yellow-colored, viscous liquid. It has a slight, but characteristic odor and a bitter, slightly burning taste.

Typical Properties

Solubility: soluble in acetone, alcohols, benzene, glycerin, glycols and water.

Stability and Storage Conditions

PEG is chemically stable in air and in solution. Although PEG is hygroscopic, it does not support microbial growth, nor do they become rancid. It should be stored in a well-closed container in a cool, dry, place. Stainless steel, aluminum, glass or lined steel containers are preferred.

8.4.6 Propylene glycol, PG (Wade, 1994)

Nonproprietary Names

Propylene glycol (BP, USP), Propylenglycolum (PhEur)

Chemical Name and CAS Registry Number

1,2-Propanediol [57-55-6]

Empirical Formula and Molecular Weight

$C_3H_8O_2$. Molecular weight is 76.09.

Structural Formula: $CH_3CHOHCH_2OH$

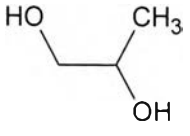


Figure 18 Chemical structure of propylene glycol (PG).

Applications in Pharmaceutical Formulation or Technology

PG has become widely used as a solvent, extractant and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, vitamins (A and D), most alkaloids and many local anesthetics.

Description

PG is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling glycerin.

Typical Properties

Boiling point: 188°C

Solubility: miscible with acetone, chloroform, ethanol (95%), glycerin and water; soluble 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Stability and Storage Conditions

PG is chemically stable when mixed with ethanol (95%), glycerin of water. But in the open at high temperatures, it tends to oxidize, giving rise to products such as propionaldaldehyde, lactic acid, pyruvic acid and acetic acid. Moreover, it is hygroscopic; so that it should be stored in and airtight containers, protected from light, in a cool, dry, place.

8.4.7 **Tween 80, Tw** (Wade, 1994)

Nonproprietary Names

Polysorbate 80 (BP, USPNF), Polysorbatum 80 (PhEur)

Chemical Name and CAS Registry Number

Polyoxyethylene 20 sorbitan monooleate [9005-65-6]

Empirical Formula and Molecular Weight

$C_{64}H_{124}O_{26}$. Molecular weight is approximately 1,310.

Structural Formula

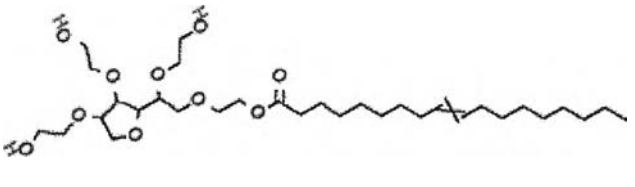


Figure 19 Chemical structure of Tween 80 (Tw).

Applications in Pharmaceutical Formulation or Technology

Tween 80 is a hydrophilic non-ionic surfactant used widely as emulsifying agent in the preparation of stable oil-in-water pharmaceutical emulsions. It may be used as solubilizing agent for a variety of substances including essential oils and oil soluble vitamins, and as wetting agent.

Description

Tween 80 is a yellow oily liquid at 25°C. It has a characteristic odor and a warm bitter taste.

Typical Properties

Solubility: soluble in ethanol and water. Insoluble in mineral oil and vegetable oil.

Stability and Storage Conditions

Tween 80 is stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. It is sensitive to oxidation. Tween 80 should be stored in a well-closed container, protected from light, in a cool, dry, place.

The properties of plasticizers and enhancers used in this study are summarized in Table 3.

Table 3 Physical properties and solubility parameters of some plasticizers and enhancers.

	MW*	sp. gr.*	Solubility parameter** ($MPa^{1/2}$)	T_g** (°C)
DBP	278.35	1.05	19.0	58.1
DEP	222.24	1.12	20.5	67.7
TEC	276.29	1.14	20.4	74.4
IPM	270.51	0.85	17.0	n/a [b]
IPP	298.51	0.85	15.3	n/a [b]
NMP	99.1	n/a [b]	23.0	n/a [b]
OA	282.47	0.89	16.0	45.2
PEG	400	1.13	23.0 [a]	70.0
PG	76.09	1.04	25.8	91.1
Tw	1,310	1.08	n/a [b]	n/a [b]

*Wade and Weller (1994), **Vesey, Farrell, and Rajabi-Siahboomi (2005),

[a] Koizumi, et al. (2004), [b] n/a (not available).