THE EFFECTS OF ADHESIVES ON PROPERTIES OF KETOPROFEN PATCHES

RASSAMEE JORADOL

**A THESIS SUBMETTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE IN PHARMACY
(PHARMACEUTICS)
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2005**

ISBN 974-04-6112-3

Thesis
Entitled

THE EFFECTS OF ADHESIVES ON PROPERTIES OF KETOPROFEN PATCHES

Rassamee Joradol
.....
Miss Rassamee Joradol
Candidate

Panee Boonsaner
.....
Asst. Prof. Panee Boonsaner
Ph.D. (Pharmaceutics)
Major-Advisor

Pojawon Lawanprasert
.....
Assoc. Prof. Pojawon Lawanprasert
Ph.D. (Pharmaceutics)
Co-Advisor

Ramm Hoonsawat
.....
Assoc. Prof. Rassmidara Hoonsawat
Ph.D.
Dean
Faculty of Graduate Studies

Ampol Mitrevej
.....
Prof. Ampol Mitrevej
Ph.D (Pharmaceutics)
Chair
Master of Science in Pharmacy
Programme in Pharmaceutics
Faculty of Pharmacy

Thesis
Entitled

THE EFFECTS OF ADHESIVES ON PROPERTIES OF KETOPROFEN PATCHES

was submitted to the Faculty of Graduate Studies, Mahidol University
for the degree of Master of Science in Pharmacy (Pharmaceutics)
on
May 20, 2005

Rassamee Joradol
.....
Miss Rassamee Joradol
Candidate

Panee Boonsaner
.....
Asst. Prof. Panee Boonsaner,
Ph.D. (Pharmaceutics)
Chair

Pojawon Lawanprasert
.....
Assoc. Prof. Pojawon Lawanprasert
Ph.D. (Pharmaceutics)
Thesis Defense Committee

S.P. Panomsuk
.....
Asst. Prof. Suwannee Panomsuk,
Ph.D. (Pharmaceutics)
Thesis Defense Committee

Ramm Hoont
.....
Assoc. Prof. Rassmidara Hoonsawat
Ph.D.
Dean
Faculty of Graduate Studies
Mahidol University

Ampol Mitrevej
.....
Prof. Ampol Mitrevej
Ph.D. (Pharmaceutics)
Dean
Faculty of Pharmacy
Mahidol University

ACKNOWLEDGEMENT

I would like to express my sincere gratitude and great appreciation to my advisor, Assistant Professor Dr. Panee Boonsaner, for her kind, meaningful guidance, invaluable suggestions and encouragement throughout my study.

My deep appreciation thanks to Associate Professor Pojawon Lawanprasert, my co-advisor, for her helpful criticism, suggestions and warm encouragement during entire study.

I am very grateful to Assistant Professor Dr. Suwannee Panomsuk for her advice and correction of this thesis and also for being member of my examining committee.

I express appreciation to the National Starch & Chemical Company for acrylic adhesives (Duro-Tak® 87-2516, Duro-Tak® 87-2852 and Duro-Tak® 87-4098) and Neoplast Company Limited for siliconized paper in the preparation of adhesive film and tensilometer and tack rolling ball equipment.

A special acknowledgement is extended to the Faculty of Pharmacy, Mahidol University for the support of equipment, location and financial support is this study.

I also want to express my special thanks for colleague and to some persons who helped and encouraged me during my study and my thesis preparation.

Finally, I would like to express my infinite gratitude to my parents, sisters and brother for their love and continuous support throughout my study.

Rassamee Joradol

THE EFFECTS OF ADHESIVES ON PROPERTIES OF KETOPROFEN PATCHES

RASSAMEE JORADOL 4336416 PYPT/M

M.Sc. IN PHARM. (PHARMACEUTICS)

THESIS ADVISORS: PANEE BOONSANER, Ph.D.,
POJAWON LAWANPRASERT, Ph.D.

ABSTRACT

Transdermal drug delivery system of ketoprofen was developed in this study. The aim of this study was to develop the transdermal drug delivery system that can reduce gastric irritation, dosing frequency and thus improve patient compliance. Ketoprofen patch was prepared by using acrylic as adhesive polymer matrix, mixture of ethanol as vehicle and Panasate 800 as enhancer in 50:50% w/w with 10%w/w of ketoprofen. The effects of class of acrylic adhesive (Duro-Tak® 87-2516, Duro-Tak® 87-2852 and Duro-Tak® 87-4098) and the concentration of acrylic adhesive (30%, 40% and 50% w/w) on skin permeation using human skin and adhesive properties were investigated. The results showed that the class of acrylic adhesive did not affect skin permeation but the adhesive properties by Duro-Tak® 87-2852 contained the highest peel and tack properties, followed by Duro-Tak® 87-2516 and Duro-Tak® 87-4098 respectively. In addition, the skin permeation of the ketoprofen patches decreased when the concentration of acrylic adhesives increased. The same results were also found in adhesive properties, where peel and tack decreased when the concentration of acrylic adhesive increased. The drug permeation profile of ketoprofen from the patches followed Fick's equation, which indicated partition control. The results of this study indicated that the ketoprofen patch with 40% w/w of Duro-Tak® 87-2852 was the best formula. Compared with the commercial topical gel, this formula (B2) showed a higher permeation rate, however, the flux of drug permeation is lower composed with that theoretically indicated.

KEY WORDS: KETOPROFEN/ TRANSDERMAL DRUG DELIVERY SYSTEM/ ACRYLIC/ ADHESIVE/ ETHANOL/ PANASATE 800/ PEEL/ TACK

180 P. ISBN 974-04-6112-3

อิทธิพลของกาวต่อคุณสมบัติของแผ่นยาคีโตโพรเฟน (THE EFFECTS OF ADHESIVES ON PROPERTIES OF KETOPROFEN PATCHES)

รัศมี จรดล 4336416 PYPT/M

ภ.ม. (เภสัชการ)

คณะกรรมการควบคุมวิทยานิพนธ์: พาณี บุญเสนอ Ph.D., พจวรรณ ลาวัณย์ประเสริฐ Ph.D.

บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อพัฒนาคีโตโพรเฟนเป็นตำรับการนำส่งยาทางผิวหนัง เพื่อหลีกเลี่ยงอาการข้างเคียงจากการใช้ยาในรูปแบบรับประทาน ลดความถี่ในการใช้ยาและทำให้ผู้ป่วยยอมรับการใช้ยามากขึ้น แผ่นยาคีโตโพรเฟนชนิดกาวอะไครลิคถูกเตรียมขึ้นโดยการใช้เอทานอลเป็นน้ำกระสายยา พานาเซต 800 เป็นสารเร่งการซึมผ่าน ในอัตราส่วน 50:50% w/w กาวอะไครลิคเป็นโพลิเมอร์ควบคุม มีความเข้มข้นของคีโตโพรเฟนในแผ่นยา 10% w/w ศึกษาผลของชนิดของกาวอะไครลิค คือ ดูรา-แทค 87-2516, ดูรา-แทค 87-2852, ดูรา-แทค 87-4098 และความเข้มข้นของกาวอะไครลิคในตำรับที่ 30%, 40%, 50% w/w ต่อคุณสมบัติการซึมผ่านของยาคีโตโพรเฟนผ่านผิวหนังของมนุษย์ และคุณสมบัติการยึดติดผิวของแผ่นยาคีโตโพรเฟน พบว่าชนิดของกาวอะไครลิคไม่มีผลต่อการซึมผ่านผิวหนังของยาคีโตโพรเฟน แต่มีผลต่อคุณสมบัติการยึดติดผิวของแผ่นยา ดูรา-แทค 87-2852 มีการยึดติดผิวดีที่สุด ตามด้วยดูรา-แทค 87-2516 และ ดูรา-แทค 87-4098 ตามลำดับ ในขณะที่อัตราส่วนของกาวอะไครลิคมีผลต่อทั้งการซึมผ่านของยาคีโตโพรเฟนและคุณสมบัติการยึดติดผิวของแผ่นยา โดยเมื่ออัตราส่วนของกาวอะไครลิคเพิ่มขึ้นในตำรับการซึมผ่านของยาคีโตโพรเฟนจะมีค่าลดลง แต่การยึดติดผิวของแผ่นยาจะเพิ่มขึ้น จากการศึกษาการซึมผ่านของแผ่นยาพบว่าเป็นไปตามสมการของฟิกค์ ซึ่งแสดงให้เห็นว่าการแพร่ของยาในชั้นผิวหนังมีผลต่อการควบคุมการซึมผ่านของยามากกว่าการแพร่ของยาในชั้นของแผ่นยาคีโตโพรเฟน จากผลการศึกษาพบว่าแผ่นยาคีโตโพรเฟนที่มีกาว ดูรา-แทค 87-2852 ในแผ่นยา 40% w/w เป็นตำรับที่ดีที่สุด ซึ่งมีการซึมผ่านของยาคีโตโพเฟนสูงว่าคีโตโพรเฟนในรูปแบบผลิตภัณฑ์เจล แต่น้อยกว่าค่าการซึมผ่านที่คำนวณได้ทางทฤษฎี

180 หน้า ISBN 974-04-6112-3

CONTENTS

CONTENTS (continued)

LIST OF TABLES

LIST OF TABLES (continued)

LIST OF TABLES (continued)

LIST OF TABLES (continued)

LIST OF TABLES (continued)

LIST OF TABLES (continued)

LIST OF TABLES (continued)

LIST OF TABLES (continued)

LIST OF FIGURES

LIST OF FIGURES (continued)

LIST OF ABBREVIATIONS

%	Percentage
°C	Degree Celsius
nm	Nanometer
cm	Centimeter
m	Meter
µg	Microgram
mg	Milligram
g	Gram
ml	Milliliter
min	Minute
hr	Hour
pH	The negative logarithm of hydrogen concentration
$t_{1/2}$	Half life
D	Diffusion coefficient
P	Partition coefficient
L	Diffusional pathlength
k_p	Permeability coefficient
J	Flux
Q	Cumulative amount per area
T_L	Lag time
SC	Stratum corneum
TDDS	Transdermal drug delivery system
NSAID	Non-steroidal anti-inflammatory drug
PSA	Pressure-sensitive adhesive
DIA	Drug-in-adhesive
S.D.	Standard deviation
S.E.	Standard error

LIST OF ABBREVIATIONS (continued)

R^2	Coefficient of determination
etc.	exectra
i.e.	id est., that is
w/w	Weight by weight
w/v	Weight by volume
V_d	Volume of distribution
UV	Ultraviolet
HPLC	High performance liquid chromatography

CHAPTER 1
INTRODUCTION

Transdermal drug delivery system (TDDS) is the system designed to deliver a drug at therapeutic level to the circulation and finally to the target organ. It prolongs drug release and, as a result prolongs activity of drug. In addition, it reduces side effects by avoids first pass gastrointestinal and hepatic metabolism, maintains a constant plasma level (sustain release dosage form) and is easy to use. TDDS can also improve patient compliance. TDDS depends on the ability of drug to penetrate the SC, in sufficient amount and to enter systemic circulation to achieve the desired therapeutic effect. Physicochemical properties of the drug and materials used in the TDDS such as lipid/water partition coefficient (log P), solubility, ionization and molecular weight influence transdermal permeation (1-2). For NSAIDs, log P is a more important parameter to predict bioavailability than solubility (2-4). A drug with log P value of 1-3 is considered a potential candidate for TDDS (4-5). Several studies show the enhancing effect of mixture of EtOH and Panasate 800. EtOH is one of the most commonly used as vehicle or solvent. Panasate 800 can enhance skin penetration of drugs having a wide range of lipophilicity, as indicated by log P value of -0.95 to 4.40. Panasate 800 activity is increase of diffusion of drug. The combination of EtOH and Panasate 800 are increase permeation rate and reduces lag time. EtOH extracts skin lipid and Panasate 800 increases diffusion, both actions give synergist effect to increase permeation of drug and reduce lag time (6-8).

TDDS is designed in five types, i.e. reservoir type, matrix type, membrane-matrix hybrid type, microreservoir type and drug-in-adhesive (DIA) type. All five types of TDDS provide different levels of transdermal permeation of the drug. Most of the TDDSs have been formulated as the DIA type because of its simplicity and minimal production cost (9). DIA type requires pressure sensitive adhesives (PSA) to maintain an intimate contact between the devices and the skin surface and also act as

matrix for drug. PSA polymers used are based on acrylic, polyisobutylene (PIB) and silicone polymers (10). Among the three classes of PSA, Acrylics has been widely used in many studies (11-13).

The properties of a good adhesive are that the adhesive must remain in intimate contact with the skin to ensure an effective drug delivery. Adhesive properties are important. Peel adhesion is the force required to peel away a strip of tape from a rigid surface. It is important in TDDS applications because the bond must provide adequate adhesion to the skin, yet allow nontraumatic removal. Tack could be defined as the property that enables an adhesive to form a bond with the surface of another material upon a brief contact under light pressure. It is important in TDDS, which are applied with finger pressure. In general, the following three types of tests to measure peel and tack are peel adhesion 180° test, tack rolling ball test and thumb tack test (10, 14).

Ketoprofen is a 2-arylpropionic acid derivative non-steroidal anti-inflammatory drug (NSAIDs), which shows potent inhibitory effects on prostaglandin synthesis. Ketoprofen is used for rheumatoid and osteoarthritis, acute gout, painful musculo-skeletal conditions. It alleviates mild and moderate pain (15). In oral dosage forms, the daily dose of 150-300 mg of ketoprofen is needed. Ketoprofen is quickly and almost completely absorbed in oral dosage form. Because of its short elimination half-life (1.5-4 hr), several doses (3-4 times) a day are required. Ketoprofen also leads to some serious adverse effects such as upper abdominal pain and gastro-intestinal ulcer. These adverse effects restrict the oral use of the drug (16). However, it may be necessary for patients to receive ketoprofen over a long period during the treatment. Thus, it is crucial to reduce or eliminate the side effects of ketoprofen. Administration of the drug via skin is a technique that can avoid these disadvantages. It avoids first-pass gastrointestinal and hepatic metabolism, maintains a constant plasma level (sustained release dosage form), improves patient compliance, and is easy to use (17).

The objective is to study the effect of adhesives in ketoprofen transdermal patches. Various acrylic adhesives and various concentrations of the adhesives are studied to determine the optimal formula by evaluation of the skin permeation and the adhesive properties. *In vitro* skin permeation through human epidermis is investigated by the Franz diffusion cell, and the in vitro cumulative amount ($\mu g/cm^2$) and time (hr)

are plotted. Flux (μg/cm^2/hr) and lag time (hr) obtained from the permeation study of the different formulae are compared. The adhesive properties of the transdermal patches are investigated by peel adhesion 180^o test, tack rolling ball test and thumb tack test.

CHAPTER 2
OBJECTIVES

The objectives of the present study were:

1. To investigate the effects of the acrylic adhesives on drug permeation of ketoprofen patches in drug-in-adhesive (DIA) design by determining the flux, the permeability coefficient and the lag time.
2. To investigate the effects of the adhesives on the adhesive properties of the DIA by peel adhesion 180^{o} test, tack rolling ball test and thumb tack test.

CHAPTER 3
LITERATURE REVIEW

1. Skin structure

The skin covers an area of approximately 2 m^2 and provides the contact between the body and the external environment. It prevents the loss of water and the ingress of foreign materials. Skin influences transdermal delivery through its control of the drug transport across the barrier layers. These barriers are multilayered organ composed of epidermis, dermis and subcutaneous tissue. The skin structure is illustrated in Figure 1 (17, 18).

1.1 Epidermis

The epidermis is the outermost layer. The multilayered envelope of the epidermis varies in thickness, depending on cell size and the number of cell layers. It is divided into four layers, stratum germinativum (basal layer), stratum spinosum, stratum granulosum (granular layer), and stratum corneum (horny layer). Stratum corneum (SC) is the nonviable part (dead cell) while the other layers are viable epidermis. The normal thickness of SC is about 15 μm. SC consists of many layers of compacted, dehydrated, elongated cells (corneocytes) and intercellular lamellae. These horny cells have lost their nuclei and are physiologically rather inactive. They are formed and continuously replenished by the slow upward migration of cells produced by the stratum germinativum, which is a regenerative layer of the epidermis. SC is replenished about every 2 weeks in a mature adult. In normal SC, the cells have water content of only approximately 20% (w/w) compared to the normal physiological level of 70% in the physiologically active stratum germinativum. The SC requires minimum moisture content of 10% (w/w) to maintain flexibility and softness. The SC is responsible for a barrier function of the skin, and behaves as a primary barrier to percutaneous absorption. The SC consists of protein (75-85%) mainly keratin, lipid (5-15%) including cholesterol sulfate and neutral lipids.

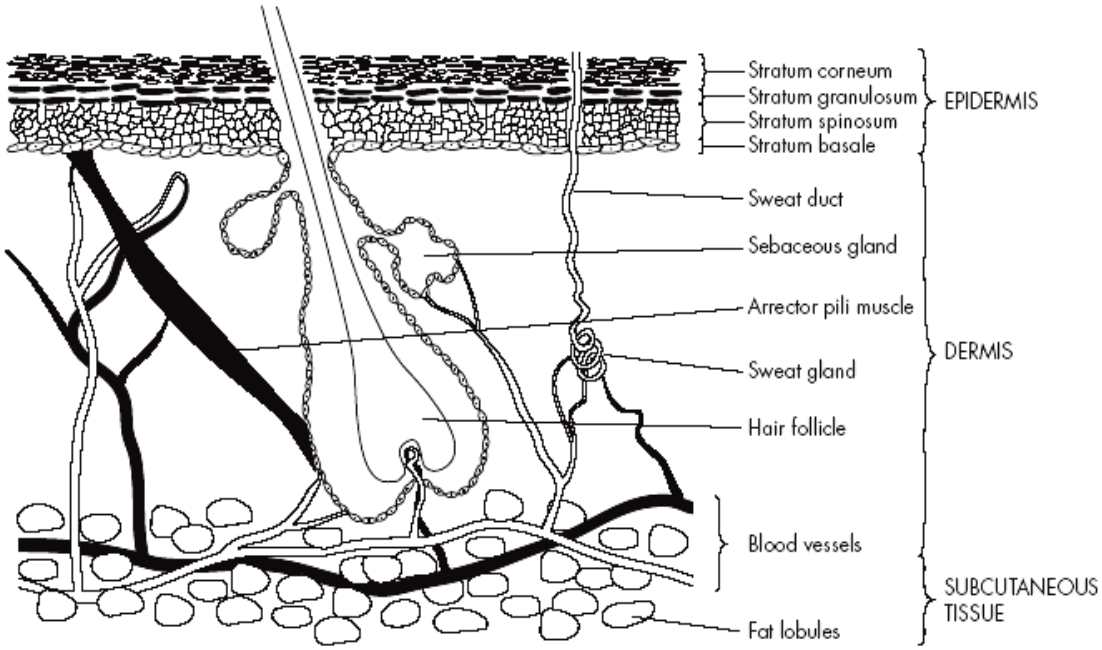


Figure 1. Illustration of the structure of skin (18).

Corneocytes are the end product of differentiation of the cells produced in the viable epidermis. Keratin, deposited within the corneocytes, is a family of α-helical polypeptides ranging from 40,000 to 70,000 Dalton in size. Intercellular lamellae, which are situated in the intercellular spaces of the SC and mainly consists of multiple lipid bilayers arranged in broad sheets. The distance of lipid lamellae corresponds to their thickness of two bilayer membranes. The picture of the SC, which emerges from the above considerations, is referred as the two-compartment model or the bricks and mortar model. In this model, the keratinized corneocytes act as protein "bricks" embedded in a lipid "mortar" (Figure 2). These bilayers form regions of semicrystalline, gel and liquid crystals domains. The lipids in the intercellular lamellae are composed mainly of ceramides, fatty acids, and cholesterol. Unlike all other biological membranes, those in the SC do not contain phospholipids (19).

1.2 Dermis

The dermis, at 3 to 5 mm thick, makes up the bulk of the skin. It is much thicker than the overlying epidermis on which it supports. The dermis is the site of nerve endings, lymphatic ducts and blood supply. The blood supply is essential for the systemic uptake of drugs into circulation. Venous drainage and arterial supply located in the dermis consist of an unusual arrangement of a cutaneous plexus to supply the appendages and the upper dermis and epidermis. It contains numerous shunts opening into the papillae of the epidermis/dermal junction. The epidermis/dermal junction represent the major site for transdermal drug penetration. The skin appendages i.e., eccrine gland, apocrine gland, sebaceous gland, hair are also in this layer (20).

1.3 Subcutaneous tissue

The subcutaneous fat spreads all over the body as a fibrofatty layer. This is a sheet of fat-containing areola tissue, known as the superficial fascia, which attaches the dermis to the underlying structures (17). The thickness of this layer varies greatly from one body site to another. The subcutaneous fat provides a mechanical cushion and a thermal barrier, it synthesized and stores readily available high-energy chemicals (18).

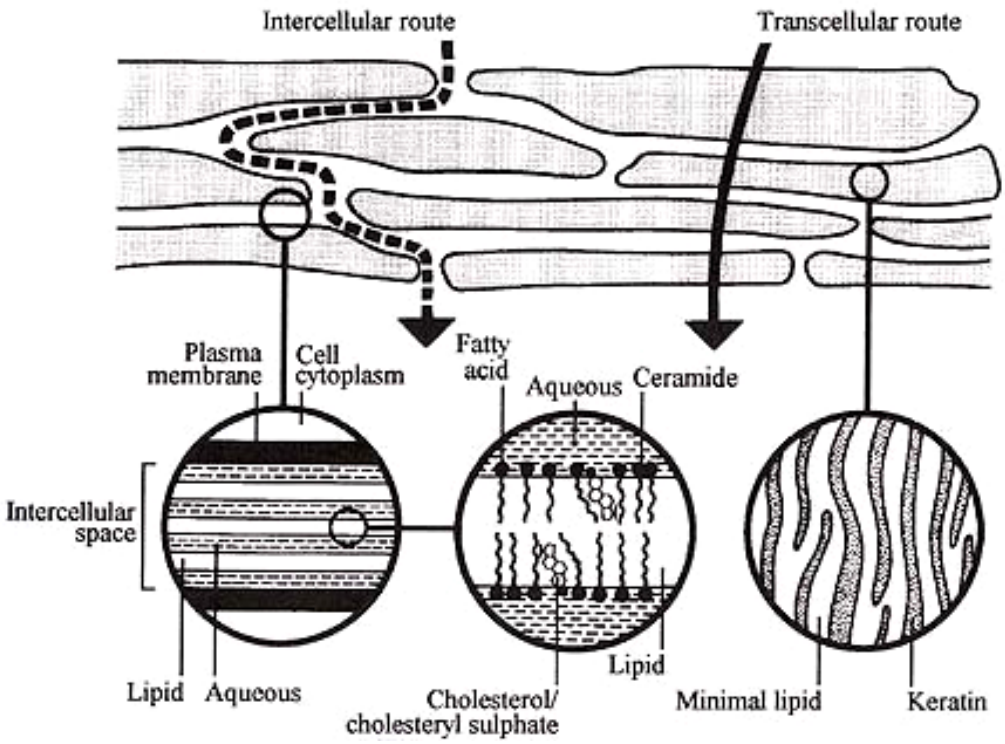


Figure 2. The brick and mortar model of the stratum corneum (19).

2. Transdermal drug delivery system (TDDS)

Transdermal drug delivery system (TDDS) is the system designed to deliver a drug to the circulation and finally to the target organ. Figure 3 is the diagram of in transdermal drug delivery (21). The phenomenon of skin permeation can be visualized as consisting of a series of steps in sequence: sorption of a penetrate molecule onto the skin layers of stratum corneum, diffusion through it and the viable epidermis, and finally, at the papillary layer of the dermis, the molecule is taken up into the microcirculation of subsequent systemic distribution. TDDS delivers a drug through the skin into blood circulation at the therapeutic level. It will also be necessary for the delivered drug to reach target sites and maintain concentration at the target at therapeutic level. However, during this transport process, the drug can undergo severe biochemical degradation and the end products might ineffectiveness and toxicity. Therefore, the drug substances that are used in their controlled release system should not easily degrade during administration and the drug can be released as plateau state in the range between toxic level and minimum effective level. An ideal transdermal controlled release rate is illustrated in Figure 4 (22). TDDS prolongs drug release, thus prolongs activity of drug. It eliminates a side effect of drug such as gastrointestinal irritation. Several TDDS have been marketed, containing drug, for instance, scopolamine, nitroglycerin, estratiol, clonidine, isosorbide dinitrate, fentanyl, nicotine, estradiol/norethisterone acetate and testosterone. A list of drugs available as transdermal patches and their applications is illustrated in Table 1 (23).

2.1 Advantages of transdermal drug delivery system (17, 24)

Transdermal drug delivery presents a number of advantages over classical drug delivery systems administered via other routes (oral, parenteral):

- bypass of the hepatic first-pass metabolism
- avoidance of the problems of the gastrointestinal environment such as gastric irritation
- production of constant plasma concentrations of drugs
- reduction in repeat dosing invervals
- ability to discontinue administration by removal of the system
- ease of self-administration

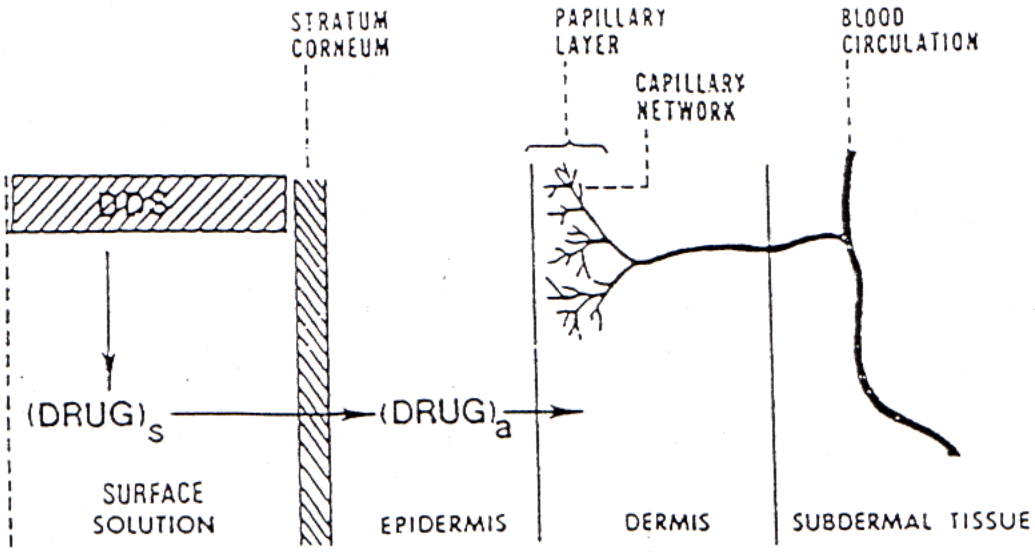


Figure 3. Schematic diagram of the skin permeation of drug delivery from the transdermal device (17).

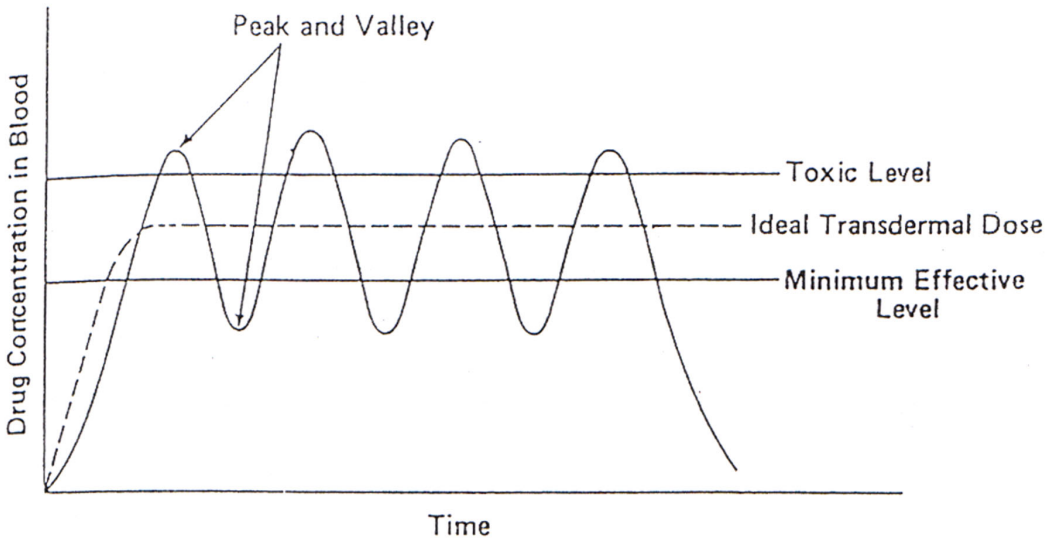


Figure 4. Hypothetical blood levels pattern from a conventional multiple dosing schedule, and the idealized pattern from a transdermal controlled release system (22).

Table 1. Marketed transdermal patches and their applications (23).

Drug	Application(s)
Scopolamine	Motion sickness
Nitroglycerin	Angina pectoris
Estradiol	For relief of post menopausal symptoms and prevention of osteoporesis
Clonidine	Hypertension
Isosorbide dinitrate	Angina pectoris
Fentanyl	Moderate to severe chronic pain
Nicotine	Smoking cessation
Estradiol/Norethisterone acetate	Hormone replacement therapy
Testosterone	Hormone replacement therapy

- good patient compliance
- substitute for oral or parenteral administration in certain clinical situations (pediatrics, geriatrics, nausea, etc.)
- adaptability to drugs with a short half-life
- suitability for drugs producing a therapeutic response at very low plasma concentration

2.2 Selection of drug candidates for transdermal drug delivery (25, 26)

The drug, which can be delivered transdermally, should be readily permeated. The drug criteria for determine the feasibility of transdermal delivery is considered as follows:

- Compound with low molecular weight (100-500 Dalton) contain higher diffusion coefficient than high molecular weight compound.
- Drug should have short half-life because TDDS is a sustained release system.
- Drug should be potent. Since the TDDS has a limited surface area, so it can keep in small amount of drugs.
- To avoid disadvantage of the other route i.e. to prevent the overdose of the narrow therapeutic drugs that using by intravenous.
- Drug should not be the cause of topical irritant and/or allergic response
- The log P value of drug should be 1-3. Drug, with log P less than 1 means that the drug permeation from the device into SC is low. However, drug with log P more than 3, mean that the drug is preferably remain in the SC, so deliver into blood circulation is low.

2.3 Skin transport

There are three potential pathways of drug penetration through the skin: (1) via the sweat ducts; (2) via across the continuous SC or (3) through the hair follicles (Figure 5). The permeation through normal intact skin via the skin appendages (sweat glands and hair follicles) may act as diffusion shunts. The appendages have a small fractional surface area, approximately 0.1% of the total skin area, and are believed to provide an insignificant pathway for most drug permeation.

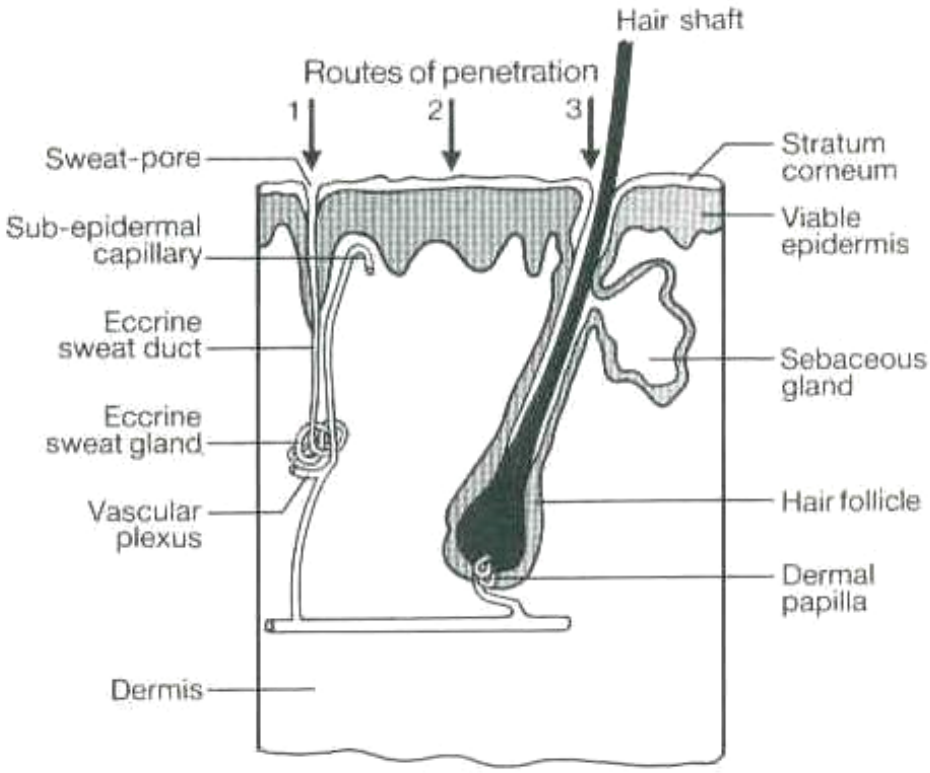


Figure 5. Simplified diagram of skin structure and macroroutes of drug permeation: (1) via the sweat ducts; (2) across the continuous stratum corneum or (3) through the hair follicles with their associated sebaceous glands (20).

The SC route is the major route of drug to across the skin. Two potential micropathway exist through the SC, the transcellular and intercellular route (Figure 2) These two pathways have been proposed to explain the ability of molecules with a wide difference in physicochemical properties to permeate the skin. Lipophilic penetrations (log P >2) transverse the SC mainly via the intercellular lipid pathway whereas polar drug could penetration preferentially into the polar pathway in intercellular route (27-29). The sequential steps in percutaneous penetration are show in Figure 6 (26).

1. Diffusion or transport of penetrant to the skin surface
2. Partitioning of the chemical into the SC
3. Diffusion through (the intercellular lipids of) the SC
4. Partitioning of the chemical from the lipophilic SC into the aqueous viable epidermis
5. Diffusion through the viable epidermis and upper dermis
6. Uptake of penetrant into a cutaneous blood vessel and systemic access

In Figure 6, the predominant events involve partition and diffusion. Primarily the molecular size of the diffusant and the level of interaction between the diffusant and diffusion medium determine the drug transport. The skin is a metabolically active organ. Metabolism of drug occurs in the SC and viable epidermis by enzyme resulting in drug loses. When a drug permeated into a cutaneous blood vessel, the drug is delivered to target site by the circulation. The concentration of drug in blood should be at therapeutic concentration. The skin, consisting of lipid structure, provides a significant barrier to the penetration of highly lipophilic drug into blood. Highly hydrophilic drugs are poor penetrants since they have a little pathway to transverse and poor partition into the SC (26). Penetration of drug is better when drug possess balanced lipophilic-hydrophilic characteristics and have reasonable solubility in both lipid and aqueous phases (19). It should be noted that the skin provides the rate-limiting step when considering permeation.

2.4 Factors affecting percutaneous absorption (30-32)

The factors that influence the penetration of the skin barrier can be divided into physiological and physicochemical characteristics.

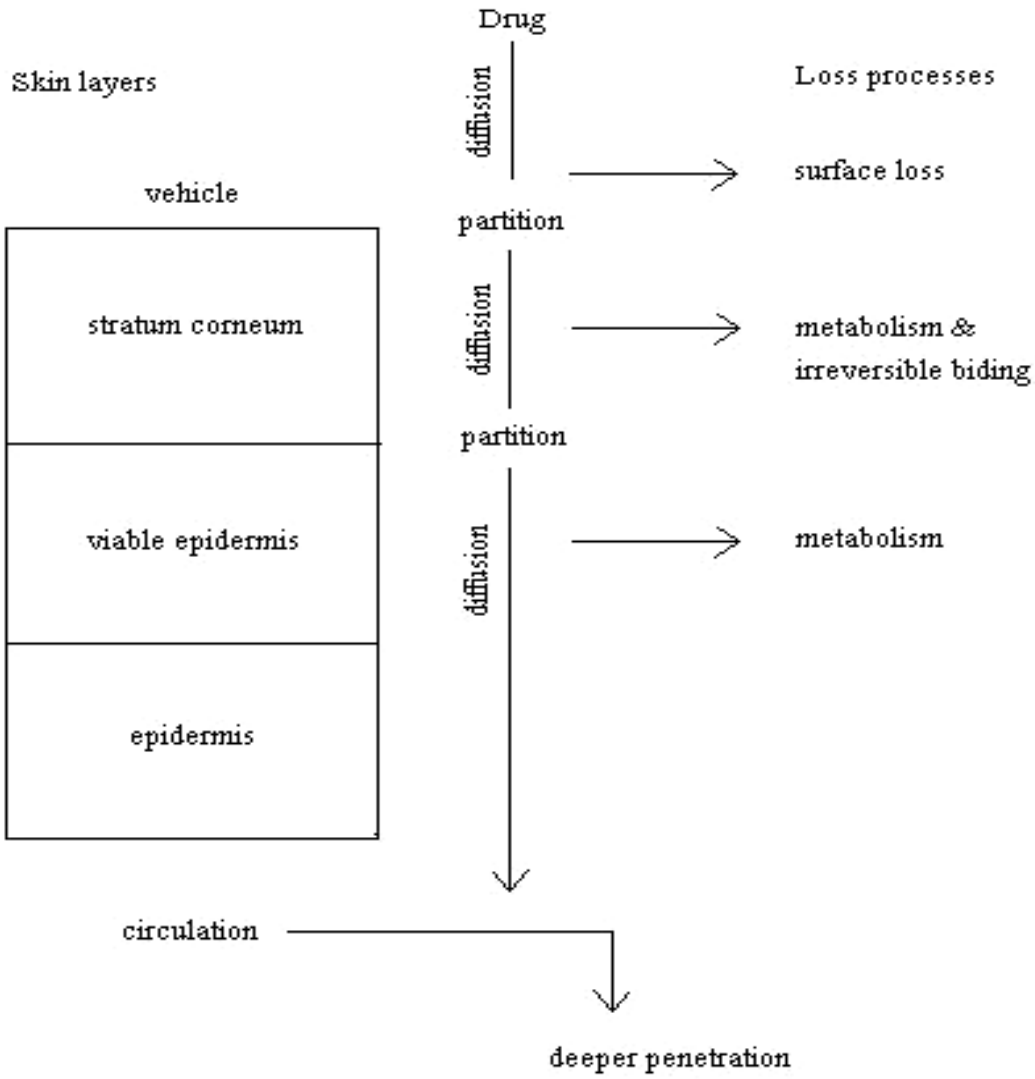


Figure 6. Sequential physicochemical steps involved in percutaneous absorption. (26).

2.4.1 Physiological factors

2.4.1.1 Skin condition

The skin is a barrier to penetration, if it is intact. Probability the most widespread cause of an alteration in skin condition is a disease. In general, in disease characterized by a defective SC, percutaneous absorption increases. Psoriatic skin is an example. The absorption through psoriatic skin is enhanced. This may be due to alteration in epidermis structure as well as the change in vascular perfusion. In contrast, condition such as eczema, which results in thickened skin with maintenance of an intact structure and lack of parakeratosis, may retard absorption because of the increase in absorptive path length. Even a mild dermatitis may increase permeation by deranging epidermal function so that an abnormal SC grows. Removal of the skin barreier by cellophane stripping will enhance the absorption of most substances. Chemical agents such as acids, alkalies or mustard gas injure barrier cells and increase water loss (33).

2.4.1.2 Skin age

Skin permeability depends on the thickness and integrity of the skin, particularly the SC. The epidermis of the preterm infant has a higher permeability than that of older infants (33). The full-term infants (37-40 weeks gestation) show a histological SC that is thicker than that of the age (50-76 years) (34). Children are more susceptible to the toxic effects of drugs and chemicals, partly because of their greater surface area per unit body weight (31). In adult, the effect of aging on the skin is visually apparent (26).

2.4.1.3 Regional skin sites

Variation in penetration rates have been demonstrated for full thickness cadaver skin, isolated from different sites. These permeations may be inversely proportional to the thickness of the skin. In addition, the absorption of some small polar compound seemed greater in areas where follicles are large or more numerous, such as forehead and scalp, because these compounds prefer to pass through the so call “aqueous pore pathway”. The most fundamental physicochemical

work tentatively ranks the order of diffusivity in decreasing order as: scrotum, jaw, angle, forehead, scalp, back, forearm, palm and foot arch (plantar) (31, 35).

2.4.1.4 Species variation

Mammalian skins from different species show wide differences in anatomy in such characteristics as the thickness of the SC, the numbers of sweat glands and hair follicles per unit surface area. These differences affect the penetration pathways and the penetration resistance of skin. In spite of limitations, animal must be used in studies of percutaneous absorption because biological dangerous substances are under many restrictions when applied to human subjects. Sato et al. studied the skin permeability of nicorandil using the skin samples from hairless mouse, hairless rat, guinea pig, dog, pig and human. It was found that the skin permeability of nicorandil in hairless mouse was the highest among the six species studied, and those in pigs and humans agreed. Animal skin has been much used to obtain skin penetration data but it is best to use human skin whenever possible (36).

2.4.1.5 Racial differences

White skin is slightly more permeable than black skin, which correlates with observations that black skin has both more cell layers within the SC and higher lipid content that reduce permeability through skin. Leopold CS, et al. study of white, Hispanic, black and Asian skin ranked them in order of permeability to methyl nicotinate as black < Asain < white< Hispanic. The corneocyte s of black, white and Oriental skin is of a similar size, but that are differences in spontaneous desquamation (31).

2.4.1.6 Skin hydration

Hydration of the SC is one of the most important factors in increasing the permeation rate of most substances that permeate skin. Hydration is the result from perspiration that accumulates after application of an occlusive vehicle or covering on the surface (37). Under occlusive conditions, the SC is changed from a tissue, which normally contains very slight water (5-10%) to the one, which may contain as much as 50% water. The water-saturated skin is soften, swell and wrinkle,

and its permeability will increase. The important point to consider is the thermodynamic activity of water in the barrier phase. It was found that the presence of greater amounts of bound water causes a corresponding increase in the mobility of the epidermal components. This motion may increase the effective diffusion coefficient of water and there by give rise to the nonlinear activity in the SC (38-39).

2.4.1.7 Temperature

The permeation rate of substances through skin can be changed by temperature variation. Raising skin temperature results in an increase the rate of skin permeation. The energy for permeation is activated. The plot of the log permeability constant against the reciprocal of temperature is linear. Under occlusive condition, sweat cannot evaporate nor can heat radiate as readily and the surface temperature may rise by a few degree (33).

2.4.2 Physicochemical factors (3, 4, 40)

2.4.2.1 Lipid/water partition coefficient

The partition coefficient of a drug is the governing factor in dictating which pathway it will follow through the skin. Thus, the value of log P is an important factor. The drug with high partition coefficient was good partition into skin. Lipophilic drugs are highly permeated through intercellular route. Hydrophilic drugs are expected to permeate via the transappendageal route whereas the intercellular route will dominate for lipophilic drugs. The lipid bilayers are the main structure in the intercellular route, and are the rate-limiting step in the permeation of drug via the intercellular route. The intercellular route is not exclusively lipoidal. There are proteins associated with the lipid domains, and a thin layer of water is found between the polar head groups in the lipid bilayers. Thus, it is feasible that a hydrophilic permeant may partition into these more polar areas within the lipid bilayers, and hence also traverse the tissue via the intercellular route. This has led to the proposal of a mixed permeation model where permeation for most drugs is largely via the continuous intercellular lipid domains. Both the lipid and polar regions of the bilayers could provide the micro-routes depending on the partition coefficient of the permeant.

The drugs must partition from patch into skin and partition from skin into blood. Drugs have a balanced lipophilic/hydrophilic character and a drug with a log P value of 1 to 3 is considered to be a potential candidate for transdermal delivery.

2.4.2.2 Solubility

Solubility is the potential for a drug to be released from the patch. For a drug to move from the patch, a concentration gradient between the patch and the skin is needed. The formulation with the drug at solubility is associated with the highest concentration gradient and hence the flux is high. Besides that, when the drug is at its solubility, the drug will show the highest thermodynamic activity, i.e. the drug is ready to move out of the patch as quickly as it can. The two unfavorable points of high solubility are the drug dissolving in this vehicle prefers to be in the vehicle rather than partitions into the skin, and high solubility means high amount of drug is needed at solubility, which leads to the cost of the formulation. Thus, the vehicle that shows an optimal solubility will be preferred.

2.4.2.3 Ionization

Ionization of drug can influence the skin permeation to some degree. The ionized drugs can cross the skin via the transappendageal route, but the amounts passed may be somewhat less than the unionized species, which pass largely via the intercellular route. Therefore, to increase the amount of drug permeating through the skin, the drug in the formulation should be in the unionized form. A way to do is to formulate a drug in an organic solvent in which the drug will be in the unionized form. However, pure solvent cannot be used because it can damage the skin. Thus, the chosen organic solvent is mixed with water in a certain ratio. Water must be buffered to a chosen pH such that the drug is in an unionized form. Selection of buffer at two pH units below the pK_a of a weakly acidic drug or two pH units above pK_a of a weakly basic drug will produce negligible ionization.

2.4.2.4 Molecular weight

Molecular weight influences the diffusion coefficient of a molecule. Smaller molecules diffuse faster than larger molecules do. However, most

conventional therapeutic agents (small organic molecules) tend to lie within a relatively narrow range of molecular weights (100-500 Dalton). Within such a narrow range, the influence of a molecular size appears to be relatively minor.

2.5 System design for TDDS (9, 17)

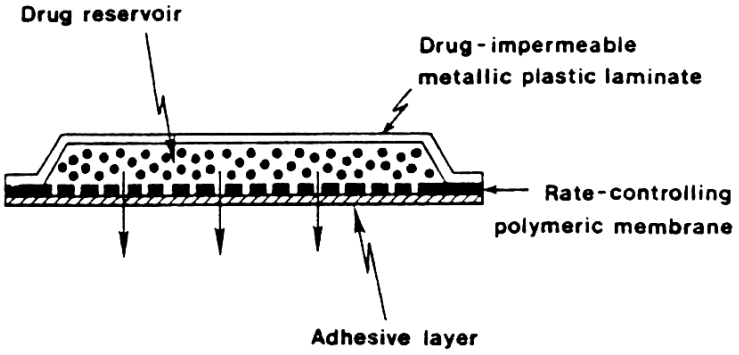
In each designs, several components present in TDDS. They are backing layer, adhesive and release liner. Backing layer protect the patch from the outer environment. Adhesive sticks the patch on the skin. Release liner protects the patch during the storing period and it is removed prior to use (40).

2.5.1 Reservoir Type

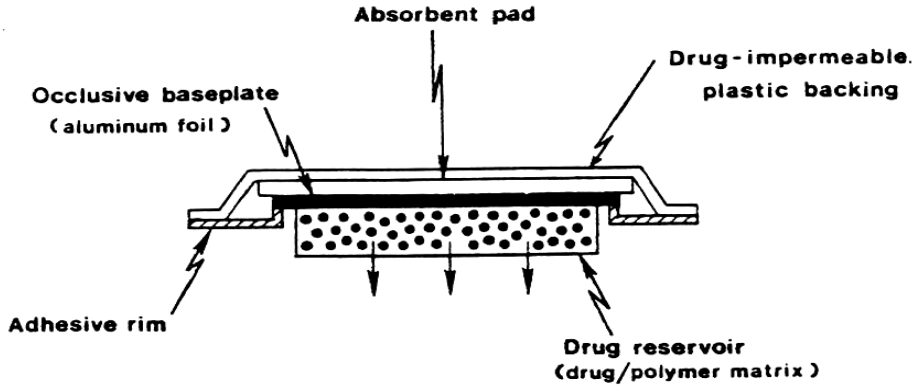
A drug reservoir is put between a rate-controlling polymeric membrane and drug-impermeable backing laminate. In the drug reservoir compartment, the drug is dispersed homogeneously in polymer matrix. Then, it is suspended in an unleachable and viscous liquid medium to form a pastelike suspension, or dissolved in a solvent to form a clear drug solution. The rate-controlling polymeric membrane can be either a microporous or a nonporous polymeric membrane, e.g., ethylene-vinyl acetate copolymer with specific drug permeability. On the external surface of the polymeric membrane, a thin layer of adhesive polymer can be applied to provide intimate contact of the system with the skin surface (Figure 7a).

2.5.2 Matrix Type

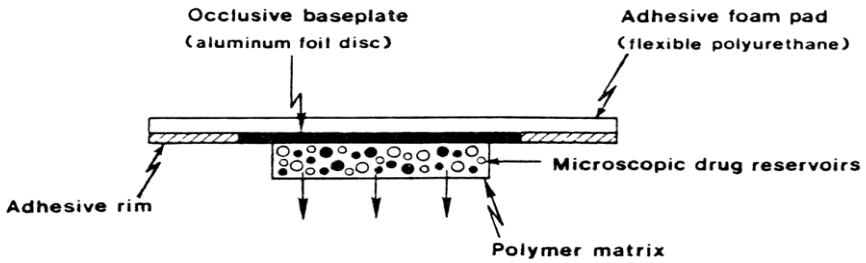
The drug is dispersed in the polymer matrix. The medicated polymer is molded into medicated disks with a defined surface area and controlled thickness. It is mounted onto an occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing. The adhesive polymer is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk (Figure 7b). In solution matrices, the concentration levels of the drug are at or below saturation level, whereas in dispersion matrices the drug levels are excess of its saturated concentration. The rate of drug release from matrix devices falls off with time, as the drug in the skin-contacting side of the matrix is depleted.



(a)



(b)



(c)

Figure 7. (a) Reservoir-type transdermal drug delivery system (17).
(b) Matrix-type transdermal drug delivery system (17).
(c) Microreservoir-type transdermal drug delivery system (17).

2.5.3 Membrane-Matrix Hybrid Type.

The TDDS is essentially an adaptation of the reservoir-type. The liquid-type formulation of the drug reservoir is replaced with a solid polymer matrix. Therefore, this TDDS differs from the reservoir type only in the composition of the reservoir and may still be represented schematically by Figure 7a. Drug permeation may be controlled by the rate-controlling membrane and/or the polymeric matrix, depending on the duration of application and the physicochemical properties of the drug, the reservoir and the membrane.

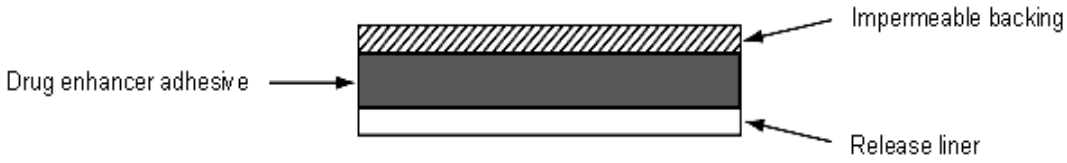
2.5.4 Microreservoir Type

This system can be considered a hybrid of the reservoir and matrix dispersion system. 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 in a lipophilic polymer by high shear mechanical force to form thousands of unleachable microscopic drug reservoirs (Figure 7c). This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains, which produces a medicated polymer disk with a constant surface area and a fixed thickness and then mounted at the center of an adhesive pad.

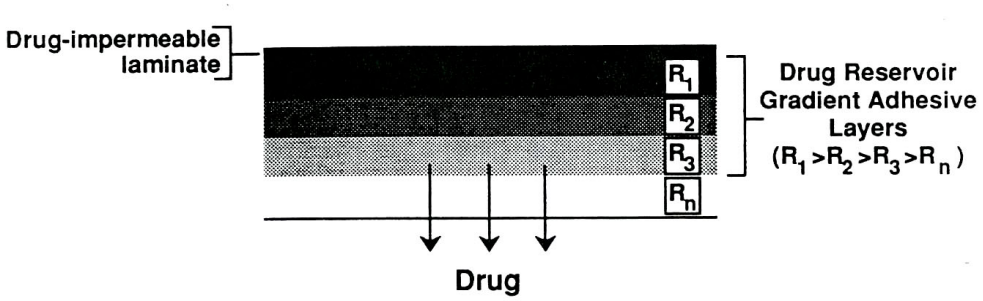
2.5.5 Drug-in-Adhesive Type

The drug-in-adhesive type TDDS can be made of single or multilaminate adhesive layers which function both as the drug reservoir and the rate-controlling matrix. The release of drug from the adhesive polymer matrix is similar to that obtained from a matrix-type TDDS. The single layer drug-in-adhesive is formulated by incorporating the drug directly in a pressure-sensitive adhesive polymer (Figure 8a).

With the advance in adhesive science and polymer technology, most of the polymer matrix drug dispersion-type TDDS can be modified to have the drug loading level varied in an incremental manner by forming a gradient of drug reservoir along the diffusion path across the multilaminate adhesive layers. The thickness of diffusional path through which the drug molecules diffuse increases with time. To



(a)



(b)

Figure 8. (a) Drug-in-adhesive type transdermal drug delivery system (17).
(b) Multilaminate drug-in-adhesive transdermal drug delivery system (17).

compensate for this time-dependent increase in diffusional path due to drug release, the drug loading level in the multilaminate adhesive layers is also designed to increase proportionally (Figure 8b). In theory, this design should yield a more constant drug release profile.

All five types of TDDS provide different levels of transdermal permeation of the drug. Most of the TDDSs have been formulated as the DIA type because of its simplicity and minimal production cost (9, 17).

3. Method for quantification of skin permeation (41-43)

The skin barrier property of stratum corneum affects percutaneous absorption, resulting in the small amount of drug permeation. *In vitro* permeation method is used to quantify the permeation of drug into and through the skin. The permeation is expressed in terms of flux, J (μg/cm^2/hr), the amount of drug permeation (μg) per unit area (cm^2) per time interval (hr).

Diffusion cells consist of two compartments, which are clamped together to connect between the donor and receptor compartments. The donor compartment contains the drug in suspension or solution (donor phase) and the receptor compartment contains the receptor phase. Diffusion cells for *in vitro* skin permeation studies are of two designs.

3.1 Diffusion cells

3.1.1 Side-by-side type (Horizontal design) (Figure 9a)

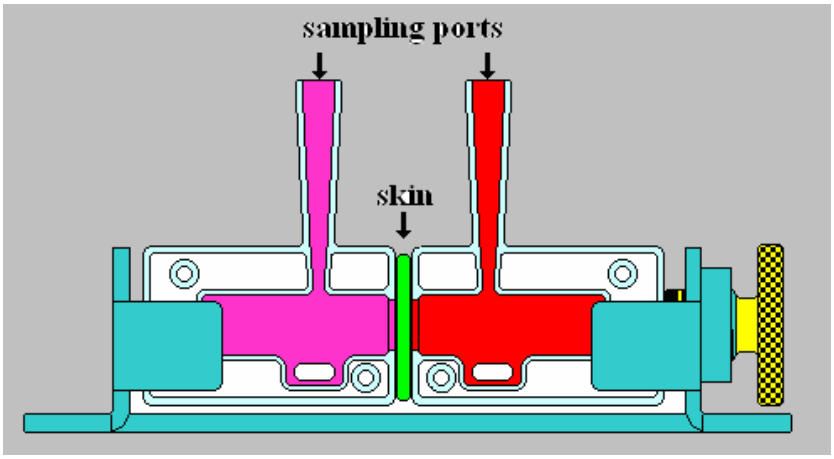
The donor and receptor compartments of the diffusion cells are set at the same level of equal volumes. The skin separates the two phases. Magnetic stirrers are positioned beneath each cell to produce synchronous stirring of the bars in both cells. The drug is delivered by the horizontal movement of drug from the donor phase through the skin and into the receptor phase. The donor and receptor compartments are under an enclosed system. The temperature of both phases can be controlled and set at the same degree. This condition is the advantage of the horizontal design for studying diffusion and partition parameters, which require the controlled temperature and mixing at all time in both phases.

3.1.2 Franz diffusion cell (Vertical design) (Figure 9b)

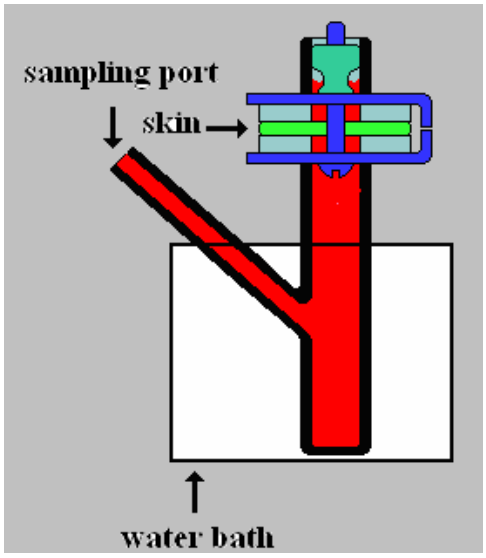
The Franz diffusion cell is one of the most widely used systems for *in vitro* skin permeation studies. This cell consist a small donor compartment and only a magnetic bar stirs the receptor compartment. The drug delivery is by the vertical movement of drug from the donor phase through the skin and into the receptor phase. The donor compartment can be closed or opened to ambient conditions. Only the receptor compartment is enclosed in a water bath for temperature control. In the receptor phase, the speed of stirring must be selected in order to avoid the problem of poor mixing. The time to complete mixing in the receptor compartment is not reached until 30 minutes had passed. However, mixing is inadequate in the side-arm of the receptor cell. This type of diffusion cells is suitable for studying permeation of a drug from a transdermal patch formulation or from a small size donor phase because they can be placed onto the skin in the donor phase.

3.2 Receptor phase

The receptor phase used in the *in vitro* permeation must dissolve the drug and has the properties as similar as the blood in terms of buffer system, pH, buffering capacity, and isotonicity. Phosphate buffer saline (PBS) is designed to mimic physiological fluid. PBS contains phosphate buffer system, has a pH of 7.4, and has buffering capacity and isotonicity nearly to the blood. It is the first choice for hydrophilic and moderately lipophilic permeants (up to a log P of around 2). Lipophilic permeants have a low solubility in aqueous solution. Therefore, the drug can reach the solubility and precipitate in receptor phase. The concentration of drug in the receptor is fixed at solubility and cannot be used to calculate the flux at steady state condition. Thus, a receptor phase must be substituted to increase drug solubility. These receptor phases are bovine serum albumin (BSA) (3% in buffer) (44), PEG 400 (10-40% in normal saline) (45) and ethanol (25% in water) (46). The concentration of BSA or PEG or ethanol must not be too high since it can damage the skin. The concentration of the permeant in receptor phase must be kept at sink condition with respect to the donor phase to ensure that the flux of the permeant through the skin is not retarded (8).



(a)



(b)

Figure 9. (a) Side-by-side diffusion cell

(b) Franz diffusion cell

3.3 Temperature

The temperature of the cells is controlled by using water-jackets or dousing the cells into a water bath. Temperature control of the receptor phase is essential in order to avoid additional extrapolations from fluctuating ambient conditions. The receptor medium was controlled at 37 ^{o}C resulting in the skin surface temperature at 32 ^{o}C. This temperature is the surface skin condition. The receptor compartment is stirred to prevent local concentrations of drug and to minimize static diffusion boundary layers, thereby minimizing diffusion resistance. These conditional controls of the temperature and the receptor phase are maintained throughout the experiment.

3.4 *In Vitro* Permeation (4, 41)

Percutaneous absorption of drug is a passive diffusion process. The drug will move down a concentration gradient from the donor phase to the receptor phase. The cumulative amount of drug penetrated (μg/cm^2) and time (hr) under steady-state conditions are plotted. The steady-state flux is obtained from Fick's law.

$$\frac{dQ}{dt} = \frac{DKC_o A}{L} \qquad \text{(Eq 1)}$$

$$J = \frac{d(Q/A)}{dt} = \frac{DKC_o}{L} \qquad \text{(Eq 2)}$$

Where Q is the cumulative amount of drug (μg), t is time (hr), d(Q/A)/dt, the rate of change of cumulative amount of drug that penetrates per unit area per time, is termed the flux (J; μg/cm^2/hr), D is diffusion coefficient (cm^2/hr), K is partition coefficient, C_o is the concentration of drug in donor phase (μg/ml), A is area of skin (cm^2) through which the permeation of the drug take place, L is diffusional pathlength (cm).

The permeability coefficient of drug through a membrane (k_p) may be defined by the expression

$$k_p = \frac{DK}{L} \qquad \text{(Eq 3)}$$

The term of k_p describe the total effects of D, K in a formulation as it is difficult to identify that the changes are due to diffusivity or partitioning. It should also be noted that the skin is a heterogeneous membrane and hence a variety of simplifying assumptions have been made in the derivation of the above equation.

When equation 3 is substituted into equation 2 will give

$$J = k_p C \qquad \text{(Eq 4)}$$

The lag time is obtained by extrapolating the steady-state portion of the cumulative penetration curve to the time axis (Figure 10) where drug release = 0.

The above describes that the rate-limiting step of permeation process is partition control. The main barrier is SC and the Q/t plot is linear.

If the rate-limiting step is in the formulation, the drug diffusion through the patch to the interphase is the slowest step. This is called diffusion control. The rate of drug release from diffusion control is defined by Higuchi's equation. (47-48).

In solution matrices, the concentration levels of the drug are at or below saturation levels, whereas in dispersion matrices the drug levels are far in excess of its saturated concentration. For a solution matrix, the release rates at any given time are given by Eq. 5 (49).

$$\frac{dQ}{dt} = 2C_o\left(\frac{D_p}{\pi\, l^2 t}\right)^{1/2} \qquad \text{Eq. 5}$$

At the steady state, a Q versus $t^{1/2}$ drug release profile is obtained as defined by Eq. 6.

$$\frac{Q}{t^{1/2}} = 4C_o\left(\frac{D_p}{\pi\, l^2}\right)^{1/2} \qquad \text{Eq. 6}$$

where C_o is the drug loading dose, l is the thickness of the matrix.

In the case of dispersion matrix, this case differs from the previous one in that initially the matrix is saturated with dissolved solute, with some excess solute dispersed uniformly as small particles. Under conditions when solute diffusion in the matrix is the controlling mechanism, it has been shown that the release rate at any

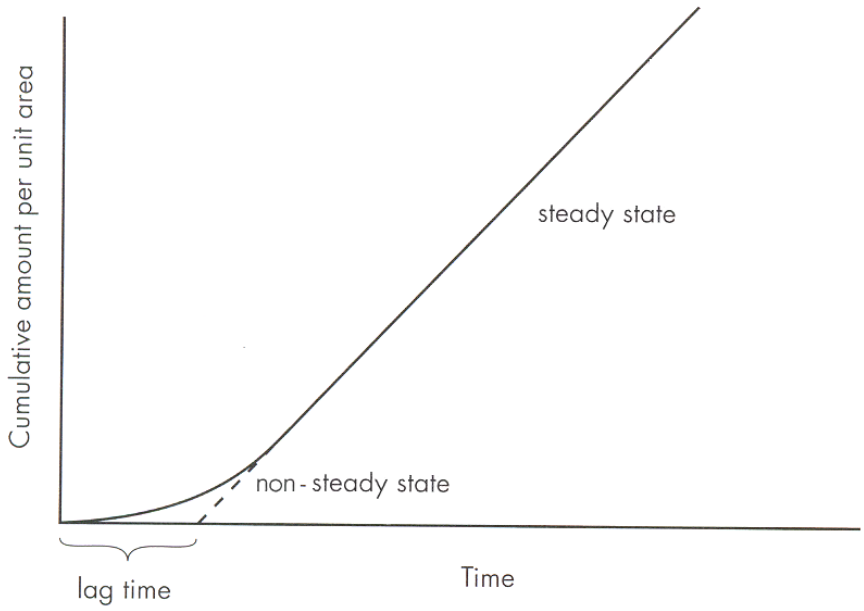


Figure 10. The permeation profile (amount of drug permeated through skin as a function of time) (4).

time (t) is given by Eq. 7

$$\frac{dQ}{dt} = \left(\frac{C_o C_p D_p}{2t} \right)^{1/2} \quad \text{Eq. 7}$$

At steady state, a Q versus $t^{1/2}$ drug release profile is obtained as Eq. 8.

$$\frac{Q}{t^{1/2}} = \left[(2C_o - C_p) C_p D_p \right]^{1/2} \quad \text{Eq. 8}$$

where C_p is a solubility of the drug in the polymer matrix, D_p is a diffusivity of the drug in the polymer matrix.

The rate of drug release from matrix devices falls off with time, as the drug in the drug in the skin-contacting side of the matrix is depleted.

Release of a drug from the TDDS through the skin can follow either a partition control or a matrix diffusion control depending on the permeation profile at steady state. If diffusion of the drug through the matrix is slower than partition of the drug through the skin, the permeation profile of $Q/t^{1/2}$ is linear. In addition, if partition of the drug through the skin is slower than diffusion of the drug through the matrix, the permeation profile of Q/t plot is linear (50).

4. Pressure-sensitive adhesive (PSA)

Pressure-sensitive adhesive (PSA) have been used for decades in medical devices, tapes and dressing. Their characteristics make them ideal for use as TDDS. Most TDDS require PSA to maintain an intimate contact between the devices and the skin surface. In general, PSA 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. They also do not require water/solvents or heat in order to achieve adhesion and their stability are good since PSA are not sensitive to environmental humidity or temperature degradation. Furthermore, the drug release from polymer is an important parameter for the selection of polymer adhesive because using different polymers can control different drug release. PSAs used in currently available TDDS are listed in Table 2. There are three classes of PSA commonly used

in TDDS. They are polyacrylate copolymer (acrylics), polyisobutylene (PIBs) and polysiloxanes (silicones) (10-13, 51-52).

4.1 Acrylic PSA

Acrylics are made by the copolymerization of acrylic esters with acrylic acid that produce a polymer with a saturated hydrocarbon backbone. Acrylic esters that contain four or more carbon atoms in the esterified alcohol group are specially suited for use as PSA. As these acrylic polymers are saturated polymers, they are resistant to oxidation and do not require stabilizers. In addition to their favorable biocompatibility and good skin adhesion property, acrylic PSA provide the advantages of good compatibility with a wide range of drugs and excipients, ease of processing, and flexibility in tailoring the polymer properties. Modification of the adhesive properties is achieved by copolymerization or cross-linking.

4.2 Polyisobutylene PSA

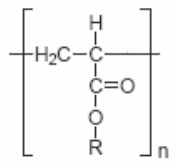
PIBs are homopolymers of isobutylene with a long, straight hydrocarbon chain and a terminal unsaturation. They are available in a wide range of molecular weights. The low molecular weight polyisobutylenes are soft, tacky and white semisolids. The high molecular weight polyisobutylenes are used as high strength backbone polymers in PSA. PIBs are used by varying the concentration of the low and high molecular weights. PIBs resist the effects of weathering, aging, or heat. The lack of polarity of these tacky polymers results in weak adhesion to substrates. This weak adhesion has been overcome by the addition of resins and tackifiers, which impart a certain degree of polarity to these polymers. Other additives such as waxes, oils, solvents, and other polymers may be added as plasticizers to modify the tack and cohesive strength.

4.3 Silicone PSA

Silicones are prepared by the reaction of a linear polydimethylsiloxane fluid with a solvent-soluble and a low molecular weight silicate resin. The linear polydimethylsiloxane possesses a backbone of alternating silicon and oxygen bonds, and is terminated by silanol groups. The silanol groups in polydimethylsiloxane and silicate resin condense to form a stable siloxane bond. Each silicon atom is attached

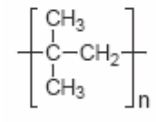
Table 2. Pressure-sensitive adhesives used in TDDS (23).

Transdermal Device	Drug	Adhesive Type
Nitro-Dur II®	Nitroglycerin	Acrylic
Nitroderm TTS®	Nitroglycerin	Silicone
Transderm-Nitro®	Nitroglycerin	Silicone
Deponit-5®	Nitroglycerin	PIB
Minitran®	Nitroglycerin	Acrylic
Kimite-patch®	Scopolamine	PIB
Frandol Tape®	Isosorbide dinitrate	Acrylic
Catapress TTS-1	Clonidine	PIB

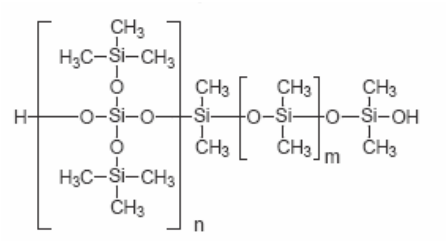


R = H, ethyl, butyl and 2-ethylhexyl

(a)



(b)



(c)

Figure 11. (a) Acrylic PSA structure (10).

(b) PIB PSA structure (10).

(c) Silicone PSA structure (10).

to two methyl groups. These adhesives have a very low glass transition temperature and hence possess a high degree of flexibility. They are capable of adhesion to both high and low energy surfaces, and do not require stabilizers. The flexibility of silicone PSAs offers formulators a variety of alternatives that can be chemically tailored during the formulation process or physically modified during the coating process to meet the individual requirements of different transdermal devices.

PSA's matrix is limited by its dimension and its physical application. High loading capacity polymer has benefit in increasing either amount of active drug or chemical enhancer in adhesive matrix in order to enhance permeation rate of drug. Kim et al. (53) indicated polyacrylate matrix had more loading capacity than PIB and silicone adhesive matrices and drug loading could be saturated in adhesive polymer. It can be incorporated with adjuvant such as enhancers and plasticizers in order to enhance the permeation rate o f drug and improve physical properties of matrix film. Moreover, it is usually less irritating than silicone adhesives, and is available in porous grades that are air and water vapor permeable (40, 54). Many studies have shown the release rate of drug from acrylic is better than PIB and silicone. Roy et al. found that the release rate of fentanyl from the acrylic adhesive was about 2-3 times higher than the silicone and PIB (55). Therefore, acrylic adhesive is a suitable carrier to deliver drug through skin and should be used for developing the PSA matrix system (10-12, 54).

Because PSA is appealing adhesives, many researches have been studied on the release rate of drugs on different types of PSAs. Park et al. studied the effects of the adhesives (Duro-Tak® D-2516, Duro-Tak® D-2287, Duro-Tak® D-2510, Duro-Tak® D-4098 and Gelva® G-737, Gelva® G-788) and enhancers (dimethyl sulfoxide, N-Methyl-2-pyrrolidone, oleic acid, Transcutol, propylene glycol, polysorbate 20, oleyl alcohol, lauryl alcohol) on skin permeation of captopril. Duro-Tak® 87-2287 resulted in the highest skin permeation rate, while Duro-Tak® 87-4098 showed the lowest permeation rate. Propylene glycol, oleyl alcohol and lauryl alcohol resulted in a pronounced enhancing effect on the skin permeation of captopril, while dimethyl sulfoxide, N-methyl-2-pyrrolidone, oleic acid, Transcutol, and polysorbate 20 showed no significant enhancing effect (56). Kim J.H. investigated the effects of various vehicles on the percutaneous absorption of tacrine in solution formulation and in PSA

matrix across the hairless mouse skin. The permeation profiles of tacrine from solutions were different depending on vehicles used. The flux of tacrine increased significantly as its concentration in the solutions increased. The permeation rate of tacrine was higher in acrylic adhesives with hydroxyl functional group and without functional group than in polyisobutylene adhesive matrix. The maximum flux obtained from PSA matrix seemed to be high enough to obtain therapeutic effect (53). Gwak and Chun investigated the feasibility of developing a new tenoxicam plaster; the effects of vehicles, penetration enhancers and solubilizer on the in vitro permeation of tenoxicam from several PSA matrices (Duro-Tak® 87-2510, Duro-Tak® 87-2100, Duro-Tak® 87-2196) were studied. Among PSA used, Duro-Tak® 87-2510 showed much higher release rate than either Duro-Tak® 87-2100 or Duro-Tak® 87-2196. The relatively high flux rate was obtained with the combination of diethylene glycol monoethyl ether (DGME) - propylene glycol monolaurate (PGML) (40:60 v/v) as vehicle with 3% oleic acid (OA) as enhancer and 5% tromethamine (TM) as solubilizer and a Duro-Tak® 87-2510 (57).

5. Adhesive properties of PSA (9-14)

Adhesive is an important component in transdermal patches, so its properties should be studied. The properties of a good adhesive are that the adhesive must remain in intimate contact with the skin to ensure an effective drug delivery. Peel, tack and shear strength (creep resistance) are basic adhesive properties. Peel adhesion is the force required to peel away a strip of tape from a rigid surface. Tack could be defined as the property that enables an adhesive to form a bond with the surface of another material upon a brief contact under light pressure. Shear strength is the measurement of the cohesive strength of an adhesive polymer (58). In general, the following three types of tests can be used to confirm the tack and peel properties.

5.1 Peel adhesion 180^{o} test

Peel adhesion is measured by determining the force per unit width required to break the bond between the transdermal patch adhesive and steel plate. The transdermal patch sample is peeled back at 180° from the steel plate at standard rate 30 cm/min, under ambient conditions. The testing procedure involves the use of a

tensilometer tester. Adhesion is an attraction force between two difference materials, which are an adhesive and steel plate in this case. The steel plate is used in a place of the skin. Adhesive failure is needed as the patch is peeled, and any part of the patch (the adhesive) will not be left on the steel plate, which represents the skin. In contrast, cohesive failure is not preferred. Cohesion is an intermolecular force binding the molecules within the adhesive. If cohesion is destroyed when peeling the patch from the steel plate, some part of the adhesive may be left on the steel plate, which is not desired.

5.2 Tack rolling ball test

The tack is measured by rolling of the stainless steel ball (7/16 inch) on inclined track (slope, 22.5˚) to come into contact at the bottom with horizontal upward-facing adhesive tape. The distance the ball traveled out along the tape is taken as the measure of tack. The distance the ball rolled gave an inverse compressed scale of tack; the greater the distance, the less tacky the adhesive, but not in proportion to the ratio of distance.

5.3 Thumb tack test

The test is the most simple and straightforward test for evaluation of the adhesive skin bonding. The adhesive skin bonding is measured by vary the pressure and time of contact and evaluate the difficulty in pulling the thumb from the adhesive. This method is possible to perceive how easily, quickly, and strongly the adhesive can form a bond with the skin.

Minghetti *et al*. evaluated adhesive properties of patches by measuring the thumb tack test, the tack rolling ball test, and the peel adhesion 180º tests. Peel used to find a suitable adherent to substitute a stainless steel since stainless steel is not suitable to perform the quality control test of the prepared patches. Therefore five alternative materials (rubber, polysiloxane, polyethylene, nylon, polyvinyl chloride) are selected with the aim of finding a more suitable adherent. The patches are prepared using five different mixtures of acrylic copolymer (hydrophilic adhesive copolymer and a hydrophobic nonadhesive copolymer) as matrices. The good results were obtained using the polyethylene plate as an adherent. The tack rolling ball test

does not seem suitable for patches made of acrylic copolymer because the results are influenced by very small variations in operative conditions (temperature, relative humidity, sample preparation, ball push). Thumb tack test is subjective, but useful in development studies since it is the only one indicative of the adhesive skin bonding. Based on these three tests, Minghetti et al. concluded that the peel adhesion 180º tests are the most reliable among those considered (14).

6. Ketoprofen

Ketoprofen, 2-(3-benzoylphenyl) propionic acid, is a potent non-steroidal anti-inflammatory drug (NSAID). The molecular weight of ketoprofen is 254.29 with the empirical formula ($C_{16}H_{14}O_3$). The chemical structure is shown Figure 11. Ketoprofen possess a chiral center but normally used as the racemate (S- and R- enantiomers). The active s-enantiomer is an effective enantiomer for anti-inflammatory of arthritis. Ketoprofen has a carboxylic group, therefore the pK_a will be an important determinant in ionization and hence permeation. For a range of carboxylic acid, experimental values of pK_a in the mixed solvent (by potentiometry at 25°) were linearly related to literature pK_a values determined in water. A derived equation was used to convert the experimental pK_a of 7.84 for ketoprofen in aqueous dimethyl sulphoxide (20:80 w/w) to a pK_a of 4.45 in water (59). The pK_a affects skin permeability because the skin permeability of a drug increases with the increase in the unionized fraction. Melting point of ketoprofen is 93°-96° (59-60). Its partition coefficient (log P) in buffer pH 7.4 is 0.97 (60) and calculated log P 2.81 (61)

Ketoprofen are stable at room temperature when it is protected from light and moisture. Exposure of aqueous solutions of ketoprofen (as the sodium salt) to ultraviolet light at 254 nm or daylight, for one hour at room temperature, was reported to yield (3-benzoylphenyl) ethanol and (3-benzoylphenyl) ethanone. Sample that was protected from light showed negligible decomposition over 24 months (59-61).
Ketoprofen shows potent inhibitory effects on prostaglandin synthesis by inhibition of both cyclooxygenase and lipoxygenase. Ketoprofen is used in the musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and in mild to moderate pain (15).

The pharmacokinetic parameters for ketoprofen after the first and last doses

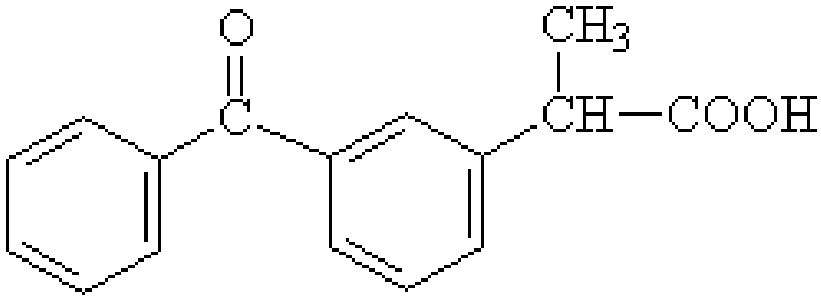


Figure 12. Structure of Ketoprofen (15).

are summarized in Table 3. No statistically significant differences in the pharmacokinetic parameters were noted between single and multiple doses for extended-release ketoprofen, suggesting that there was no accumulation after multiple doses (62). The absolute bioavailability of ketoprofen is $\geq$ 92%. Ketoprofen is extensively (> 95%) bound to plasma albumin. Its volume of distribution (V_d) is 0.1 to 0.2 L/kg. In synovial fluid, which is the proposed primary site of action for NSAID in rheumatoid arthritis, concentration of ketoprofen has been found. Ketoprofen accumulate in synovial fluid, but not in plasma, following repeated doses. It has a synovial fluid than in plasma. The disposition of ketoprofen in synovial fluid does not appear to be stereoselective (16). For patients with rheumatoid arthritis, efficacy of ketoprofen is shown by improvement in physician and patient's global assessments (62).

Ketoprofen is rapidly and almost completely absorbed, with peak concentration occurring between 0.5 and 2 hours when given orally. The usual dosage for inflammatory condition is 150 to 300 mg daily. The dose is divided to 3-4 times a day due to the short terminal phase half-life of ketoprofen (1.5-4 hr) (16). For children older than 12 years and adults who suffer rheumatoid arthritis or osteoarthritis, the dosage is 50-75 mg 3-4 times/day up to maximum of 300 mg/day. For mild to moderate pain the dose is 25-50 mg every 6-8 hr up to a maximum of 300 mg/day (15).

Oral therapy of ketoprofen is very effective, but the clinical use is often limited because of the adverse effects such as vomiting, irritation and ulceration of the gastrointestine. More recently, topical formulations have been developed for the treatment of acute minor musculoskeletal injuries, sprains, and strains (63-65). The 2.5% w/w ketoprofen gel is able to reduce pain of the soft-tissue injury (63). The 1% ketoprofen gel (Pluronic F-27) is also effective against the inflammatory response of paw edema in rats (65). Thus, the topical preparations offer several advantages consisting of rapid penetration, significantly greater elimination half-life (17 to 27 hr), high joint tissue/the plasma concentration ratios (resulting in a prolonged local therapeutic effect) and avoidance of undesirable systemic side effect. Topical preparation is effective and safe, and is accepted by the patient (63-64).

Table 3. Pharmacokinetic profiles of extended-release ketoprofen (62).

Pharmacokinetic variable	Ketoprofen	
	Single dose (n = 15)	Steady state (n = 7)
C_{max} (μg/ml)	4.1 ± 1.2	3.1 ± 1.1
T_{max} (hr)	9.7 ±2.5	8.0 ± 3.1
$T_{1/2}$ (hr)	7.1 ± 3.6	7.4 ± 2.6
AUC (μg·hr/ml)	52 ± 13	47 ± 8
Cl/F (L/hr)	4.0 ± 1.1	4.3 ± 0.6

CHAPTER 4
MATERIALS AND METHODS

MATERIALS

1. Ketoprofen (L.B.S and Laboratory Limited Partner)
2. Duro-Tak® 87-2516 (Batch no. EKY-186, Nation Starch&Chemical, USA)
3. Duro-Tak® 87-2852 (Batch no. BAD-33, Nation Starch&Chemical, USA)
4. Duro-Tak® 87-4098 (Batch no. HBD-11, Nation Starch&Chemical, USA)
5. Panasate 800 (Nihon Yushi, Japan)
6. Ethanol (Merck, Germany)
7. Acetonitrile (Scharlau, Barcelona, Spain)
8. Methanol (Scharlau, Barcelona, Spain)
9. Sterile water for injection (General Hospital Products, Thailand)
10. Disodium hydrogen phosphate dodecahydrate (Carlo Erba, Italy)
11. Sodium dihydrogen phosphate (Carlo Erba, Italy)
12. Sodium chloride (S. Tong Chemicals, Thailand)
13. Potassium monophosphate (Carlo Erba, Italy)
14. Cellulose acetate membrane filter, 0.45 μm (Sartorius, Germany)
15. Cidex (Johnson & Johnson Medical, Thailand)
16. Formaldehyde (Lab-scan, Ireland)
17. Human skin

EQUIPMENTS

1. Rotary evaporator (Model A3S, Tokyo Rikakikai Co.Ltd., Japan)
2. High performance liquid chromatograph (Shimadzu, Japan)
3. Column (Column HiQ Sil C18, KYA Technologies, Japan)

4. Single beam spectrophotometer (Spectronic 601, Milton Roy, USA)
5. Analytical balance (AA-200 DS, Denver Instrument, USA)
6. Franz diffusion cells (Tailor-made, glass, BecThai)
7. Ultrasonic bath (Thermomix-1440, Germany)
8. pH meter (SA 502 pH meter, Orion, USA)
9. Centrifuge (Hettich Universal 30F, Germany)
10. Stirrer (Model RW 20, IKA-Labortechnik, Germany)
11. Autopipett (Gilson Medical Electronics, France)
12. Tensilometer (Model 0172071, Hounsfield, USA)
13. Tack Rolling Ball (Neoplast Co., Ltd., Thailand)
14. Lab coater (Mathis, German)

METHODS

1. Solubility Determination

Excess amount of ketoprofen is added to the 50:50% w/w EtOH:Panasate 800 in screw-capped vials. The contents are stirred by an externally driven teflon coated magnetic bar at 32±1 ºC until equilibrium was obtained, i.e., for 24 hours. The saturated solution was centrifuged at 5000 rpm with the radius of 7 cm for 10 minutes. Ketoprofen was analysed by UV spectrophotometry at 255 nm.

2. Preparation of Ketoprofen Transdermal Patches

Appropriate amount of ketoprofen was used to obtain final concentration of 10% w/w in patch. Ketoprofen was dissolved in 50:50% w/w EtOH:Panasate 800. The mixture was added to the PSA solution and stirred until uniform. The uniform mixture was rapidly centrifuged at 3000 rpm with the radius of 7 cm for 10 minutes to remove air bubbles. The clear mixture was casted onto backing membrane with 0.05 mm using a casting knife (66). The cast was set at room temperature for 10 minutes and subsequently oven-dried at 90ºC for 15 minutes using a Lab coater in order to remove the residual organic solvents. The patches were covered with a silicone-coated polyester protective release liner (Appendix K).

The permeation rates of transdermal patches were determined to investigate the effects of different kinds of adhesives and concentrations as follows:

2.1 Effects of class of PSA

Transdermal patches were prepared in DIA design using different three class of acrylic adhesive. They were Duro-Tak® 87-2516, Duro-Tak® 87-2852 and Duro-Tak® 87-4098.

2.2 Effects of PSA concentration

Transdermal patches in 50:50% w/w of EtOH:Panasate 800 were prepared by using 30%, 40% and 50% w/w of acrylic adhesive in formulation.

3. The *in vitro* Skin Permeation of Ketoprofen Transdermal Patches

3.1 Skin permeation study

Human skin was used for the permeation study. Human epidermal membrane was prepared by the heat separation technique. Epidermal layer was separated from the split-thickness skin by immersing each skin section in water at 60ºC for 2 minutes, then the epidermis separated from the dermis using a forceps. The epidermis was wrapped in aluminum foil and stored at –20ºC until use (68).

The drug permeation from ketoprofen patch was studied using Franz-diffusion cells. The epidermis was mounted on diffusion cells with the dermal side facing downwards into the phosphate buffer saline at pH 7.4 at 37 ºC. The ketoprofen patch was placed in intimate contact with the stratum corneum side of the epidermis. The cells were maintained at 37 ^{o}C. A sample of 0.5 ml was removed and it was replaced with a fresh phosphate buffer. Ketoprofen concentration in the sample was analyzed by HPLC with UV detector.

3.2 Calculation of permeation parameters

The skin permeation rate was determined from the slope of the plot between the cumulative amount of permeation per unit area (μg/cm^2) and time. The rate of

skin permeation (flux) was the slope of the plot. Flux was obtained from Fick's law (Eq.1).

$$\frac{dQ}{dt} = \frac{DKC_o A}{L}$$

Lag time (T_L) was calculated from the intercept.

$$T_L = \frac{L^2}{6D} \qquad \text{Eq. 9}$$

where Q was the cumulative amount of ketoprofen (μg), t was the time (hr), D was the diffusion coefficient (cm^2/hr), K was the partition coefficient, C_o was the concentration in donor phase (μg/mL), A was the area (cm^2) through which the permeation of the drug takes place, T_L was the lag time (hr), and L was the diffusional path length.

4. Evaluation of the Patch Properties

The patch properties were evaluated as follows.

4.1 Adhesive properties

The adhesive properties could be determined by the following test. The method was performed in five replications.

4.1.1 Peel adhesive 180° test (Figure 14)

The patches were cut into strips of 1 centimeter wide. The strips were laid on stainless steel plate, and then smoothed with 2 kg roller for two rounds. The strips were pulled from the plate at a 180º angle with a rate of 30 cm/min. The matrix had to be striped cleanly from the plate, and left no visually noticeable residue. The force that was used to pull the strips was expressed in Newton (N) per width of the patch (N/cm). Peel adhesive values were the average from five determinations.

4.1.2 Tack rolling ball test (Figure 15)

Adhesive patches were cut into strips. A horizontal upward-facing adhesive was placed at the bottom of the track. A stainless steel ball was rolled down an inclined track (21°, 30'). The distance that the ball travels on the strip gave an

inverse compressed scale of tack. The greater the distance was, the less tacky the adhesive will be. There was no direct proportion between the distance travel and the tack scale. In this study, the distance travel was taken as the tack value. When the distance of the rolling of the ball on the adhesive tape was greater than 15 cm, the tack value was considered to be zero.

4.1.3 Thumb tack test

A sample was pressed lightly by a thumb for a short time and then withdrawn. The score of how easily, quickly and strongly the adhesive attaches to the skin, was determined by the investigators. They would compare the difficulty of pulling the thumb from the patch by the score value between 1 and 3 that showed by (+) level. (+) as poor adhesion, (++) as fairly good adhesion and (+++) as good adhesion. The higher value means the adhesive was strongly attached.

4.2 Content uniformity of ketoprofen patch

The patch was randomly cut in rectangular 1 cm^2 size and accurately weighed. The sample was dissolved in 50 ml of 95% ethanol. Then it was sonicated in ultrasonic bath. The concentration of drug is determined by UV spectrophotometer at 255 nm. The method was performed in ten of replications and evaluated.

4.3 Evaluation of film thickness

The film thickness of patch was measured using a micrometer. The results were the average of 20 pieces determination.

5. Analytical Method

5.1 UV spectrophotometry

A 0.2 mg/ml of ketoprofen in 95% ethanol was used as a stock solution. It was appropriately diluted by 95% ethanol to the concentration in the range of 2.0-10.0 μg/ml.

The standard solutions were analyzed by UV spectrophotometer at the wavelength of 255 nm, using 95% ethanol as the blank. The absorbance and the

corresponding concentration of the ketoprofen standard solution were plotted and analyzed by linear regression.

5.2 High performance liquid chromatography

A 0.2 mg/ml of ketoprofen in 95% ethanol was used as a stock solution. It was appropriately diluted by phosphate buffer saline to the concentration in the range of 1.0-5.0 μg/ml. Their peaks areas were plotted in the standard curve and the various concentrations of ketoprofen in phosphate buffer saline.

The sample from *in vitro* permeation was centrifuged at 5000 rpm for 15 minutes in order to eliminate particles. The sample was diluted by phosphate buffer saline and analyzed by HPLC method. The HPLC system used is the following condition:

Column **:** HiQ Sil C18 (4.6mmI.D. x 250mmL)
Mobile Phase **:** 35% acetronitrile in phosphate buffer
Flow rate **:** 1.0 ml/min
Detector **:** UV detector is set at 265 nm.
Injection volume **:** 20 μl

Figure 13. A tensilometer used in peel adhesion 180° test

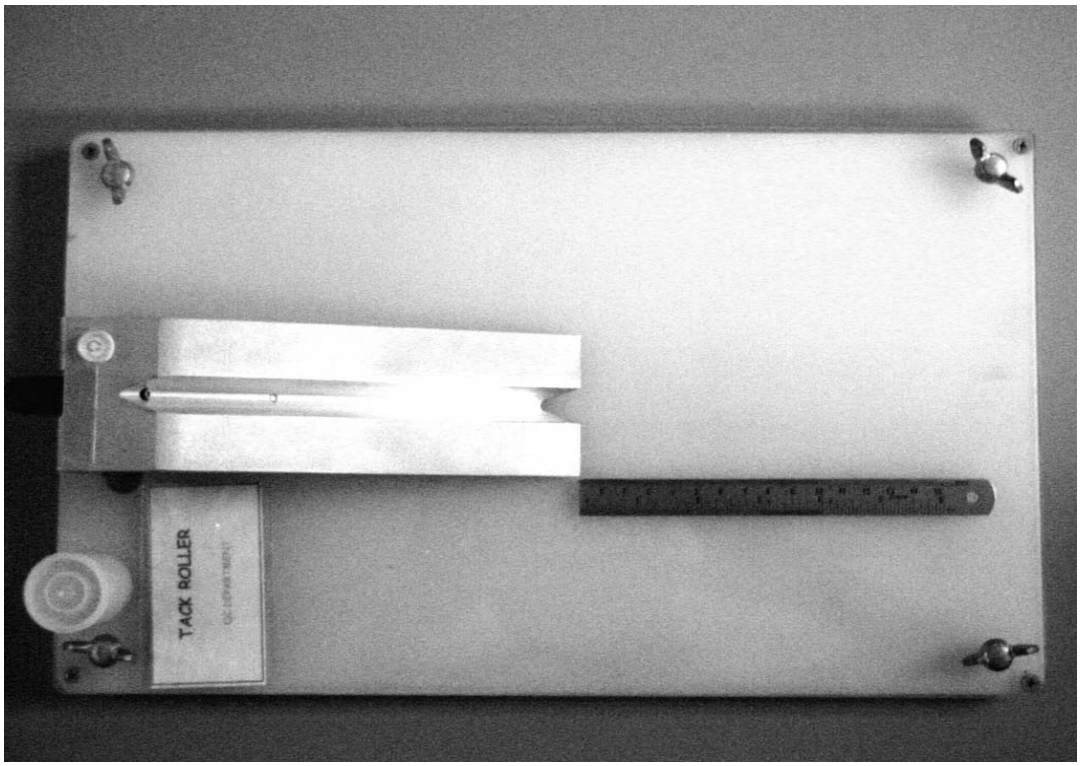


Figure 14. Equipment used in tack rolling ball test

Figure 15. Lab coater.

CHAPTER 5
RESULTS AND DISCUSSION

1. Quantitative analysis of ketoprofen

1.1 UV-spectrophotometry

The concentration of ketoprofen was determined using UV-spectrophotometer at wavelength 255 nm. Figure 17 showed the linear relationship between the absorbance and the concentration of ketoprofen in EtOH. The standard concentrations were 2.0-10.0 μg/ml. The linear regression was obtained from the standard curve of the absorbance (y) and the concentration (x), with the coefficient of determination (R^2) of 0.9997.

1.2 High performance liquid chromatography (HPLC)

HPLC was the method for determination of ketoprofen concentrations in the samples withdrawn from the receptor phases. The receptor phase used is PBS. The chromatographic condition used clearly separated ketoprofen peak from the other peak represented in the chromatograms. The standard curve was obtained by plotting the peak areas of ketoprofen versus the concentrations of ketoprofen. The standard concentrations were ranged from 1.0 to 5.0 μg/ml. The linearity of the standard curve was obtained by using linear regression analysis (Figure 18). The linear relationship of the standard curve was obtained with the R^2 of 1. Figure 19(a) and 19(b) showed the chromatograms of ketoprofen analysis from the standard solution and from the sample, respectively. The retention time of ketoprofen peak from the standard solution was 3.359 minutes and from the sample was 3.330 minutes, respectively.

2. Solubility of ketoprofen in mixture EtOH-Panasate 800

When a drug is at its solubility, skin permeation will show the highest flux. The reason is that the concentration gradient is highest at solubility.

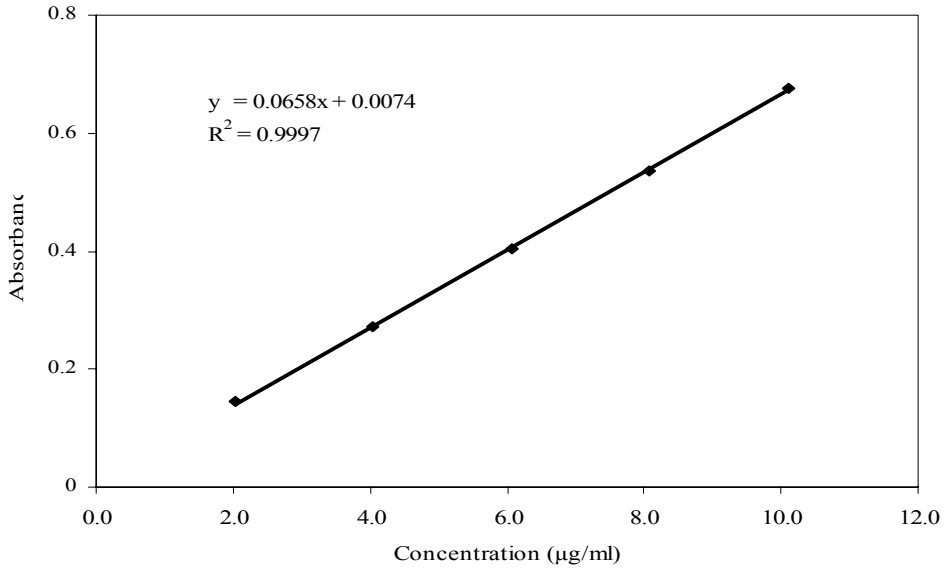


Figure 16. Standard curve of Ketoprofen in ethanol at 255 nm by UV spectrophotometry

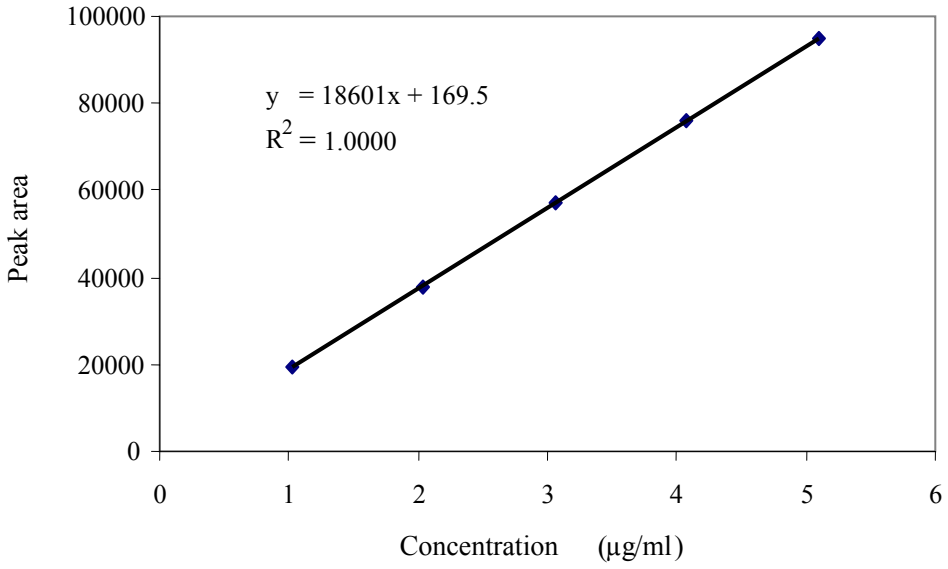
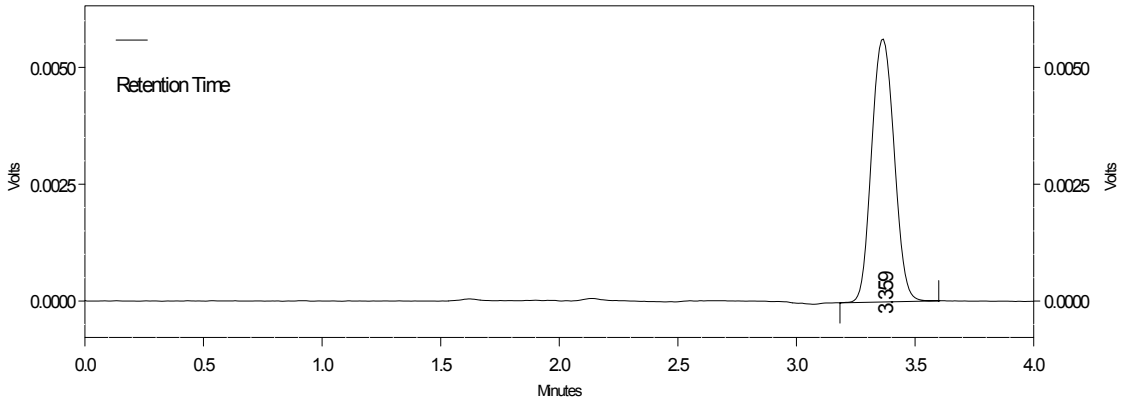
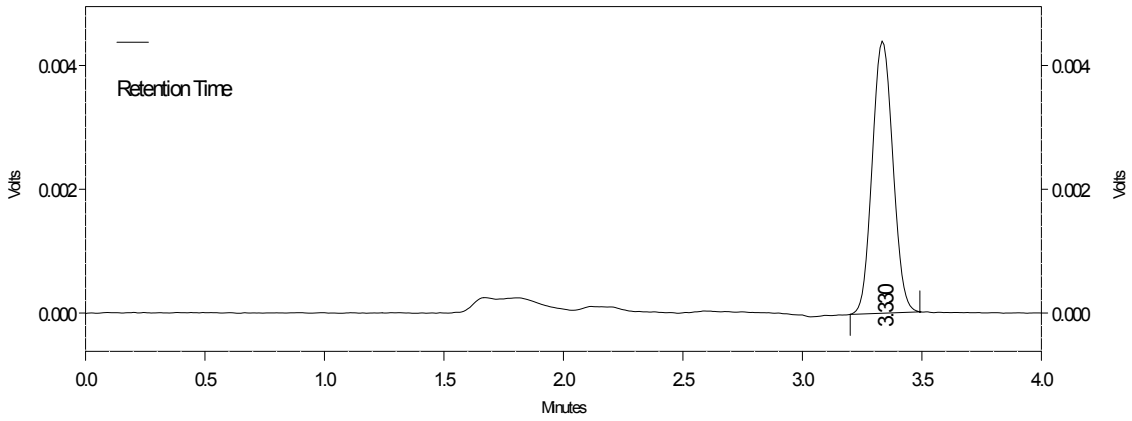


Figure 17. Standard curve of Ketoprofen in PBS by HPLC



(a)



(b)

Figure 18. (a) HPLC chromatogram of Ketoprofen from the standard solution
(b) HPLC chromatogram of Ketoprofen from the receptor phase

Furthermore, at solubility, the thermodynamic activity of a drug in the formulation will be the highest value, i.e. the drug is ready to move out of the patch as quickly as it can, and this increases the permeation rate. Many studies indicated the enhancing effect of mixture of EtOH and Panasate 800. EtOH increases the permeation by extracting intercellular lipid in the SC and reduces barrier function of the SC, resulting in increasing amount of drug through the skin (69). Panasate 800 reduces the lag time by increasing the diffusion of the drugs in the SC and viable skin (70-73). Kim DD et al. (74-75) showed the optimum fraction of EtOH and Panasate 800 for dideoxynucleoside-type. Permeation rates of these drugs reached a maximum at 50:50% v/v of EtOH:Panasate 800. This study used the mixture of EtOH:Panasate 800 in 50:50% w/w for accuracy of measurement. Acrylic adhesive used is a high viscosity solution, thus volumetry is inaccurate, so weighing is suitable for measuring its amount. In addition, EtOH will evaporate from the adhesive patch when placed in the Lab coater. To control the final quality of the patch, the weight of the patch was controlled after the evaporation such that the constant weight was obtained after a certain evaporation time. Therefore, the preparation processes preferred by-weight measuring. Tungjitlikitskul S. showed that the optimum fluxes are obtained from the formula containing the fractions of EtOH and Panasate 800 between 40:60%w/w, and 60:40% w/w when investigation was performed in 0-100% w/w of the fraction (76). The 50:50% w/w was the ratio in the middle of the range, thus it should give the maximum flux. The solubility of ketoprofen in the mixture of EtOH and Panasate 800 (50:50% w/w) is 39.7% w/v (397 ± 7.60 mg/ml, n = 3). *In vitro* permeation was studied by Franz diffusion cell. During the experiment, back diffusion of water molecule from aqueous receptor phase to donor phase could occur. When ketoprofen was in the donor phase at solubility, ketoprofen can precipitate in this situation. Therefore, 80% solubility of the ketoprofen was chosen to prevent this problem, and at the same time to keep the value of thermodynamic activity close to maximum (43, 77). Then, the highest flux at solubility could be calculated. The 80% solubility of ketoprofen was 31.7% w/v and can be converted to 33.5% w/w (Appendix A).

3. *In vitro* permeation study

The permeation of ketoprofen through skin was investigated by Franz

diffusion cell. The collection of samples from R1, R2, R3 and R4 were performed up to 18 hr. The concentration of ketoprofen in the PBS was determined by HPLC method with UV detector at 265 nm. The permeability parameters e.g. lag time, flux, and k_p of ketoprofen from R1-R4 were shown in Table 4 and the graphs of the permeation were illustrated in Figure 20-23. R1 was the formula at 80% solubility of ketoprofen. The flux from this formula was 362.63 μg/cm^2/hr and lag time was 2.48 hr. The calculated highest flux (at solubility) was 453.29 μg/cm^2/hr. This flux was higher than the theoretically calculated flux, 346.5 μg/cm^2/hr (Appendix C). During distribution within the market, the drug at solubility can precipitate before reaching the patient. Therefore, the drug concentration can be lowered to below solubility , but still aim to the theoretical calculated flux. Cho YJ et al. (67) showed the k_p can be lowered as the concentration increased. This occurred due to the fact that diffusion coefficient is a function of concentration. At high concentration, diffusion coefficient was decreased. Thus although the drug concentration was decreased, the k_p may increase. The flux of formulation R1 was higher than R2 ($p<0.05$). However when the k_p's were compared, R2 (2.80 x 10^{-3} cm/hr) was higher than R1 (1.14 x 10^{-3} cm/hr) with $p<0.05$ although the concentration of R1 was more than R2 about 3 times. This result was similar to the result of Cho YJ. The enhancing effect of Panasate 800 was assured by comparing the skin permeation of formulation R2 and R3. Table 4 showed that the concentration of ketoprofen in 50:50% w/w EtOH:Panasate 800 (R2) was 10.08% w/w and that in EtOH (R3) was 10.11% w/w. The k_p's of R2 and R3 were 2.80 x 10^{-3} and 1.44 x 10^{-3} cm/hr, respectively. They were significantly different ($p<0.05$). The lag time from R2 (3.89 hr) was significantly lower than R3 (6.76 hr) ($p<0.05$). These results indicated that enhancing effect of Panasate 800 was promoted by the decrease in the lag time. Previous reports had shown that Panasate 800 in EtOH binary system was effective in decreasing the lag time and increasing the flux *in vitro* permeability of ketoprofen, ibuprofen, alcofenac and theophylline (11, 37, 63-66). Goto et al. (11) showed that the best formulation was 60% v/v Panasate 800 in combination with EtOH and it gave the peak *in vitro* flux of ketoprofen at 313.9 μg/cm^2/hr using hairless mouse skin. The lag time for EtOH/Panasate 800 (3.7 hr) was shorter than 100% EtOH (8.1 hr) due to the enhancing effect of Panasate 800 since it increased the effective diffusion of the drug in SC. Jaeckle E et al. studied the

effects of different ointments based on the penetration of ketoprofen through human epidermis and artificial lipid barriers. The permeability of skin pretreated with triglycerides (Witepsol® H5) showed the highest k_p, followed by the untreated, the pretreated with petrolatum and wool alcohols ointments respectively. The same order of k_p were shown for both of human epidermis and artificial lipid barriers. This highest k_p and flux through human epidermis was 1.71 x 10^{-2} cm/hr and 1.71 μg/cm^2/hr (78). Microemulsion was investigated because microemulsion presented many advantages, i.e. tiny droplet size, storage stability, low preparation cost, and the absence of organic solvents. Paolino D et al. studied percutaneous adsorption of ketoprofen on human epidermis from topical microemulsion. Conventional formulation (w/o, o/w cream and gel) and microemulsion that contained lecithin with or without oleic acid were compared. Lecithin microemulsions significantly increased the skin permeation of ketoprofen and decrease lag time with respect to conventional formulation, due to the smaller size of the droplet in microemulsion and the solubilizing and enhancing effects of lecithin. The presence of oleic acid in the microemulsion, as an enhancer, seems to exert no significant effect on the permeation of ketoprofen. Lecithin microemulsion was the best formulation. The flux of lecithin microemulsion was 4.511 μg/cm^2/hr and k_p was 0.22 x 10^{-3} cm/hr (79). The flux and k_p of ketoprofen through human epidermis pretreated with triglycerides and lecithin microemulsion preparation were lower than the solution preparation (R2) in this study, although R2 provided the flux that was lower than the theoretical flux.

R4 is the commercial product (Profenid® gel) which was used on the skin topically for rheumatoid arthritis to exert the local effect. TDDS aims to the systemic effect. Therefore, the flux from this commercial gel (9.77 μg/cm^2/hr) was intended to show the lowest value in the limit. The concentration of ketoprofen in the commercial gel, 2.5% w/w, was equivalent to 16.5 mg/ml (Appendix B). When comparison was made between R2 and R4, it was found that the k_p from R2 (2.80 x 10^{-3} cm/hr) was higher than R4 (0.59 x 10^{-3} cm/hr) with $p<0.05$. In addition, the flux from R2 was higher than R4. Therefore, formulation R2 was the formulation that could be modified to the TDDS.

The adhesive was the essential component in TDDS but it could reduce the permeation rate of drug, so the appropriate concentration of adhesive in formulation

Table 4. Permeation parameter of Ketoprofen across human skin (R1-R4)

Formula	Composition	Concentration of ketoprofen		n	Lag time	Flux	k_p
		(% w/w)	(μg/ml) x 10^3		(hr)	(μg/cm^2/hr)	(cm/hr) x 10^{-3}
R1	EtOH:Panasate	33.50	317.0	10	2.48 ± 0.82	362.63 ±23.43	1.14 ± 0.07
R2	EtOH:Panasate	10.08	87.6	10	3.89 ± 10.10	245.35 ± 44.29	2.80 ± 0.51
R3	EtOH	10.11	81.9	11	6.76 ± 0.95	117.85 ± 22.82	1.44 ± 0.28
R4	Profenid® Gel	2.50	16.5	10	6.86 ± 0.66	9.77 ± 2.96	0.59 ± 0.18

was evaluated. Preliminary study (Appendix I) showed that the concentration of adhesives at 25% and 75% w/w did not give the satisfactory property of the patches. At 25% w/w, the patches did not attach well on the skin and ketoprofen precipitated within 24 hr. At 75% w/w, the patches were very sticky and very good attachment on skin. Thus, the concentration between 30%, 40% and 50% w/w were studied in more detail.

A, B, and C were formulation with the same mixture with R2 but the acrylic adhesives in various concentration were added. Table 5 showed the composition of each formula. Comparison of A, B, and C with R2 could indicate the effect of adhesive on permeation rate. Pressure-sensitive adhesive act as adhesive in TDDS and acrylic adhesive are the frequent choice. Three classes of acrylic adhesive was used in this study were Duro-Tak® 87-2516, Duro-Tak® 87-2852 and Duro-Tak® 87-4098. Duro-Tak® 87-2516 was an acrylate-vinylacetate self-curing pressure sensitive adhesive with OH-functional group. Duro-Tak® 87-2852 was an acrylic self-curing pressure sensitive adhesive with COOH-functional group. Duro-Tak® 87-4098 was an acrylate-vinylacetate non-curing pressure sensitive adhesive with no OH and COOH-functional group (Appendix K). The functional group with acrylic adhesive may affect to the permeation rate of drug (67, 80). Kokubo T. et al. showed that the extent of the drug-polymer interaction was greatly influenced by the polar functional groups of the PSA polymer. Two acrylic-type (2-ethylhexylacrylate and acrylic acid copolymer, 2-ethylhexylacrylate and acrylamide copolymer) were used, and dipropylphthalate, aminopyrine, ketoprofen and lidocaine were selected as model drug based on molecular weight but different functional group. PSA containing acrylic acid strongly interacted with the amide of lidocaine, amine of aminopyrine and with carboxylic acid of ketoprofen. This is shown by the effect to flux the and the lag time. PSA containing acrylamide did not interact with lidocaine or aminopyrine, although it markedly interacted with ketoprofen (80). The effect of different classes and concentration of acrylic adhesives on the *in vitro* permeation of ketoprofen was investigated by Franz cell experiment. The permeability parameters e.g. flux and lag time of ketoprofen in PBS from A, B, and C were shown in Table 6 and permeation of ketoprofen were illustrated in Figure 24-32.

When the adhesive was mixed with the drug in DIA design, the permeation of

Table 5. Composition of Ketoprofen patches.

Formula	Concentration of Ketoprofen (%w/w)	Class of acrylic adhesive	Concentration of Acrylic adhesive (%w/w)	Concentration of EtOH:Panasate (%w/w)
A1	10	Duro-Tak® 87-2516	30	60
A2	10	Duro-Tak® 87-2516	40	50
A3	10	Duro-Tak® 87-2516	50	40
B1	10	Duro-Tak® 87-2852	30	60
B2	10	Duro-Tak® 87-2852	40	50
B3	10	Duro-Tak® 87-2852	50	40
C1	10	Duro-Tak® 87-4098	30	60
C2	10	Duro-Tak® 87-4098	40	50
C3	10	Duro-Tak® 87-4098	50	40
R2	10	-	-	90

Table 6. Permeation parameter of Ketoprofen across human skin (A1-A3, B1-B3 and C1-C3)

Formula	Concentration of ketoprofen (% w/w)	n	Lag time (hr)	Flux ($\mu g/cm^2/hr$)	k_p (cm/hr) x 10^{-3}
A1	10.15	10	4.44 ± 0.70	26.11 ± 2.84	2.61 ± 0.28
A2	10.12	10	4.04 ± 1.33	21.40 ± 3.81	2.14 ± 0.038
A3	10.08	10	4.75 ± 1.35	13.95 ± 2.07	1.39 ± 0.21
B1	10.11	11	4.18 ± 1.61	25.60 ± 4.59	2.56 ± 0.46
B2	10.14	10	3.34 ± 0.59	20.38 ± 3.46	2.04 ± 0.35
B3	10.06	10	4.72 ± 1.06	13.00 ± 2.02	1.30 ± 0.20
C1	10.23	10	4.76 ± 1.03	26.01 ± 5.09	2.60 ± 0.51
C2	10.21	12	4.93 ± 2.14	19.82 ± 4.81	1.98 ± 0.48
C3	10.13	11	3.61 ± 1.71	14.18 ± 2.56	1.42 ± 0.26

Table 7. Coeffecients of determination of linear regression analyses of 10% w/w Ketoprofen patches

Formula	n	Coefficient of determination (R^2)	
		Q/t	$Q/t^{1/2}$
A1	10	0.9989 ± 0.0015	0.9924 ± 0.0035
A2	10	0.9986 ± 0.0013	0.9938 ± 0.0036
A3	10	0.9989 ± 0.0004	0.9931 ±0.0018
B1	11	0.9969 ± 0.0035	0.9922 ± 0.0085
B2	10	0.9986 ± 0.0009	0.9922 ± 0.0042
B3	10	0.9988 ± 0.0011	0.9935 ± 0.0032
C1	10	0.9997 ± 0.0003	0.9965 ± 0.0029
C2	12	0.9993 ± 0.0009	0.9972 ± 0.0026
C3	11	0.9989 ± 0.0012	0.9971 ± 0.0015

drug from the patch through the skin into blood circulation can be diffusion-controlled or partition-controlled. If the process of drug diffusion in the patch is the rate-limiting step, $Q/t^{1/2}$ plot will be linear and it is called the diffusion control. If the process of drug partition from skin through interphase is the rate-limiting step, Q/t plot will be linear and it is called the partition control. In this study, the coefficient of determination (R^2) for linear regression of each kinetic were calculated and compared, as presented in Table 7. Q/t plot shows higher coefficient of determination (R^2) than $Q/t^{1/2}$. The result indicates that all patches had the permeation patterns followed better on the Q/t plot.

3.1 Effect of different classes of acrylic adhesive

The permeation of ketoprofen from the patches containing different classes of acrylic adhesive across the human skin was studied and presented in Table 7. A1, B1 and C1 contained the same concentration (30% w/w) but different classes of acrylic adhesives. A1 provided the flux of 26.11 μg/cm^2/hr, followed by C1 (26.01 μg/cm^2/hr) and B1 (25.60 μg/cm^2/hr). The fluxes between A1, B1 and C1 were not different significantly ($p>0.05$). Comparison between A2, B2 and C2, 40% w/w of adhesive, provided the flux of 21.40 μg/cm^2/hr by A2, followed by B2 (20.38 μg/cm^2/hr), and C2 (19.82 μg/cm^2/hr). The three fluxes were not significantly different ($p<0.05$). At 50% concentration of adhesive, comparison between A3, B3 and C3, provided the flux of 14.18 μg/cm^2/hr by C3, followed by A3 (13.95 μg/cm^2/hr), and B3 (13.00 μg/cm^2/hr). The fluxes were not significantly different ($p>0.05$).

When comparison was made in lag time, A1 (4.44 hr), B1 (4.18 hr) and C1 (4.76 hr) which contained 30% adhesive, they were not significantly different ($p>0.05$). At 40% w/w of acrylic adhesive, B2 showed the lag time of 3.34 hr, followed by A2 (4.04 hr) and C2 (4.93 hr) respectively. B2 was the lowest lag time within the group. At 50% w/w of acrylic adhesive, C3 showed the lag time of 3.61 hr, followed by B3 (4.72 hr) and A3 (4.75 hr). C3 was the lowest lag time within the group.

Many studies evaluated TDDS patches with several adhesives. Kim J.H. investigated the effects of various acrylic PSA matrixes on the percutaneous

absorption of tacrine across the hairless mouse skin. The permeation rate of tacrine was higher in acrylic adhesives with hydroxyl functional group and without functional group than in carboxyl functional group due to the interaction between amine group of tacrine and carboxyl group of acrylic adhesive but lack of interaction between drug and hydroxyl and no functional group of acrylic adhesive (53). Gwak and Chun investigated the feasibility of developing a new tenoxicam plaster. The effects of several PSA matrices, OH functional group with non-crosslink (Duro-Tak® 87-2510), COOH functional group with self-crosslink (Duro-Tak® 87-2100) and COOH functional group with non-crosslink (Duro-Tak® 87-2196), on the *in vitro* permeation of tenoxicam were studied. Among PSA used, Duro-Tak® 87-2510 showed much higher release rate than either Duro-Tak® 87-2100 or Duro-Tak® 87-2196. This might be the interaction between amide group of tenoxicam and carboxyl group of Duro-Tak® 87-2100, Duro-Tak® 87-2196 (57). Kokubo T. et al. also showed the strongly interaction between carboxyl group of acrylic adhesive and the amide of lidocaine. The interaction between carboxyl group of acrylic adhesive and amine of aminopyrine and carboxylic acid of ketoprofen also occurred but with less strength. However, acrylic with amide group did not interact with lidocaine or aminopyrine, although it interacted with ketoprofen (78). From the above studies, the carboxyl group of acrylic adhesive interacted with many drugs. However, in this study, the permeation rate of ketoprofen in carboxyl acrylic adhesive (Duro-Tak® 87-2852) did not differ from the permeation rate of ketoprofen in hydroxyl adhesive (Duro-Tak® 87-2516) or no functional group adhesive (Duro-Tak® 87-4098).

3.2 Effect of different concentration of acrylic adhesive

Table 7 showed the flux and the lag time of formulae. Formulation A1, A2, and A3 contained acrylic adhesive Duro-Tak® 87-2516 with 30%, 40%, and 50% w/w respectively. Among this three formulae, A1 provided the highest flux of 26.11 $\mu g/cm^2/hr$, followed by A2 (21.40 $\mu g/cm^2/hr$) and A3 (13.95 $\mu g/cm^2/hr$). The three fluxes were significantly different ($p<0.05$). Formulation B1, B2, and B3 contained acrylic adhesive Duro-Tak® 87-2852 with 30%, 40%, and 50% w/w respectively. Among these three formulae, B1 provided the highest flux of 25.60 $\mu g/cm^2/hr$, followed by B2 (20.38 $\mu g/cm^2/hr$) and B3 (13.00 $\mu g/cm^2/hr$). They were significantly

different ($p<0.05$). For Duro-Tak® 87-4098, formulation C1, C2, and C3 contained acrylic adhesive at 30%, 40% and 50% w/w respectively. C1 provided the highest flux of 26.01 μg/cm^2/hr, followed by C2 (19.82 μg/cm^2/hr) and C3 (14.18 μg/cm^2/hr). They are significantly different with $p<0.05$). Skin permeation flux was increased when the concentration of adhesive was decreased. At 50% concentration of all classes of adhesive (A3, B3 and C3) permeation are the lowest. Because of the high concentration of acrylic adhesive used, 50%, the patch was in viscous state. The drugs diffuse at slow rate through adhesive and take more time. Therefore, permeation rate of drug was decreased.

Lag time at 30% w/w of acrylic adhesive, A1 (4.44 hr), A2 (4.04 hr) and A3 (4.75 hr) were not significantly different ($p>0.05$). At 40% w/w of adhesive, the lag time of the formulations were: B1 (4.18 hr), B2 (3.34 hr) and B3 (4.72 hr). B2 provided the lowest lag time, followed by B1 and B3. At 50% w/w of adhesive, C3 provided the lowest lag time of 3.61 hr, followed by C1 (4.76 hr) and C2 (4.93 hr). Therefore, these results could indicate the effect of concentration of adhesive on the flux but not on the lag time.

In this study, DIA design, adhesive reduced the flux from the patch around 10 times when comparison was made between the patches formulae (formulation A, B and C) and R2. However, adhesive is an important component because the patch must stick to the skin. The increase in adhesive concentration of adhesive of 10%, from 30% to 40% w/w, the flux was decreased at a lower rate than the increase of concentration of adhesive from 40% to 50% w/w. When only the flux was considered, the formulation with 30% and 40% w/w of acrylic adhesive were satisfactory in this study.

Ketoprofen had been studied using other patch design. Shailesh K et al. prepared ketoprofen patches in a reservoir design by using Carbopol® polymer, types C-934P and 940, to act as the reservoir and oleic acid as the enhancer. The results of permeation on human skin indicated a maximum flux of 7.778 μg/cm^2/hr and k_p of 0.889 x 10^{-3} cm/hr from the patches with C-934P, ethylvinyl acetate (Cotran® No. 9702) as rate-controlling membrane and oleic acid at 35% (81). The flux and k_p were compared to B3, which showed the lowest flux and k_p among the formulae in this

study. This showed that all the formulae in this study were better. Because of the permeation rate of ketoprofen from the reservoir type with Cotran® No. 9702 was the lowest, the reservoir type which used the rate-controlling membrane with higher release rate might provide the higher rate.

4. Physical properties of ketoprofen formulae

The physical properties of ketoprofen patches were investigated in terms of peel 180^{o} test, tack rolling ball test, and thumb tack test.

4.1 Peel adhesion 180^{o} test

The peel adhesion force is measured by determining the force per unit width required to break bond between the transdermal patch adhesive and a steel plate. Adhesive failure wherein the adhesive peeled cleanly from the steel plate is considered acceptable whereas cohesive failure wherein a residue of the adhesive is left on the steel plate was regarded as unacceptable. The loss of cohesive strength could perceive adhesive residue left on the skin following removal of the patch. From the peel adhesive force (Table 8), comparison between the class of adhesive at same concentration (30% w/w of acrylic adhesive), B1 showed the highest force of 0.1532 N/cm), followed by A1 (0.0522 N/cm) and C1 (0.0149 N/cm). They were significantly different ($p<0.05$). At 40% w/w of acrylic adhesive, B2 showed the highest peel force of 0.1563 N/cm, followed by A2 (0.0609 N/cm) and C2 (0.0479 N/cm). At 50% w/w, B3 showed the highest peel adhesion of (0.2991 N/cm), followed by A3 (0.1268 N/cm) and C3 (0.1130 N/cm). B3 was significantly differently from A3 and C3. The adhesive B showed the highest peel adhesion value than A and C. The effect of concentration of adhesive, Duro-Tak® 87-2516, were shown by A1, A2 and A3 which contained the adhesive with 30%, 40% and 50% w/w respectively. It could be ranked as A3 (0.1268 N/cm) > A2 (0.0609 N/cm) >A1 (0.0522 N/cm). For Duro-Tak® 87-2852, B1, B2, B3 contained 30%, 40%, and 50% w/w of adhesive respectively. B3 showed the highest peel force of 0.2991 N/cm, followed by B2 (0.1563 N/cm) and B1 (0.1532 N/cm). For Duro-Tak® 87-4098, C1, C2, C3 contained 30%, 40% and 50% w/w of adhesive respectively. C3 showed the highest peel force of 0.1130 N/cm, followed by C2 (0.0479 N/cm) and C1 (0.0149

Table 8. Peel adhesion 180˚ test of 10% w/w Ketoprofen patches (n = 5)

Formulation	Peel 180° Test (N/cm)		
	T = 0 month	T = 1 month	T = 2 month
A1	0.0522 ± 0.0015	0.0514 ± 0.0037	0.0498 ± 0.0024
A2	0.0609 ± 0.0204	0.0606 ± 0.0020	0.0559 ± 0.0033
A3	0.1268 ± 0.0041	0.1158 ± 0.0088	0.1134 ± 0.0070
B1	0.1532 ± 0.0139	0.1520 ± 0.0162	0.1492 ± 0.0188
B2	0.1563 ± 0.0276	0.1535 ± 0.0101	0.1489 ± 0.0198
B3	0.2991 ± 0.0794	0.2677 ± 0.0279	0.2005 ± 0.0458
C1	0.0149 ± 0.0035	0.0185 ± 0.0037	0.0161 ± 0.0042
C2	0.0479 ± 0.0077	0.0481 ± 0.0099	0.0456 ± 0.0093
C3	0.1130 ± 0.0251	0.1191 ± 0.0133	0.1153 ± 0.0117

N/cm). They are significantly different with $p<0.05$. This result could indicate the effect of concentration of adhesive in formulation as the peel adhesion values increased when the concentration of acrylic adhesive increased. It was also observed that all the prepared patches were stripped cleanly from the palette and left no visually noticeable residue. This result showed that all formulation showed good cohesive properties. Since the formulations are expected to be kept in the market a long time before use, adhesive properties should be unchanged. Table 8 showed that the peel adhesion forces were not altered significantly when kept for 2 month.

The patient must remove the patch after a certain period of use. The patch with the high peel adhesion value provided trauma to the patient when he removed the patch from the skin. However, the feeling of the patients varied for each person. Therefore, the optimal value of peel adhesion was not proposed. A range of values that was not too high or not too low was accepted. The acceptable value of peel adhesion can be decides together with the thumb tack test.

4.2 Tack rolling ball test

The distance of the ball rolled gives an inverse compress scale of tack: the greater the distance, the less tacky the adhesive. The reciprocal of roll out distance is taken as the tack value. If the rolling of ball on the adhesive tape is more than 15 cm, the tack value is considered zero. Only the distance within 15 cm showed the tack property. The lower distance provided the higher tack property. From Table 9, the distance of ball rolled on the all formulation was not more than 15 cm, thus the patches showed some tack property. The results of tack property when compared with the same concentration at 30% w/w of different class of acrylic adhesive was B1 (5.67 cm) > A1 (6.07 cm) > C1 (8.42 cm). They are significantly different ($p<0.05$). At 40% w/w, B2 (4.13 cm) showed the highest tack property, followed by A2 (4.66 cm) and C2 (6.24 cm) respectively. They are significantly different ($p<0.05$). At 50% w/w, B3 (2.65 cm) showed the highest tack property, followed by A3 (3.29 cm) and C3 (4.80 cm) respectively. They were significantly different ($p<0.05$). This result showed the formulation B provided the highest tack property, followed by formulation A and C respectively. Duro-Tak® 87-2516, A3 (3.29 cm) > A2 (4.66 cm) > A1 (6.07 cm). They were significantly different ($p<0.05$). For Duro-Tak® 87-2852, B3 showed the

Table 9. Tack rolling ball test of 10% w/w Ketoprofen patches (n = 5)

Formulation	Tack Rolling Ball Test (cm)		
	T = 0 month	T = 1 month	T = 2 month
A1	6.07 ± 0.0671	6.04 ± 0.0962	5.97 ± 0.1204
A2	4.66 ± 0.0652	4.80 ± 0.1225	4.74 ± 0.1140
A3	3.29 ± 0.0822	3.24 ± 0.0652	3.33 ± 0.1037
B1	5.67 ± 0.0570	5.79 ± 0.1084	5.77 ± 0.0671
B2	4.13 ± 0.0447	4.20 ± 0.0354	4.16 ± 0.1084
B3	2.65 ± 0.0500	2.72 ± 0.0758	2.68 ± 0.0908
C1	8.42 ± 0.0570	8.50 ± 0.0791	8.52 ± 0.1037
C2	6.24 ± 0.1084	6.31 ± 0.1194	6.29 ± 0.0418
C3	4.80 ± 0.0791	4.94 ± 0.0962	4.88 ± 0.1151

significantly different ($p<0.05$). These results showed the effect of concentration of acrylic adhesive in the formulation depended on the class of adhesive. The formula highest tack property of 2.65 cm, followed by B2 (4.13 cm) and B1 (5.67 cm). They were significantly different ($p<0.05$). For Duro-Tak® 87-4098, C3 showed the highest tack property (4.80 cm), followed by C2 (6.24 cm) > C1 (8.42 cm). They were containing adhesive at high level was considered to possess higher tack property than the lower one. Since the formulations were expected to be kept in the market a long time before use, adhesive properties should be unchanged. Table 9 showed that the tack property was not alterated significantly when kept for 2 month.

All formulation showed the distance within the range of 2.65-8.42 cm. The distance traveled of more than 15 cm is considered the lack of tack property, the short distance (nearly 0) provided the high tack property. A well-performed patch should be able to stick to the skin but not too difficult to remove off. That is, the tack value should be around the middle of the range. Formulae A3 and B3 were considered as too high for the tack value.

4.3 Thumb tack test

In theory, tack refers to the "quick-stick" characteristic of the adhesive or the perception of stickiness when touched with minimal pressure. From Table 10 the tack properties of the ketoprofen patches containing different concentration of adhesive analyzed with thumb tack test increased with an increase in the concentration of adhesive in the formula. From the thumb tack test, it was found that the formulations at 50% w/w adhesive (A3, B3, C3) showed tight feeling or good tack adhesion on the skin. While the formulation at 40% w/w adhesive (A2, B2, C2) showed good stickiness on the skin and lack of slide property or fair adhesion. Formulation at 30% w/w adhesive (A1, B1, C1) slide on the skin as the patch are touched i.e. it is poorly adhere to the skin. The formulation with 40% and 50% w/w of adhesive could attach on skin with good feeling, and they were acceptable formulation when considered the tack property by thumb tack test. The result did not show the effect of different class of acrylic adhesive but it showed the effect of concentration.

Table 10. Thumb tack test of 10% w/w Ketoprofen patches prepared (n = 5)

Formulation	Thumb tack test		
	T = 0	T = 1	T = 2
A1	+	+	+
A2	++	++	++
A3	+++	+++	+++
B1	+	+	+
B2	++	++	++
B3	+++	+++	+++
C1	+	+	+
C2	++	++	++
C3	+++	+++	+++

\+ means Poor adhesion

++ means Fairly good adhesion

+++ means Good adhesion

4.4 Film thickness

Since the vehicle in these formulation could volatilize when dried in the Lab coater. The production method should be repeatable each time. The thickness of patch could indicate the precision of the method. The transdermal patches were prepared by using Lab coater that set thickness before drying at 0.05 cm. Table 11 showed average thicknesses of 10% w/w ketoprofen transdermal patches in formulation A1, A2, A3, B1, B2, B3, C1, C2, C3, which were insignificantly different ($p > 0.05$). Therefore, the result showed the good precision of the production method.

4.5 Content of ketoprofen patch

This process was used to confirm the accuracy and precision of formulation process. The actual content of ketoprofen in the patches was determined by UV spectrophotometer at wavelength of 255 nm. The amount of drug content was calculated from standard curve of ketoprofen in ethanol as shown in Figure 1. It was stated in USP 24 that content uniformity of transdermal patch should be within the range of 85.0% to 115.0% of label amount (% LA) and the relative standard deviation (RSD) of the 10 dosage units should be less than or equal to 6.0% (80). Table 12 showed the content uniformity of 10% w/w ketoprofen patches prepared by using different classes and concentration of acrylic adhesives. In this study, the percent label amount and RSD were within the range. Thus, all ketoprofen patches conformed to the requirement of USP 24 and showed the accuracy and precision of formulation in this study.

Skin permeation of formulation with 30% (A1, B1 and C1) and 40% w/w (A2, B2 and C2) of adhesive were satisfactory. When the adhesive property was included, formulation with 40% w/w of adhesive showed the optimal value of peel and tack property. However, B2 provided the shortest lag time and it showed the highest peel adhesion. Therefore, B2 was the best formulation in this study. All the formulation contained an equal thickness and conformed by the requirement of USP 24. Therefore, the best formulation in this study was the formula containing 10% w/w ketoprofen in the mixture of 50:50% w/w EtOH:Panasate 800 and 40% w/w Duro-Tak® 87-2852. The formula was produced using the DIA design.

Table 11. The film thickness of 10% w/w Ketoprofen patches (n = 20)

Formulation	Average film thickness (cm)
A1	0.0242 ± 0.00052
A2	0.0243 ± 0.00055
A3	0.0243 ± 0.00047
B1	0.0241 ± 0.00055
B2	0.0242 ± 0.00049
B3	0.0242 ± 0.00049
C1	0.0241 ± 0.00051
C2	0.0242 ± 0.00037
C3	0.0242 ± 0.00037

Table 12. The content uniformity of 10% w/w Ketoprofen patches (n = 10)

Formulation	Ketoprofen content (% w/w)	Theoretical content (% w/w)	% LA ± SD	%RSD
A1	10.09 ± 0.063	10.00	100.94 ± 0.630	0.62
A2	10.10 ± 0.057	10.00	101.02 ± 0.570	0.56
A3	10.10 ± 0.081	10.00	101.00 ± 0.808	0.80
B1	10.11± 0.074	10.00	101.10 ± 0.741	0.73
B2	10.13 ± 0.073	10.00	101.31± 0.734	0.72
B3	10.14 ± 0.074	10.00	101.41 ± 0.739	0.73
C1	10.10 ± 0.072	10.00	101.02 ± 0.723	0.72
C2	10.13 ± 0.090	10.00	101.28 ± 0.904	0.89
C3	10.06 ± 0.061	10.00	100.63 ± 0.611	0.61

$$\%\text{Label amount (LA)} = \frac{(\%\text{Ketoprofe n content} \times 100)}{\%\text{Theoretic al content}}$$

$$\%\ \text{Re latve standard deviation (RSD)} = \frac{(SD \times 100)}{\text{Mean}}$$

CHAPTER 6
CONCLUSION

Ketoprofen transdermal patches having a sustained release and good skin adhesion properties were developed in this study by using Duro-Tak® 87-2516, Duro-Tak® 87-2852 and Duro-Tak® 87-4098 as polymer matrix, EtOH as vehicle and Panasate 800 as enhancer. The ketoprofen transdermal patches were investigated using *in vitro* skin permeation through human epidermis and adhesive properties. The effects of different functional group and concentration of acrylic adhesive were studied. The experimentral results can be summarized as follows:

1. Different functional group of acrylic adhesives did not showed any different in *in vitro* skin permeation. The concentration of acrylic adhesive in the formulation affected the skin permeation by decreasing the flux when the concentration of acrylic adhesive in the patches increased.
2. Adhesive properties of the patches were evaluated by using peel adhesion 180° test, tack rolling ball test and thumb tack test. The results showed that the patches with 40% and 50% w/w of acrylic adhesive gave the better film with good adhesive properties than the patches with 30% w/w.
3. Considering the skin permeation and the adhesive properties studies, it can be concluded that B2 flux (40% w/w of Duro-Tak® 87-2852) was lower than theoretical flux. However, B2 was the best formulation in this study.
4. The appearances of the ketoprofen patches were transparent and smooth. These was no lot-to-lot variation of thickness of all formulation. The content uniformity of ketoprofen and relative standard deviation in all patches were with in range requirement of the USP 24.

REFERENCES

1. Kramer SD. Absorption prediction from physicochemical parameters. PSTT 1999;2(9):373-80.
2. Beetge E, Plessis JD, Muller DG, Goosen C, Rensburg FJ. The influence of the physicochemical characteristics and pharmacokinetic properties of selected NSAIDs on their transdermal absorption. Int J Pharm 2000;193:261-4.
3. Goosen C, Plessis J, Muller DG, Rensberg LF. Correlation between physicochemical charactertics., pharmacokinetic properties and transdermal absorption of NSAID's. Int J Pharm 1998;163:203-9.
4. Adrian CW. Theoretical aspects of transdermal drug delivery. In: Adrian CW, editor. Transdermal and Topical Drug Delivery. Illinois: Pharmaceutical Press; 2003: p. 27-49.
5. Finnin BC, Morgan TM. Transdermal penetration enhancers: Applications, limitations, and potential. J Pharm Sci 1999;88(10):955-8.
6. Lee CK, Uchida T, Nogochi E, Kim NS, Gato S. Skin permeation enhancement of tegafur by ethnol/Panasate 800 or ethanol/water binary vehicle and combined effect of fatty acids and fatty alcohols. J Pharm Sci 1993;82(11):1155-9.
7. Lee CK et al. Skin permeability of various drugs with different lipophilicity. J Pharm Sci 1994;83(4):562-5.
8. Goto S, Uchia T, Lee CK, Yasutake TD, Zhang JB. Effect of various vehicles on ketoprofen permeation across excised hairless mouse skin. J Pharm Sci 1993;82(9):959-63.
9. Chien YW, Patani GA. Transdermal Drug Delivery Devices: System Design and Composition. In: Swarbrick J, Boylan JC, editor. Encyclopedia of Pharmaceutical Technology. Vol. 18. New York: Marcel Dekker; 1999. P. 309-37.

10. Martin CM. Pressure-Sensitive Adhesives: Science and Engineering. In: Chien YW, editor. Transdermal Controlled Systemic Medications. New York: Marcel Dekker; 1987. p. 93-112.
11. Tan HS, Pfister WR. Pressure-sensitive adhesives for transdermal drug delivery systems. PSTT 1999;2(2):60-9.
12. Kandavilli S, Nair V, Panchagnula R. Polymers in transdermal drug delivery systems. Pharm Tech 2002;May:62-80.
13. Hopp MS. Developing custom adhesive systems for transdermal drug delivery products. Pharm Tech 2002;Mar:30-6.
14. Minghetti P, Cilurzo F, Montanari L. Evaluation of adhesive properties of patches base on acrylic matrices. Drug Dev Ind Pharm 1999;25(1):1-6.
15. Charies L, Lora L, Naomi B, Leonard L. Drug in formation handbook 4th ed. Ohio: American pharmaceutical association; 2002:816-8.
16. Jamali F, Brocks DR. Clinical Pharmacokinetics of ketoprofen and its enantiomers. Clin. Pharmacokinet 1990;19(3):197-217.
17. Chien YW. Transdermal drug delivery and delivery systems. In: Chien YW, editor. Novel drug delivery systems. 2nd ed. New York: Marcel Dekker; 1992. p. 301-80.
18. Adrian CW. Structure and function of human skin. In: Adrian CW, editor. Transdermal and Topical Drug Delivery. Illinois: Pharmaceutical Press; 2003. p. 1-25.
19. Wertz PW, Downing DT. Stratum corneum: Biological and Biochemical considerations. In: Hadgraft J and Guy RH, editors. Transdermal drug delivery. New York: Marcel Dekker; 1989. p. 1-22.
20. Barry BW. Structure, function, disease, and topical treatment of human skin. In: dermatological formulations (percutaneous absorption). Marcel Dekker: New York and Basel; 1988. p. 1-40.
21. Chien YW. Logics of transdermal controlled drug administration. Drug Dev Ind Pharm 1983;9:497-520.
22. Kydonieus AF. Fundamentals of transdermal drug delivery. In: Kydonieus AF, Berner B, editor. Transdermal delivery of drugs. Vol. I. Boca Raton (FL): CRC Press 1987; p. 3-16.

23. Kanikkanan N. Structure-activity relationship of chemical penetration enhancers in transdermal drug delivery. Curr Med Chem 2000;7:593-608.
24. Rolland A. Particulate carriers in dermal and transdermal drug delivery: myth or reality?. In: Rolland A, editor. Pharmaceutical particulate carriers therapeutic application. Marcel Dekker; 1993. p. 367-420.
25. Guy RH, Hadgraft J. Drug parameters important for transdermal delivery. In: Kydonieus AF, Berner B, editors. Transdermal delivery of drugs Vol. III. Boca Raton (FL): CRC press; 1987. p. 3-22.
26. Guy RH, Hadgraft J. Selection of drug candidates for transdermal drugs delivery. In: Hadgraft J, Guy RH, editors. Transdermal drug delivery. New York: Marcel Dekker; 1989. p. 59-81.
27. Jatz JL. Scratching the surface: Rationale and Approaches to skin permeation. In: Jatz JL, editor. Skin permeation fundamentals and application. Wheaton: Allured Publishing; 1993. p. 11-31.
28. Williams AC, Barry BW. Skin absorption enhancers. Therapeutic Drug Carrier Systems 1992;9(3,4):305-53.
29. Guy RH, Hadgraft J. Structure-activity correlations in percutaneous absorption. In: Bronaugh R, Maibach H, editors. Percutaneous absorption, 2nd ed, New York: Marcel Dekker; 1989. p. 95-109.
30. Barry Bw. Transdermal drug delivery. In: Aulton ME, editor. Pharmaceutical(The science of dosage form design). New York: Marcel Dekker; 2002. p. 499-533.
31. Keith RB, Kenneth AW, Adam CW. Methods for Studying Percutaneous Absorption. In: Kenneth AW, editor. Dermatological and Transdermal Formulations. New York: Marcel Dekker; 2002. p. 197-269.
32. Chien YW. Transdermal controlled-release drug administration. In: Chien YW, editor. Novel drug delivery systems. New York: Marcel Dekker; 1982. p. 149-217.
33. Idson B. Percutaneous absorption. J Pharm Sci 1975;64(6):901-24.
34. Fisher LB. Studies on the permeability of infant skin. In: Bronaugh RL, Maibach HI, editors. Percutaneous absorption. New York: Marcel Dekker; 1994. p. 135-45.

35. Shah AK, Wei G, Lanman RC, Bhargava VO, Weir SJ. Percutaneous absorption of ketoprofen from different anatomical sites in man. Pharm Res 1996;13(1): 168-72.
36. Bartek MJ. Labudde JA, Maibach HI. Skin permeability in vivo comparison in rat, rabbit, pig and man. J Invest Dermatol 1972;58(3):114-23.
37. Barry BW. Properties that influence percutaneous absorption. In. Barry BW, editor. Dermatological formulations. New York: Marcel Dekker; 1983. p. 127-233.
38. Wiedmann TS. Influence of hydration on epidermal tissue. J Pharm Sci 1988;77(12):1037-41.
39. Behl CR, Flynn GL, Kurihara T, et al. Hydration and percutaneous absorption: I influence of hydration on alkanol permeation through hairless mouse skin. J Invest Dermatol 1987;5:43-51.
40. Adrian CW. Topical and transdermal formulations. In: Adrian CW, editor. Transdermal and Topical Drug Delivery. Illinois: Pharmaceutical Press; 2003. p. 169-94.
41. Friend DR. *In vitro* skin permeation techniques. J Control Rel 1992;18:235-48.
42. Kakuji T. Design and Calibration of *In Vitro* Permeation Apparatus. In: Chien YW, editor. Transdermal Controlled Systemic Medications. New York: Marcel Dekker; 1987. p. 127-58.
43. Adrian CW. Experimental design. In: Adrian CW, editor. Transdermal and Topical Drug Delivery. Illinois: Pharmaceutical Press; 2003. p. 51-82.
44. Brown DWC, Ulsamer AG. Percutaneous penetration of hexachlorophene as related to receptor solutions. Food Cosmet Toxicol 1975;13:81-6.
45. Valia KH, Chien YW, Shinal EC. Long-term permeation kinetiecs of estradiol(I): Effect of drug solubilizer-poly-ethylene glycol 400. Drug Dev Ind Pharm 1984;10:951-81.
46. Scott RC, Leahy DE, Evans JR, Bole E. *In vitro* percutaneous model for quantitative structure-absorption studies. J Pharm Pharmacol 1986;38(Suppl.):66P.
47. Higuchi T. Physical chemical analysis of percutaneous absorption process from creams and ointments. J Soc Cosmet Chem 1960;11:85-97.

48. Higuchi T. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52(12):1145-9.
49. Chandrasekaran SK, Shoaw JE. Controlled transdermal delivery. In: Baker R, editor. Controlled release of bioactive materials. New York: Academic Press; 1980. p. 99-106.
50. Chien YW. Developmental Concepts and Practice in Transdermal Therapeutic Systems. In: Chien YW, editor. Transdermal Controlled Systemic Medications. New York: Marcel Dekker; 1987. p. 25-81.
51. Sugibayashi K, Morimoto Y. Polymers for transdermal drug delivery systems. J Controlled release 1994;29:177-85.
52. Merkle HP. Transdermal delivery systems. Clin Pharmacol 1989;11(3):135-53.
53. Kim JH, Cho YJ, Choi HK. Effect of vehicles and pressure sensitive adhesives on the permeation of tacrine across hairless mouse skin. Int J Pharm 2000;196(1):105-113.
54. Richard WB, Jorge H. Materials Selection for Transdermal Delivery Systems. In: Jonathan H, Richard HG, editors. Transdermal Drug Delivery: Developmental Issues and Research Initiatives. New York: Marcel Dekker; 1989. p. 293-311.
55. Roy SD, Gutierrez M, Flynn GL, Cleary GW. Controlled transdermal delivery of fentanyl: characterizations of pressure-sensitive adhesives for matrix patch design. J Pharm Sci 1996;85(5):491-5.
56. Park ES. Effects of adhesives and permeation enhancers on the skin permeation of captopril. Drug Dev Ind Pharm 2001;27(9):975-80.
57. Gwak HS, Chun IK. *In vitro* percutaneous absorption of tenoxicam from pressure-sensitive adhesive matrices across the hairless mouse skin. Arch Pharm Res 2001;24(6):578-83.
58. Minghetti P, Cilurzo F, Tosi L, Casiraghi A, Montanari L. Design of a New Water-Soluble Pressure-Sensitive Adhesive for Patch Preparation. AAPS PharmSciTech 2003;4(1):1-8.
59. Lund W, editor. Pharmaceutical codex. 12th ed. London: The pharmaceutical Press; 1994. p. 933-6.
60. Liversidge GG. Analytical profiles of drug substance.10

61. Hadgraft J, Plessis J, Goosen C. The selection of non-steroidal anti-inflammatory agents for dermal delivery. Int J Pharm 2000;207(1-2):31-7.
62. Caldwell JR. Comparison of the efficacy, safety, and pharmacokinetic profiles of extended-release ketoprofen and piroxicam in patients with rheumatoid arthritis. Clin Ther 1994;16(2):222-35.
63. Parel RK, Lesweel PF. Comparison of ketoprofen, piroxicam, and diclofenac gel in the treatment of acute soft-tissue injury in general. Clin Ther 1996;18(3):497-507.
64. Moore RA, Tramer MR, Carroll D, Wiffen PJ, McQuay HJ. Quantitiative systematic review of typically applied non-steroidal anti-inflammatory drugs. BMJ 1998;316:333-8.
65. Chi SC, Jun HW. Anti-inflammatory activity of ketoprofen gel on carrageenan induced paw edema in rats. J Pharm Sci 1990;79(11):974-7.
66. Misra A, Upadhyay P. Apparatus for preparing adhesive-dispersion transdermal patches on a laboratory scale. Int J Pharm 1996;132:267-70.
67. Cho YJ, Choi HK. Enhancement of percutaneous absorption of ketoprofen: effect of vehicles and adhesive matrix. Int J Pharm 1998;169:95-104.
68. Kligman AM, Philadelphia EC. Preparation of isolate sheets of human stratum corneum. Arch Derm 1963;88:702-5.
69. Suhonen TM, Bouwstra JA, Arto U. Chemical enhancement of percutaneous absorption in releation to stratum corneum structural alterations. J Control Rel 1999;59(2):149-61.
70. Lee CK, Uchida T, Noguchi E, Kim NS, Goto S. Skin Permeation Enhancement of Tegafur by Ethanol/Panasate 800 or Ethanol/Water Binary Vehicle and Combined Effect of Fatty Acids and Fatty Alcohols. J Pharm Sci 1993;82(11):1155-9.
71. Uchida T, Lee CK, Sekiya N, Goto S. Enhancement Effect of and Ethanol/Panasate 800 Binary Vehicle on Anti-inflammatory Drug Permeation across Excised Hairless Mouse Skin. Biol Pharm Bull 1993;16(2):168-71.
72. Lee CK, Uchida T, Kitagawa K, Yagi A, Kim NS. Effect of Hydrophilic and Lipophilic Vehicles on Skin Permeation of Tegafur, Alclofenac and

Ibuprofen with or without Permeation Enhancers. Biol Pharm Bull 1993;16(12):1264-9.

73. Lee CK, Kitagawa K, Uchida T, Kim NS, Goto S. Transdermal Delivery of Theophylline Using an Ethanol/Panasate 800-Ethylcellulose Gel Preparation. Biol Pharm Bull 1995;18(1):176-80.
74. Kim DD, Chien YW. Transdermal Delivery of Dideoxynucleoside-Type Anti-HIV Drugs. 2. The Effect of Vehicle and Enhancer on Skin Permeation. J Pharm Sci 1996;85(2):214-9.
75. Kim DD, Chien YW. Comparison of Skin Permeation of Dideoxynucleoside-Type Anti-HIV drugs: Alone Versus Combination. Drug Dev Ind Pharm 1996;22(11):1047-54.
76. Tungjitlikitskul S. Effeciency of penetration enhancers in the skin permeation of ketoprofen. [M.S. Thesis in Pharmaceutics]. Bangkok: Faculty of Graduate Studies, Mahidol University; 2003.
77. Davis AF, Gyurik RJ, Hadgraft J, Pellett MA, Walters KA. Formulation Strategies for Modulating Skin Permeation. In: Walter KA, editor. Dermatological and Transdermal Formulations. New York: Marcel Dekker; 2002. p. 271-317.
78. Jaeckle E, Schaefer U.F. Comparison of effects of different ointment bases on the penetration of ketoprofen through heat-separated human epidermis and artificial lipid barriers. J Pharm Sci 2003;92(7):1396-1406.
79. Paolino D, Ventura C.A, Nistico S. Lecithin microemulsions for the topical administration of ketoprofen: percutaneous adsorption through human skin and in vivo human skin tolerability. Int J Pharm 2002;244:21-31.
80. Kokubo T, Sugibayashi K, Morimoto Y. Interaction Between Drugs and Pressure-Sensitive Adhesives in Transdermal Therapeutic Systems. Pharm Res 1994;1(11):104-7.
81. Singh S.K, Roane D.S. Effect of additives on the diffusion of ketoprofen through human skin. Drug Dev Ind Pharm 1996;22(5):471-4.
82. The United States Pharmacopeia convention. USP 24 NF 19: The United States Pharmacopeia, The National Formulary. Asian ed. India: Tata Donnelley;2000. p. 2000-2.

APPENDIX A

Conversion of concentration

A. Determination of density of EtOH and Panasate 800 quantitatively

1. A 50 ml beaker was tared and it was filled with EtOH 5 ml by transferring pipet (T = 30 ˚C). The weight was recorded.
2. A 50 ml beaker was tared and it was filled with Panasate 800 5 ml by transferring pipet (T = 30 ˚C). The weight was recorded.
3. Calculate the density by equation 10:

$$D = \frac{M}{V} \qquad \text{(Eq 10)}$$

Where D is density, M is mass and V is volume.

Volume of EtOH 5 ml, weight = 3.96 g; Density = 0.792 g/ml

Volume of Panasate 800 5 ml, weight = 4.64 g; Density = 0.928 g/ml

B. Accuracy of cylinder to measure the volume

- Calculate volume by using density from A.

Weight of EtOH 5 g should have the volume = 6.31 ml

Weight of Panasate 800 5 g should have the volume = 5.39 ml

- Volume measurement by cylinder

1. A 10 ml cylinder was tared and it was filled with EtOH up to 5.00 g. Read the level by the investigator (T = 30 ˚C). The volume was recorded.
2. A 10 ml cylinder with covered foil and polymer was tared and it was filled with Panasate 800 up to 5.00 g. Read the level by the investigator (T = 30 ˚C). The volume was recorded.

Weight of EtOH 5.00 g, volume = 6.32 ml

% error = 0.16%

Weight of Panasate 800 5.00 g, volume = 5.40 ml

% error = 0.18%

As the % error of volume measured by cylinder is low, it is satisfactory to use cylinder to measure the volume of liquid.

C. Mixing volume of EtOH and Panasate 800

- Calculate the volume by using the density from B

Volume of the mixture by calculation = 11.70 ml

- Volume of the mixture by cylinder

1. A 25 ml cylinder was tared and it was filled with EtOH up to 5.00 g (T = 30 ˚C).
2. Add Panasate 800 up to the weight 10.00 g to the cylinder. Read the level by investigator (T = 30 ˚C). The volume was recorded.

Volume of the mixture by cylinder = 11.75 ml

% error = 0.43%

The error due to volume measurement by cylinder of EtOH (% error = 0.16%) and Panasate 800 (0.18%) was lower than the volume of EtOH:Panasate 800 (% error = 0.43%). However, % error of the mixture was acceptable.

D. Measure the volume of mixture of EtOH:Panasate 800 and ketoprofen

1. A 25 ml cylinder was tared and it was filled with EtOH and Panasate 4.5 g each. The volume was recorded
2. Add ketoprofen powder 1.00 g into the cylinder. The volume was recorded.

Volume of the mixture by cylinder = 10.54 ml

Volume of the mixture and ketoprofen = 11.51 ml

Density of EtOH, Panasate 800 and ketoprofen = 0.8688 g/ml

E. Measure the volume of mixture of EtOH and ketoprofen

1. A 25 ml cylinder with covered polymer was tared and it was filled with EtOH 9 g. The volume was recorded (T = 30 ˚C).
2. Add the ketoprofen powder 1.00 g into the cylinder. The volume was recorded (T = 30 ˚C).

Volume of the mixture and ketoprofen = 12.35 ml

Density of the formula = 0.8097g/ml

F. Measure the weight of mixture of EtOH:Panasate 800 and ketoprofen at solubility

1. A 10 ml cylinder with covered polymer was tared and it was filled with ketoprofen 3.97 g and fill the mixture of EtOH:Panasate 50:50% w/w up to 10 ml.
2. The weight was recorded (T = 30 ˚C).

Volume of mixture and ketoprofen = 10 ml

Weight of mixture and ketoprofen = 9.47 g

Density of the formula = 9.47/10 = 0.947 g/ml

G. Conversion of the formulation concentration's unit

1. 31.7% w/v of ketoprofen in the mixture of EtOH:Panasate 800 50:50% w/w

Density of [EtOH, Panasate 800, ketoprofen] at solubility = 0.947 g/ml

[EtOH, Panasate 800 and ketoprofen] 100 ml contain ketoprofen = 31.7 g

≡ [EtOH, Panasate 800, ketoprofen] 94.7 g contain ketoprofen = 31.7 g

≡ [EtOH, Panasate 800, ketoprofen] 100 g contain ketoprofen = 33.5 g

Thus 31.7% w/v = 33.5% w/w

2. 10.08% w/w of ketoprofen in the mixture of EtOH:Panasate 800 50:50% w/w

   Density of [EtOH, Panasate 800, ketoprofen] = 0.8688 g/ml
   [EtOH, Panasate 800, ketoprofen] 100 g contain ketoprofen = 10.08 g
   ≡ [EtOH, Panasate 800, ketoprofen] 86.88 ml contain ketoprofen = 10.08 g
   ≡ [EtOH, Panasate 800, ketoprofen] 100 ml contain ketoprofen = 8.76 g
   Thus 10.08% w/w = 8.76% w/v (87.6×10^3 µg/ml)

3. 10.11% w/w of ketoprofen in 100% EtOH

   Density of [EtOH, ketoprofen] = 0.8097 g/ml
   [EtOH, ketoprofen] 100 g contain ketoprofen = 10.11 g
   ≡ [EtOH, ketoprofen] 80.97 ml contain ketoprofen = 10.11 g
   ≡ [EtOH, ketoprofen] 100 ml contain ketoprofen = 8.19 g
   Thus 10.11% w/w = 8.19% w/v (81.9×10^3 µg/ml)

APPENDIX B

Modification of commercial gel concentration

Calculation of weight by volume of commercial gel

1. A 5 ml cylinder was tared and it was filled with charcoal powder up to 5 ml. The weight was recorded.
2. A 5 ml was tared and added to it with 1 g of commercial gel. Then the cylinder was filled with charcoal powder up to 3 ml and the weight was recorded.
3. The weight by volume of commercial gel was calculated.

Result

1. The weight of charcoal powder was 3.0308 g in a volume of 5 ml
2. The weight of commercial gel is 1.0032 g. Total weight after charcoal powder was added to a volume of 3 ml was 1.9027 g. Thus, the weight of charcoal powder was:

   1.9027-1.0032 = 0.8995 g
3. Calculate the unit of weight to volume by:

   Weight of charcoal powder 3.0328 g in the volume 5 ml

   Weight of charcoal powder 0.8995 g in the volume 1.4829 ml

   The volume of commercial gel (1.0032 g) was 3-1.4829 = 1.5171 ml

   Thus, weight by volume of commercial gel = 0.66 g/ml

   From weight by volume of gel = 0.66 g/ml, thus 1 g occupied volume 1.5151 ml.

   Concentration of ketoprofen in commercial gel = 2.5 g/100 g

   = 0.025 g/g

   = 0.025 g/1.5151 ml

   Thus, the concentration of ketoprofen in gel was 16.5 mg/ml.

APPENDIX C

Theoretical flux of Ketoprofen

Data calculation of theoretical flux of ketoprofen

Based on the pharmacokinetic parameters obtained from (2), the theoretical flux was calculated. The parameters were:

Elimination half-life (t1/2) is 3 hr

Steady state plasma concentration of ketoprofen (C_{ss}) is 3-5 µg/ml

Volume of distribution (V_d) is 150 ml/kg

The calculation used the equation:

$$t_{1/2} = \frac{0.693}{k_{el}} \qquad \text{(Eq 8)}$$

$$Input\ rate = C_{ss} \times k_{el} \times V_d \qquad \text{(Eq 9)}$$

The k_{el} of ketoprofen could be calculated from equation 8, when $t_{1/2}$ was 3 hr, thus k_{el} was 0.231 hr^{-1}.

Steady state plasma concentration of ketoprofen (C_{ss}) was averaged as 4 µg/ml.

Volume of distribution V_d was 1.5 ml/kg, when the avareaged weitht of person was 50 kg, thus V_d was 7500 ml.

Input rate could be calculated from the equation 9:

$$\begin{aligned} Input\ rate &= C_{ss} \times k_{el} \times V_d \\ &= (4\ \mu g/ml) \times (0.231\ hr^{-1}) \times (7500\ ml) \\ &= 6930\ \mu g/hr \end{aligned}$$

A transdermal patch of 20 cm^2 area, the theoretical flux to maintain the desired C_{ss} was 346.5 $\mu g/cm^2/hr$.

APPENDIX D

Permeation of Ketoprofen

Table 13. Permeation parameter of R1

Franz no.	Flux ($\mu g/cm^2/hr$)	k_p (cm/hr) x 10^{-3}	Lag time (hr)
1	375.44	1.1844	3.22
2	384.57	1.2132	3.03
3	391.59	1.2353	1.04
4	374.78	1.1823	0.91
5	336.36	1.0611	2.94
6	334.36	1.0548	3.01
7	350.55	1.1058	2.71
8	392.63	1.2386	2.58
9	341.52	1.0774	2.82
10	344.48	1.0867	2.57
Average	362.63	1.14	2.48
S.D.	23.43	0.07	0.82

Table 14. Permeation parameter of R2

Franz no.	Flux ($\mu g/cm^2/hr$)	k_p (cm/hr) x 10^{-3}	Lag time (hr)
1	280.42	3.20	4.39
2	186.03	2.12	4.65
3	188.83	2.16	5.48
4	187.17	2.14	5.45
5	251.33	2.87	3.63
6	265.76	3.03	2.45
7	265.69	3.03	2.78
8	298.22	3.40	3.62
9	295.76	3.38	3.76
10	234.33	2.68	2.69
Average	245.35	2.80	3.89
S.D.	44.29	0.51	1.09

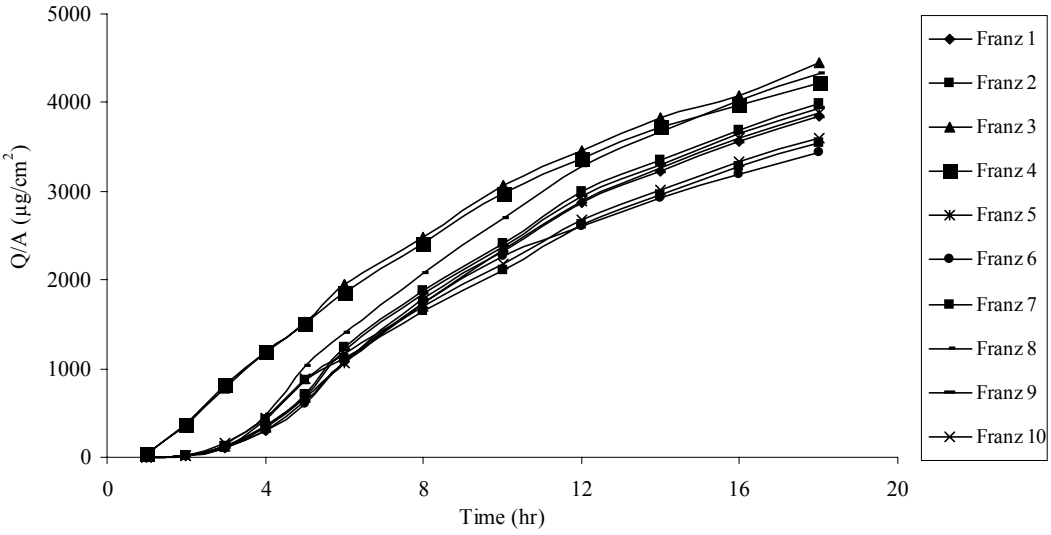


Figure 19. Skin permeation of Ketoprofen from R1

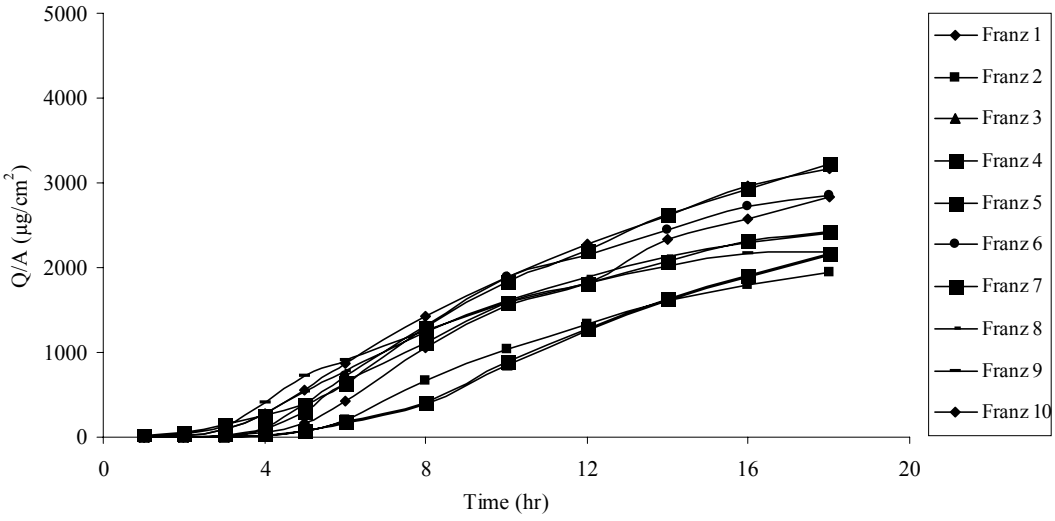


Figure 20. Skin permeation of Ketoprofen from R2

Table 15. Permeation parameter of R3

Franz no.	Flux ($\mu g/cm^2/hr$)	k_p (cm/hr) x 10^{-3}	Lag time (hr)
1	113.68	1.39	6.70
2	110.72	1.35	6.74
3	146.75	1.79	6.07
4	154.86	1.89	4.55
5	92.56	1.13	6.82
6	107.43	1.31	6.76
7	108.18	1.32	6.70
8	108.56	1.33	6.84
9	136.42	1.67	8.01
10	135.86	1.66	8.19
11	81.30	0.99	7.02
Average	117.85	1.44	6.76
S.D.	22.82	0.28	0.95

Table 16. Permeation parameter of R4

Franz no.	Flux ($\mu g/cm^2/hr$)	k_p (cm/hr) x 10^{-3}	Lag time (hr)
1	7.67	0.46	7.54
2	8.57	0.52	7.04
3	8.98	0.54	7.00
4	8.21	0.50	5.08
5	10.15	0.62	7.23
6	10.68	0.65	6.67
7	6.88	0.42	7.12
8	7.23	0.44	6.94
9	16.43	1.00	7.01
10	12.95	0.78	6.93
Average	9.77	0.59	6.86
S.D.	2.96	0.18	0.66

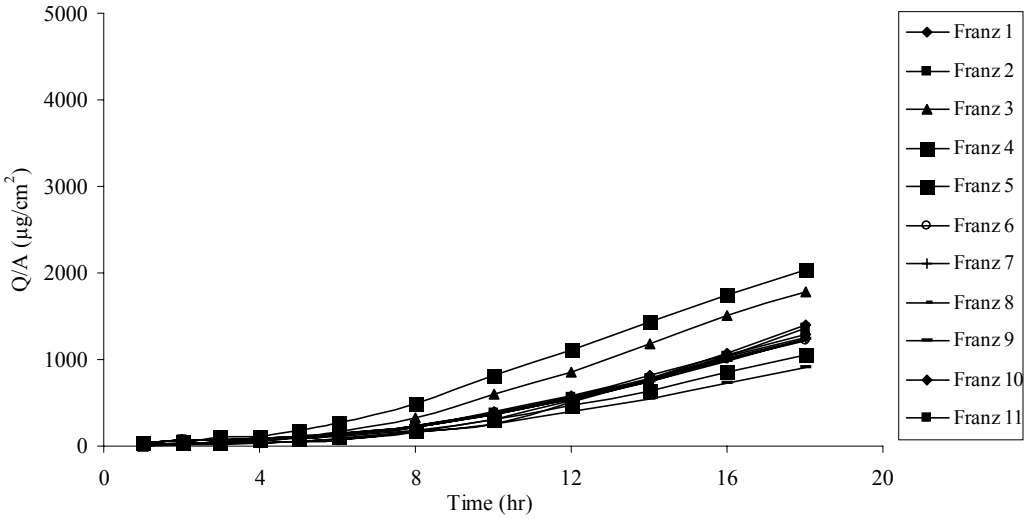


Figure 21. Skin permeation of Ketoprofen from R3

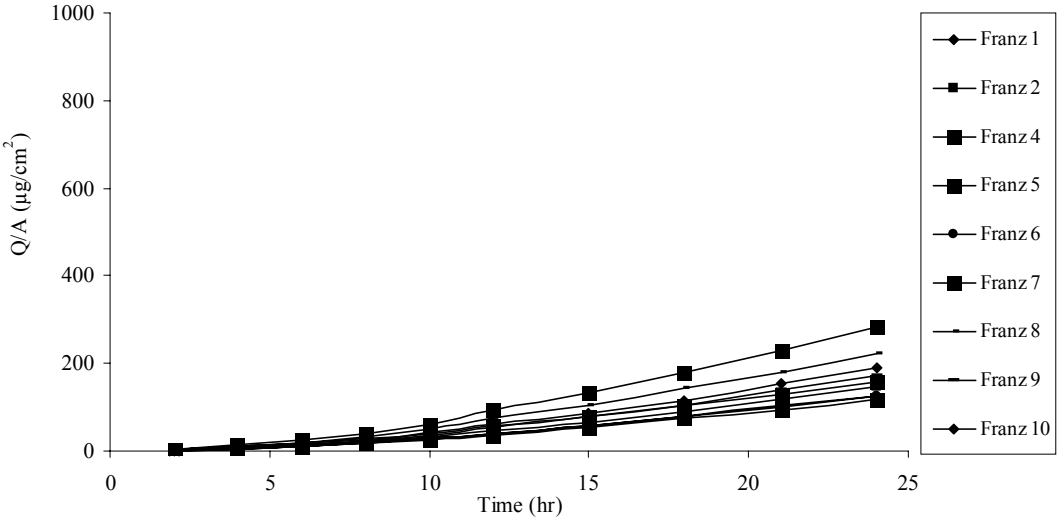


Figure 22. Skin permeation of Ketoprofen from R4

Table 17. Permeation parameter of A1

Franz no.	Flux ($\mu g/cm^2/hr$)	Lag time (hr)
1	26.77	4.14
2	24.73	4.14
3	32.51	5.22
4	25.55	4.40
5	21.96	4.81
6	27.26	5.57
7	23.26	2.95
8	25.57	4.51
9	25.95	4.38
10	27.50	4.24
Average	26.11	4.44
S.D.	2.84	0.70

Table 18. Permeation parameter of A2

Franz no.	Flux ($\mu g/cm^2/hr$)	Lag time (hr)
1	23.20	3.35
2	26.96	3.93
3	24.60	2.47
4	25.60	2.88
5	17.73	4.60
6	14.65	3.22
7	21.54	5.70
8	18.59	4.44
9	20.82	6.67
10	20.31	3.14
Average	21.40	4.04
S.D.	3.81	1.33

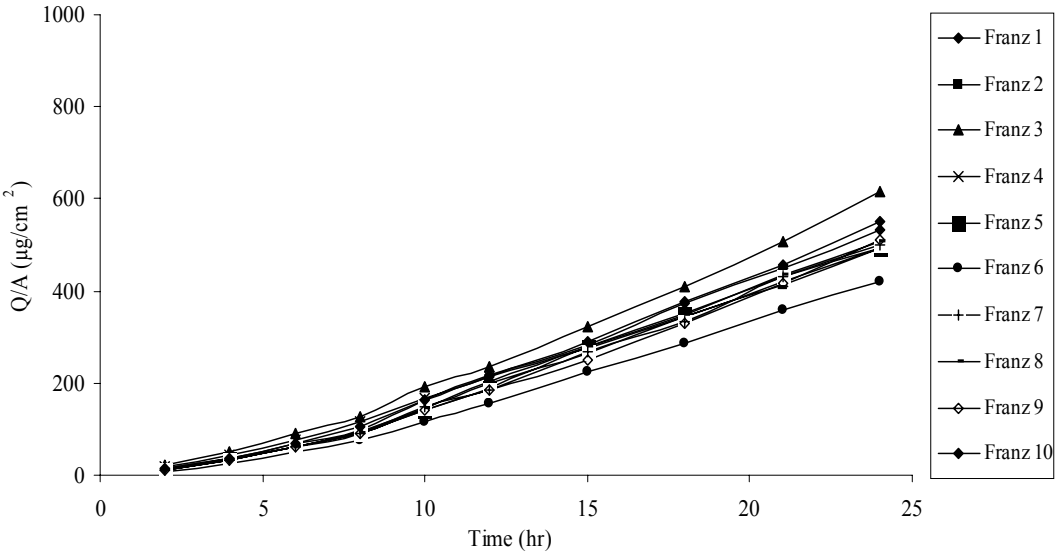


Figure 23. Skin permeation of Ketoprofen from A1

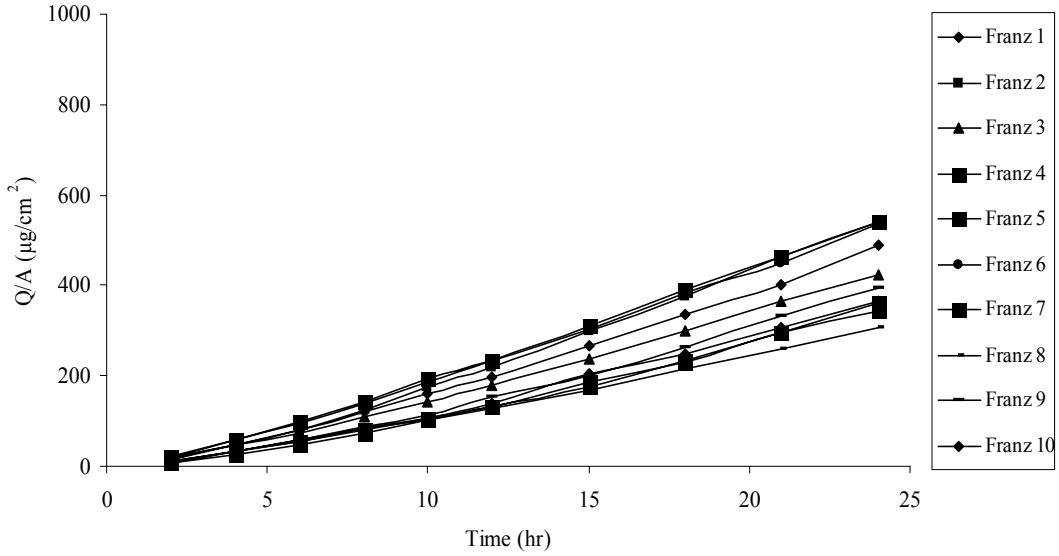


Figure 24. Skin permeation of Ketoprofen from A2

Table 19. Permeation parameter of A3

Franz no.	Flux ($\mu g/cm^2/hr$)	Lag time (hr)
1	13.91	5.94
2	11.20	3.77
3	13.63	2.79
4	11.62	6.11
5	12.18	6.90
6	13.58	3.50
7	16.87	5.14
8	17.49	5.21
9	13.98	4.65
10	15.02	3.44
Average	13.95	4.75
S.D.	2.07	1.35

Table 20. Permeation parameter of B1

Franz no.	Flux ($\mu g/cm^2/hr$)	Lag time (hr)
1	24.84	4.79
2	20.36	4.44
3	29.16	2.57
4	26.25	2.82
5	34.32	3.17
6	22.24	3.73
7	22.80	4.24
8	26.90	2.64
9	30.06	8.33
10	26.24	4.69
11	18.40	4.56
Average	25.60	4.18
S.D.	4.59	1.61

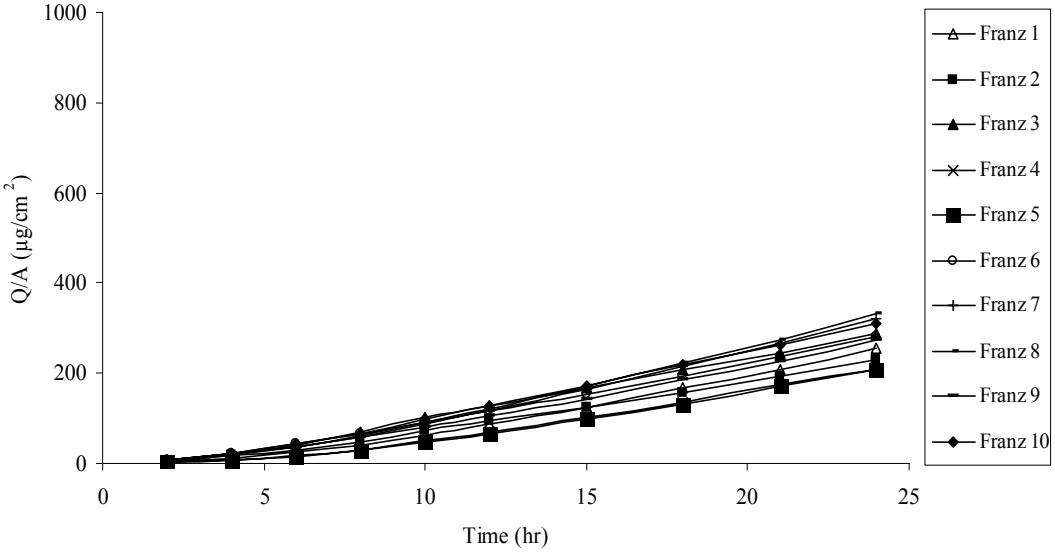


Figure 25. Skin permeation of Ketoprofen from A3

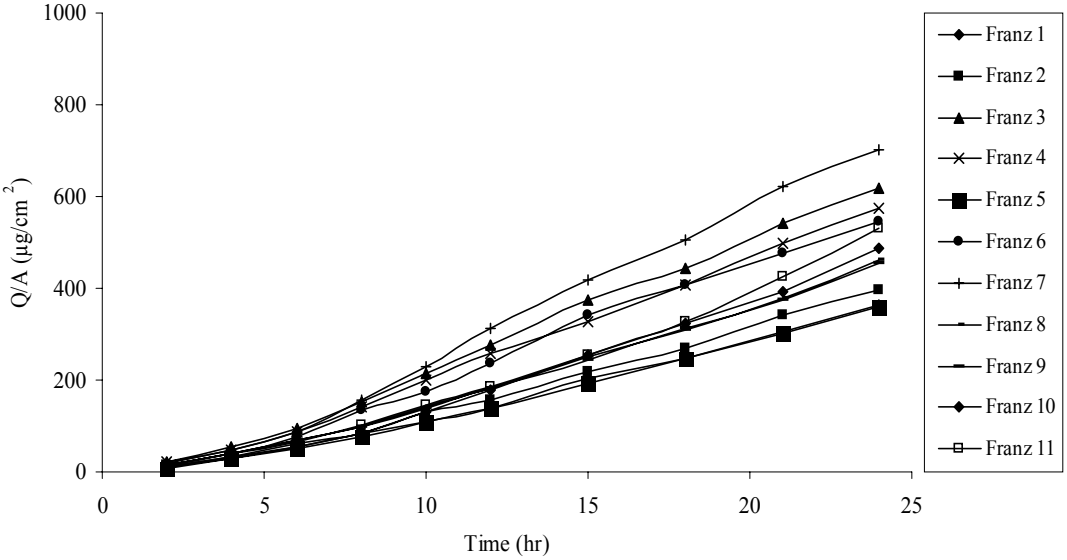


Figure 26. Skin permeation of Ketoprofen from B1

Table 21. Permeation parameter of B2

Franz no.	Flux ($\mu g/cm^2/hr$)	Lag time (hr)
1	17.71	2.80
2	16.32	4.23
3	18.32	3.15
4	22.61	4.22
5	23.37	3.58
6	24.36	3.66
7	25.80	3.42
8	16.90	2.97
9	17.47	2.85
10	20.93	2.53
Average	20.38	3.34
S.D.	3.46	0.59

Table 22. Permeation parameter of B3

Franz no.	Flux ($\mu g/cm^2/hr$)	Lag time (hr)
1	13.04	5.31
2	16.05	4.33
3	11.12	5.07
4	9.65	4.81
5	14.11	6.95
6	10.59	4.63
7	13.60	4.13
8	12.63	4.32
9	14.38	2.72
10	14.81	4.91
Average	13.00	4.72
S.D.	2.02	1.06

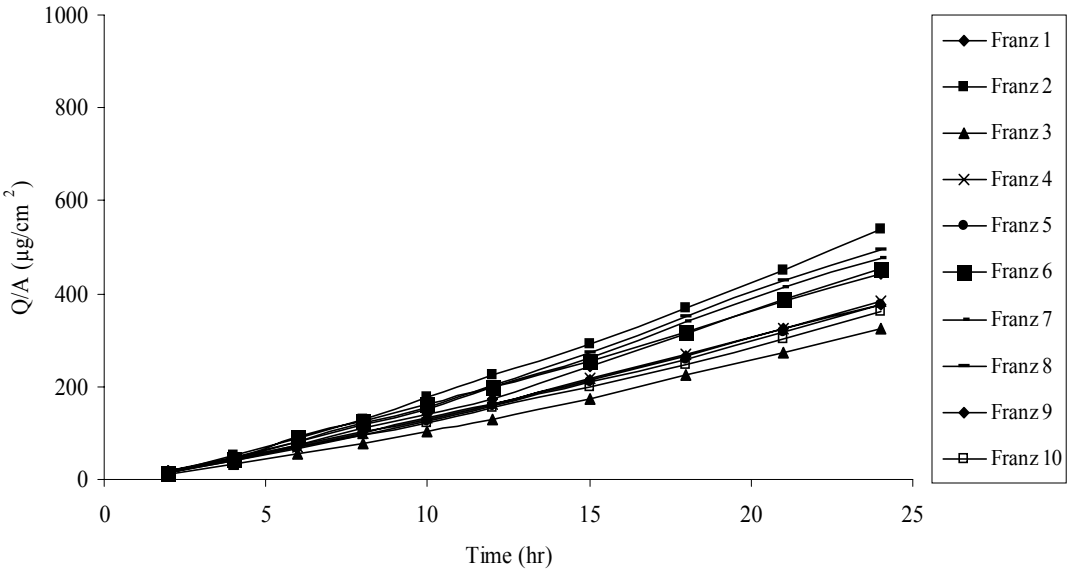


Figure 27. Skin permeation of Ketoprofen from B2

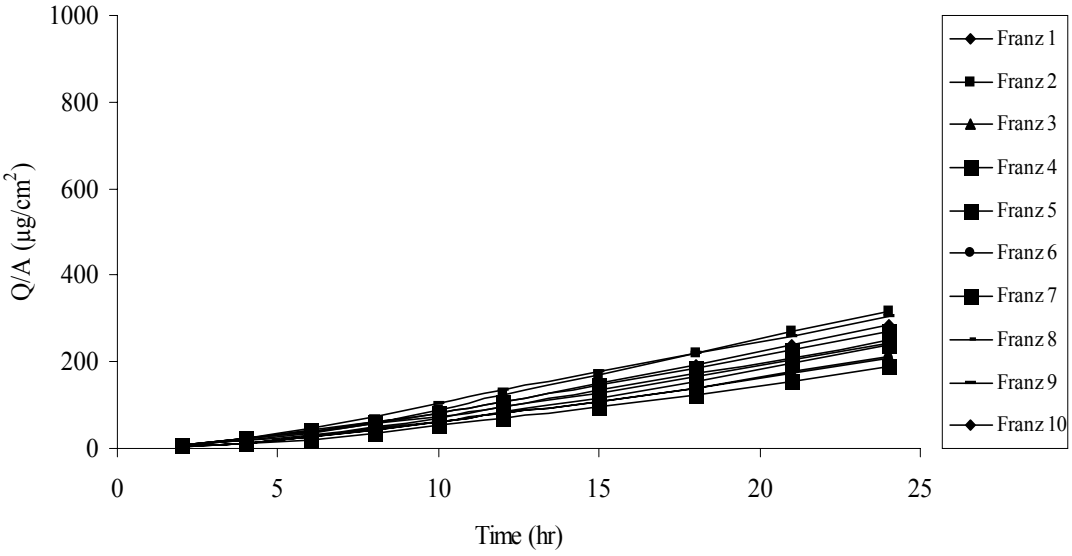


Figure 28. Skin permeation of Ketoprofen from B3

Table 23. Permeation parameter of C1

Franz no.	Flux ($\mu g/cm^2/hr$)	Lag time (hr)
1	17.66	5.62
2	30.99	3.30
3	17.57	3.21
4	29.72	3.81
5	23.18	4.71
6	28.20	4.73
7	29.85	6.05
8	30.52	5.90
9	24.58	4.90
10	27.87	5.41
Average	26.01	4.76
S.D.	5.09	1.03

Table 24. Permeation parameter of C2

Franz no.	Flux ($\mu g/cm^2/hr$)	Lag time (hr)
1	22.91	5.58
2	18.74	2.78
3	20.88	2.71
4	14.66	3.85
5	22.13	8.69
6	13.60	4.28
7	16.20	8.64
8	27.91	3.27
9	26.02	3.62
10	23.20	7.03
11	18.10	3.53
12	13.43	5.20
Average	19.82	4.93
S.D.	4.81	2.14

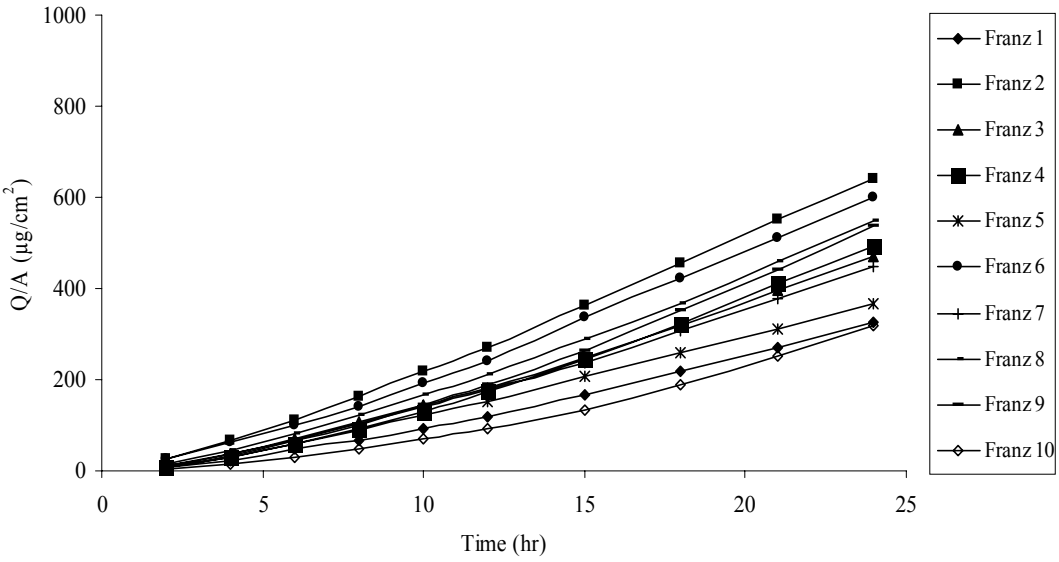


Figure 29. Skin permeation of Ketoprofen from C1

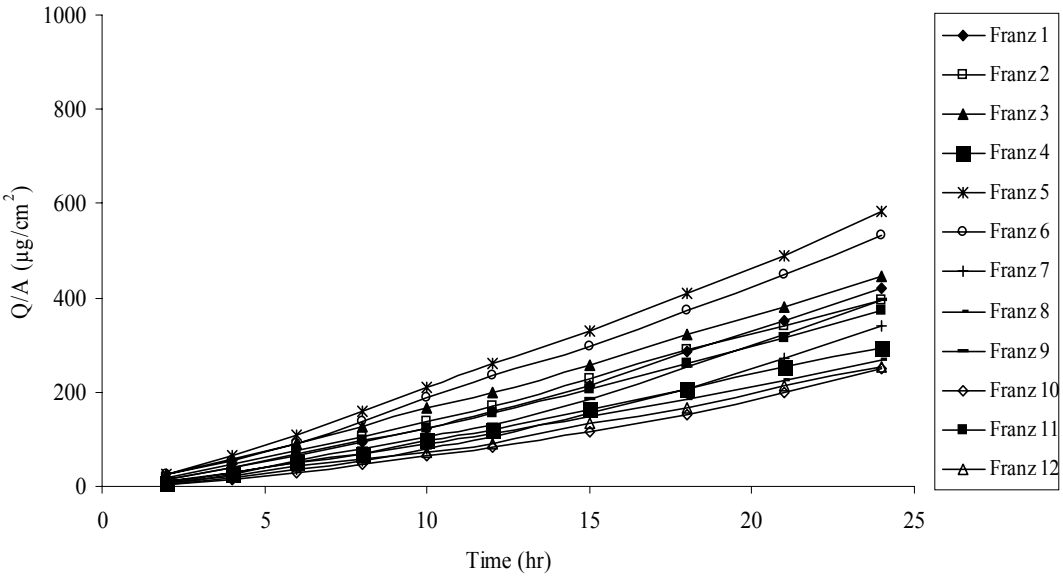


Figure 30. Skin permeation of Ketoprofen from C2

Table 25. Permeation parameter of C3

Franz no.	Flux ($\mu g/cm^2/hr$)	Lag time (hr)
1	16.60	2.83
2	15.47	2.77
3	11.83	2.69
4	11.22	2.82
5	16.12	2.70
6	15.68	2.42
7	16.53	3.25
8	11.85	2.45
9	14.35	7.16
10	16.65	6.76
11	9.64	3.91
Average	14.18	3.61
S.D.	2.56	1.71

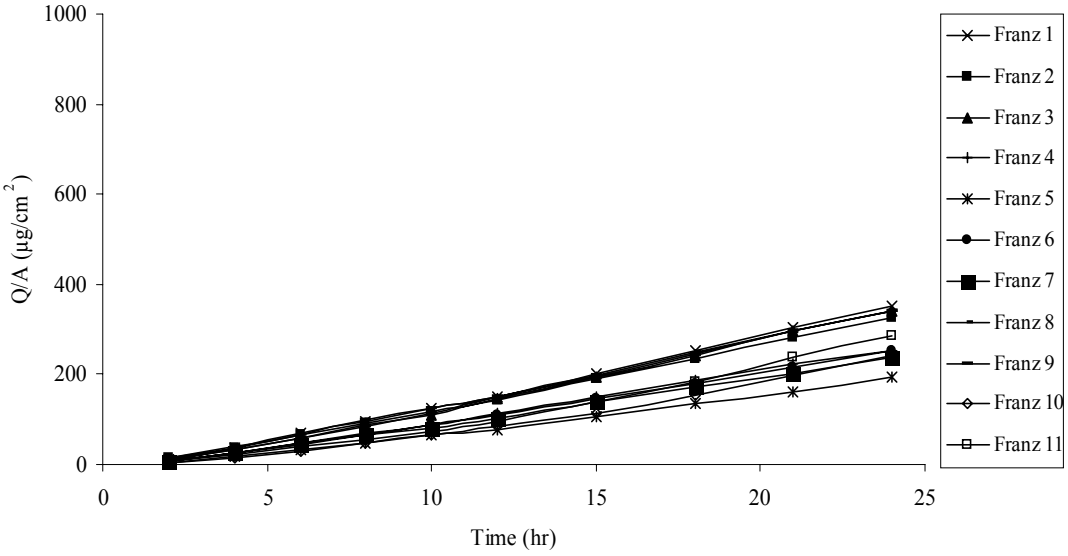


Figure 31. Skin permeation of Ketoprofen from C3

APPENDIX E

Statistically analysis data

Table 26. Comparison of descriptive data of R1-R4.

Permeabilily Parameter		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
					Lower Bound	Upper Bound		
k_p	R1	1.1192	0.0723	0.0229	1.0675	1.1709	1.03	1.21
	R2	2.8010	0.5043	0.1595	2.4402	3.1618	2.12	3.40
	R3	1.4391	0.2791	0.0841	1.2516	1.6266	0.99	1.89
	R4	0.5930	0.1802	0.0570	0.4641	0.7219	0.42	1.00
Flux	R1	362.6280	23.4332	7.4102	345.8649	379.3911	334.36	392.63
	R2	245.3540	44.2870	14.0048	213.6730	277.0350	186.03	298.22
	R3	117.8473	22.8172	6.8797	102.5185	133.1761	81.30	154.86
	R4	9.7750	2.9656	0.9378	7.6536	11.8964	6.88	16.43
Lag time	R1	2.4830	0.8211	0.2596	1.8956	3.0704	0.91	3.22
	R2	3.8900	1.0900	0.3447	3.1103	4.6697	2.45	5.48
	R3	6.7636	0.9515	0.2869	6.1244	7.4028	4.55	8.19
	R4	6.8560	0.6631	0.2097	6.3817	7.3303	5.08	7.54

Table 27. Statistically data of k_p of R1-R4 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
R1	R2	-1.6818	0.1357	0.0000*	-1.9568	-1.4068
	R3	-0.3199	0.1326	0.0209*	-0.5885	-0.0512
	R4	0.5262	0.1357	0.0004*	0.2512	0.8012
R2	R1	1.6818	0.1357	0.0000*	1.4068	1.9568
	R3	1.3619	0.1326	0.0000*	1.0932	1.6306
	R4	2.2080	0.1357	0.0000*	1.9330	2.4830
R3	R1	0.3199	0.1326	0.0209*	0.0512	0.5885
	R2	-1.3619	0.1326	0.0000*	-1.6306	-1.0932
	R4	0.8461	0.1326	0.0000*	0.5774	1.1148
R4	R1	-0.5262	0.1357	0.0004*	-0.8012	-0.2512
	R2	-2.2080	0.1357	0.0000*	-2.4830	-1.9330
	R3	-0.8461	0.1326	0.0000*	-1.1148	-0.5774

* The mean difference is significant at the 0.05 level

Table 28. Statistically data of flux of R1-R4 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
R1	R2	117.2740	12.2760	0.0000*	92.4005	142.1475
	R3	244.7807	11.9938	0.0000*	220.4791	269.0824
	R4	352.8530	12.2760	0.0000*	327.9795	377.7265
R2	R1	-117.2740	12.2760	0.0000*	-142.1475	-92.4005
	R3	127.5067	11.9938	0.0000*	103.2051	151.8084
	R4	235.5790	12.2760	0.0000*	210.7055	260.4525
R3	R1	-244.7807	11.9938	0.0000*	-269.0824	-220.4791
	R2	-127.5067	11.9938	0.0000*	-151.8084	-103.2051
	R4	108.0723	11.9938	0.0000*	83.7706	132.3739
R4	R1	-352.8530	12.2760	0.0000*	-377.7265	-327.9795
	R2	-235.5790	12.2760	0.0000*	-260.4525	-210.7055
	R3	-108.0723	11.9938	0.0000*	-132.3739	-83.7706

* The mean difference is significant at the 0.05 level

Table 29. Statistically data of lag time of R1-R4 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
R1	R2	-1.4070	0.4011	0.0012*	-2.2198	-0.5942
	R3	-4.2806	0.3919	0.0000*	-5.0747	-3.4865
	R4	-4.3730	0.4011	0.0000*	-5.1858	-3.5602
R2	R1	1.4070	0.4011	0.0012*	0.5942	2.2198
	R3	-2.8736	0.3919	0.0000*	-3.6677	-2.0795
	R4	-2.9660	0.4011	0.0000*	-3.7788	-2.1532
R3	R1	4.2806	0.3919	0.0000*	3.4865	5.0747
	R2	2.8736	0.3919	0.0000*	2.0795	3.6677
	R4	-0.0924	0.3919	0.8150	-0.8865	0.7017
R4	R1	4.3730	0.4011	0.0000*	3.5602	5.1858
	R2	2.9660	0.4011	0.0000*	2.1532	3.7788
	R3	0.0924	0.3919	0.8150	-0.7017	0.8865

* The mean difference is significant at the 0.05 level

Table 30. Comparison of descriptive data of A1, B1, C1.

Permeabilily Parameter		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
					Lower Bound	Upper Bound		
Flux	A1	26.1060	2.8388	0.8977	24.0752	28.1368	21.96	32.51
	B1	25.5973	4.5840	1.3821	22.5177	28.6768	18.40	34.32
	C1	26.0140	5.0872	1.6087	22.3748	29.6532	17.57	30.99
Lag time	A1	4.4360	0.7049	0.2229	3.9317	4.9403	2.95	5.57
	B1	4.1800	1.6157	0.4872	3.0945	5.2655	2.57	8.33
	C1	4.7640	1.0320	0.3263	4.0258	5.5022	3.21	6.05

Table 31. Statistically data of flux of A1, B1, C1 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	B1	0.5087	8.7022	0.9536	-17.0078	18.0253
	C1	0.0920	8.9070	0.9918	-17.8368	18.0208
B1	A1	-0.5087	8.7022	0.9536	-18.0253	17.0078
	C1	-0.4167	8.7022	0.9620	-17.9333	17.0998
C1	A1	-0.0920	8.9070	0.9918	-18.0208	17.8368
	B1	0.4167	8.7022	0.9620	-17.0998	17.9333

* The mean difference is significant at the 0.05 level

Table 32. Statistically data of lag time of A1, B1, C1 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	B1	0.2560	0.4770	0.5940	-0.7041	1.2161
	C1	-0.3280	0.4882	0.5050	-1.3107	0.6547
B1	A1	-0.2560	0.4770	0.5940	-1.2161	0.7041
	C1	-0.5840	0.4770	0.2270	-1.5441	0.3761
C1	A1	0.3280	0.4882	0.5050	-0.6547	1.3107
	B1	0.5840	0.4770	0.2270	-0.3761	1.5441

* The mean difference is significant at the 0.05 level

Table 33. Comparison of descriptive data of A2, B2, C2.

Permeabilily Parameter		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
					Lower Bound	Upper Bound		
Flux	A2	21.4000	3.8080	1.2042	18.6759	24.1241	14.65	26.96
	B2	20.4533	3.2599	0.9410	18.3821	22.5245	16.32	25.80
	C2	19.6130	5.2021	1.6450	15.8917	23.3343	13.43	27.91
Lag time	A2	4.0400	1.3303	0.4207	3.0884	4.9916	2.47	6.67
	B2	3.4808	0.8627	0.2490	2.9327	4.0290	2.53	5.58
	C2	5.0820	2.2386	0.7079	3.4806	6.6834	2.71	8.69

Table 34. Statistically data of flux of A2, B2, C2 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A2	B2	0.9467	4.6370	0.8391	-8.3817	10.2750
	C2	1.7870	4.8431	0.7138	-7.9561	11.5301
B2	A2	-0.9467	4.6370	0.8391	-10.2750	8.3817
	C2	0.8403	4.6370	0.8570	-8.4880	10.1687
C2	A2	-1.7870	4.8431	0.7138	-11.5301	7.9561
	B2	-0.8403	4.6370	0.8570	-10.1687	8.4880

* The mean difference is significant at the 0.05 level

Table 35. Statistically data of lag time of A2, B2, C2 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A2	B2	0.5592	0.5560	0.3197	-0.5593	1.6776
	C2	-1.0420	0.5807	0.0792	-2.2102	0.1262
B2	A2	-0.5592	0.5560	0.3197	-1.6776	0.5593
	C2	-1.6012	0.5560	0.0060*	-2.7196	-0.4827
C2	A2	1.0420	0.5807	0.0792	-0.1262	2.2102
	B2	1.6012	0.5560	0.0060*	0.4827	2.7196

* The mean difference is significant at the 0.05 level

Table 36. Comparison of descriptive data of A3, B3, C3.

Permeabilily Parameter		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
					Lower Bound	Upper Bound		
Flux	A3	13.9480	2.0701	0.6546	12.4671	15.4289	11.20	17.49
	B3	12.9980	2.0215	0.6393	11.5519	14.4441	9.65	16.05
	C3	14.1764	2.5595	0.7717	12.4569	15.8959	9.64	16.65
Lag time	A3	4.7450	1.3475	0.4261	3.7810	5.7090	2.79	6.90
	B3	4.7180	1.0623	0.3359	3.9581	5.4779	2.72	6.95
	C3	3.6145	1.7064	0.5145	2.4682	4.7609	2.42	7.16

Table 37. Statistically data of flux of A3, B3, C3 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A3	B3	0.9500	8.8150	0.9146	-16.7937	18.6937
	C3	-0.2284	8.6124	0.9790	-17.5641	17.1074
B3	A3	-0.9500	8.8150	0.9146	-18.6937	16.7937
	C3	-1.1784	8.6124	0.8918	-18.5141	16.1574
C3	A3	0.2284	8.6124	0.9790	-17.1074	17.5641
	B3	1.1784	8.6124	0.8918	-16.1574	18.5141

* The mean difference is significant at the 0.05 level

Table 38. Statistically data of lag time of A3, B3, C3 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A3	B3	0.0270	0.5527	0.9613	-1.0856	1.1396
	C3	1.1305	0.5400	0.0419*	0.0435	2.2175
B3	A3	-0.0270	0.5527	0.9613	-1.1396	1.0856
	C3	1.1035	0.5400	0.0468*	0.0165	2.1905
C3	A3	-1.1305	0.5400	0.0419*	-2.2175	-0.0435
	B3	-1.1035	0.5400	0.0468*	-2.1905	-0.0165

* The mean difference is significant at the 0.05 level

Table 39. Comparison of descriptive data of A1, A2, A3.

Permeabilily Parameter		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
					Lower Bound	Upper Bound		
Flux	A1	26.1060	2.8388	0.8977	24.0752	28.1368	21.96	32.51
	A2	21.4000	3.8080	1.2042	18.6759	24.1241	14.65	26.96
	A3	21.4000	3.8080	1.2042	18.6759	24.1241	14.65	26.96
Lag time	A1	4.4360	0.7049	0.2229	3.9317	4.9403	2.95	5.57
	A2	4.0400	1.3303	0.4207	3.0884	4.9916	2.47	6.67
	A3	4.0400	1.3303	0.4207	3.0884	4.9916	2.47	6.67

Table 40. Statistically data of flux of A1, A2, A3 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	A2	4.7060	8.9604	0.6020	-13.3411	22.7531
	A3	4.7060	8.9604	0.6020	-13.3411	22.7531
A2	A1	-4.7060	8.9604	0.6020	-22.7531	13.3411
	A3	0.0000	8.9604	1.0000	-18.0471	18.0471
A3	A1	-4.7060	8.9604	0.6020	-22.7531	13.3411
	A2	0.0000	8.9604	1.0000	-18.0471	18.0471

* The mean difference is significant at the 0.05 level

Table 41. Statistically data of lag time of A1, A2, A3 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	A2	0.3960	0.4760	0.4098	-0.5627	1.3547
	A3	0.3960	0.4760	0.4098	-0.5627	1.3547
A2	A1	-0.3960	0.4760	0.4098	-1.3547	0.5627
	A3	0.0000	0.4760	1.0000	-0.9587	0.9587
A3	A1	-0.3960	0.4760	0.4098	-1.3547	0.5627
	A2	0.0000	0.4760	1.0000	-0.9587	0.9587

* The mean difference is significant at the 0.05 level

Table 42. Comparison of descriptive data of B1, B2, B3.

Permeabilily Parameter		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
					Lower Bound	Upper Bound		
Flux	B1	25.5973	4.5840	1.3821	22.5177	28.6768	18.40	34.32
	B2	20.3790	3.4620	1.0948	17.9025	22.8555	16.32	25.80
	B3	12.9980	2.0215	0.6393	11.5519	14.4441	9.65	16.05
Lag time	B1	4.1800	1.6157	0.4872	3.0945	5.2655	2.57	8.33
	B2	3.3410	0.5863	0.1854	2.9216	3.7604	2.53	4.23
	B3	4.7180	1.0623	0.3359	3.9581	5.4779	2.72	6.95

Table 43. Statistically data of flux of B1, B2, B3 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
B1	B2	5.2183	8.6637	0.5499	-12.2209	22.6575
	B3	12.5993	8.6637	0.1527	-4.8399	30.0385
B2	B1	-5.2183	8.6637	0.5499	-22.6575	12.2209
	B3	7.3810	8.8676	0.4095	-10.4686	25.2306
B3	B1	-12.5993	8.6637	0.1527	-30.0385	4.8399
	B2	-7.3810	8.8676	0.4095	-25.2306	10.4686

* The mean difference is significant at the 0.05 level

Table 44. Statistically data of lag time of B1, B2, B3 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
B1	B2	0.8390	0.4734	0.0830	-0.1140	1.7920
	B3	-0.5380	0.4734	0.2617	-1.4910	0.4150
B2	B1	-0.8390	0.4734	0.0830	-1.7920	0.1140
	B3	-1.3770	0.4846	0.0067*	-2.3524	-0.4016
B3	B1	0.5380	0.4734	0.2617	-0.4150	1.4910
	B2	1.3770	0.4846	0.0067*	0.4016	2.3524

* The mean difference is significant at the 0.05 level

Table 45. Comparison of descriptive data of C1, C2, C3.

Permeabilily Parameter		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
					Lower Bound	Upper Bound		
Flux	C1	26.0140	5.0872	1.6087	22.3748	29.6532	17.57	30.99
	C2	19.8150	4.8119	1.3891	16.7577	22.8723	13.43	27.91
	C3	14.1764	2.5595	0.7717	12.4569	15.8959	9.64	16.65
Lag time	C1	4.7640	1.0320	0.3263	4.0258	5.5022	3.21	6.05
	C2	4.9317	2.1401	0.6178	3.5719	6.2914	2.71	8.69
	C3	3.6145	1.7064	0.5145	2.4682	4.7609	2.42	7.16

Table 46. Statistically data of flux of C1, C2, C3 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
C1	C2	6.1990	8.3568	0.4618	-10.6035	23.0015
	C3	11.8376	8.5277	0.1715	-5.3085	28.9837
C2	C1	-6.1990	8.3568	0.4618	-23.0015	10.6035
	C3	5.6386	8.1470	0.4922	-10.7419	22.0192
C3	C1	-11.8376	8.5277	0.1715	-28.9837	5.3085
	C2	-5.6386	8.1470	0.4922	-22.0192	10.7419

* The mean difference is significant at the 0.05 level

Table 47. Statistically data of lag time of C1, C2, C3 using LSD test.

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
C1	C2	-0.1677	0.6294	0.7911	-1.4332	1.0979
	C3	1.1495	0.6423	0.0798	-0.1420	2.4409
C2	C1	0.1677	0.6294	0.7911	-1.0979	1.4332
	C3	1.3171	0.6136	0.0369*	0.0833	2.5509
C3	C1	-1.1495	0.6423	0.0798	-2.4409	0.1420
	C2	-1.3171	0.6136	0.0369*	-2.5509	-0.0833

* The mean difference is significant at the 0.05 level

Table 48. Comparison of descriptive data of Peel adhesion 180˚ test at T=0 month.

Peel		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Conc.	Gr.				Lower Bound	Upper Bound		
30%	A1	0.0522	0.0015	0.0007	0.0503	0.0540	0.0502	0.0536
	B1	0.1532	0.0139	0.0062	0.1359	0.1705	0.1389	0.174
	C1	0.0149	0.0035	0.0016	0.0106	0.0192	0.0102	0.0193
40%	A2	0.0609	0.0204	0.0091	0.0356	0.0862	0.0425	0.0947
	B2	0.1563	0.0276	0.0124	0.1220	0.1906	0.1278	0.1903
	C2	0.0479	0.0077	0.0034	0.0384	0.0575	0.0392	0.0577
50%	A3	0.1268	0.0041	0.0018	0.1217	0.1318	0.1198	0.1300
	B3	0.2991	0.0794	0.0355	0.2005	0.3977	0.2146	0.4229
	C3	0.1130	0.0251	0.0112	0.0819	0.1442	0.0914	0.1474

Table 49. Statistically data of Peel adhesion 180˚ test at T=0 month (30% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	B1	-0.1010	0.0053	0.0000*	-0.1125	-0.0896
	C1	0.0373	0.0053	0.0000*	0.0258	0.0488
B1	A1	0.1010	0.0053	0.0000*	0.0896	0.1125
	C1	0.1383	0.0053	0.0000*	0.1268	0.1498
C1	A1	-0.0373	0.0053	0.0000*	-0.0488	-0.0258
	B1	-0.1383	0.0053	0.0000*	-0.1498	-0.1268

* The mean difference is significant at the 0.05 level

Table 50. Statistically data of Peel adhesion 180˚ test at T=0 month (40% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A2	B2	-0.0955	0.0128	0.0000*	-0.1234	-0.0675
	C2	0.0129	0.0128	0.3336	-0.0150	0.0409
B2	A2	0.0955	0.0128	0.0000*	0.0675	0.1234
	C2	0.1084	0.0128	0.0000*	0.0804	0.1364
C2	A2	-0.0129	0.0128	0.3336	-0.0409	0.0150
	B2	-0.1084	0.0128	0.0000*	-0.1364	-0.0804

* The mean difference is significant at the 0.05 level

Table 51. Statistically data of Peel adhesion 180˚ test at T=0 month (50% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A3	B3	-0.1723	0.0304	0.0001*	-0.2387	-0.1060
	C3	0.0137	0.0304	0.6603	-0.0526	0.0801
B3	A3	0.1723	0.0304	0.0001*	0.1060	0.2387
	C3	0.1860	0.0304	0.0001*	0.1197	0.2524
C3	A3	-0.0137	0.0304	0.6603	-0.0801	0.0526
	B3	-0.1860	0.0304	0.0001*	-0.2524	-0.1197

* The mean difference is significant at the 0.05 level

Table 52. Comparison of descriptive data of Peel adhesion 180˚ test at T=1 month.

Peel		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Conc.	Gr.				Lower Bound	Upper Bound		
30%	A1	0.0514	0.0037	0.0016	0.0469	0.0560	0.0491	0.0579
	B1	0.1520	0.0162	0.0073	0.1319	0.1722	0.1414	0.1797
	C1	0.0185	0.0037	0.0017	0.0139	0.0231	0.0139	0.0229
40%	A2	0.0606	0.0020	0.0009	0.0582	0.0631	0.0591	0.0638
	B2	0.1535	0.0101	0.0045	0.1410	0.1660	0.1413	0.1663
	C2	0.0481	0.0099	0.0044	0.0357	0.0604	0.0314	0.0563
50%	A3	0.1158	0.0089	0.0040	0.1048	0.1268	0.1053	0.1263
	B3	0.2677	0.0279	0.0125	0.2331	0.3024	0.2425	0.3144
	C3	0.1191	0.0133	0.0059	0.1025	0.1356	0.1010	0.1375

Table 53. Statistically data of Peel adhesion 180˚ test at T=1 month (30% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	B1	-0.1006	0.0062	0.0000*	-0.1142	-0.0870
	C1	0.0330	0.0062	0.0002*	0.0194	0.0465
B1	A1	0.1006	0.0062	0.0000*	0.0870	0.1142
	C1	0.1336	0.0062	0.0000*	0.1200	0.1471
C1	A1	-0.0330	0.0062	0.0002*	-0.0465	-0.0194
	B1	-0.1336	0.0062	0.0000*	-0.1471	-0.1200

* The mean difference is significant at the 0.05 level

Table 54. Statistically data of Peel adhesion 180˚ test at T=1 month (40% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A2	B2	-0.0929	0.0052	0.0000*	-0.1043	-0.0815
	C2	0.0126	0.0052	0.0329*	0.0012	0.0240
B2	A2	0.0929	0.0052	0.0000*	0.0815	0.1043
	C2	0.1055	0.0052	0.0000*	0.0941	0.1168
C2	A2	-0.0126	0.0052	0.0329*	-0.0240	-0.0012
	B2	-0.1055	0.0052	0.0000*	-0.1168	-0.0941

* The mean difference is significant at the 0.05 level

Table 55. Statistically data of Peel adhesion 180˚ test at T=1 month (50% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A3	B3	-0.1519	0.0117	0.0000*	-0.1775	-0.1264
	C3	-0.0033	0.0117	0.7860	-0.0288	0.0223
B3	A3	0.1519	0.0117	0.0000*	0.1264	0.1775
	C3	0.1487	0.0117	0.0000*	0.1231	0.1743
C3	A3	0.0033	0.0117	0.7860	-0.0223	0.0288
	B3	-0.1487	0.0117	0.0000*	-0.1743	-0.1231

* The mean difference is significant at the 0.05 level

Table 56. Comparison of descriptive data of Peel adhesion 180˚ test at T=2 month.

Peel		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Conc.	Gr.				Lower Bound	Upper Bound		
30%	A1	0.0514	0.0498	0.0024	0.0011	0.0468	0.0528	0.0465
	B1	0.1520	0.1492	0.0188	0.0084	0.1258	0.1726	0.1285
	C1	0.0185	0.0161	0.0042	0.0019	0.0109	0.0213	0.0109
40%	A2	0.0606	0.0559	0.0033	0.0015	0.0518	0.0601	0.0526
	B2	0.1535	0.1489	0.0198	0.0089	0.1243	0.1735	0.1204
	C2	0.0481	0.0456	0.0093	0.0041	0.0341	0.0571	0.0350
50%	A3	0.1158	0.1130	0.0070	0.0031	0.1043	0.1218	0.1040
	B3	0.2677	0.2005	0.0459	0.0205	0.1435	0.2574	0.1275
	C3	0.1191	0.1153	0.0117	0.0052	0.1008	0.1298	0.1005

Table 57. Statistically data of Peel adhesion 180˚ test at T=2 month (30% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	B1	-0.0993	0.0071	0.0000*	-0.1148	-0.0839
	C1	0.0337	0.0071	0.0005*	0.0182	0.0492
B1	A1	0.0993	0.0071	0.0000*	0.0839	0.1148
	C1	0.1331	0.0071	0.0000*	0.1176	0.1485
C1	A1	-0.0337	0.0071	0.0005*	-0.0492	-0.0182
	B1	-0.1331	0.0071	0.0000*	-0.1485	-0.1176

* The mean difference is significant at the 0.05 level

Table 58. Statistically data of Peel adhesion 180˚ test at T=2 month (40% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A2	B2	-0.0930	0.0081	0.0000*	-0.1106	-0.0753
	C2	0.0103	0.0081	0.2259	-0.0073	0.0279
B2	A2	0.0930	0.0081	0.0000*	0.0753	0.1106
	C2	0.1033	0.0081	0.0000*	0.0857	0.1209
C2	A2	-0.0103	0.0081	0.2259	-0.0279	0.0073
	B2	-0.1033	0.0081	0.0000*	-0.1209	-0.0857

* The mean difference is significant at the 0.05 level

Table 59. Statistically data of Peel adhesion 180˚ test at T=2 month (50% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A3	B3	-0.0874	0.0175	0.0003*	-0.1255	-0.0494
	C3	-0.0023	0.0175	0.8992	-0.0403	0.0358
B3	A3	0.0874	0.0175	0.0003*	0.0494	0.1255
	C3	0.0852	0.0175	0.0004*	0.0471	0.1232
C3	A3	0.0023	0.0175	0.8992	-0.0358	0.0403
	B3	-0.0852	0.0175	0.0004*	-0.1232	-0.0471

* The mean difference is significant at the 0.05 level

Table 60. Comparison of descriptive data of Peel adhesion 180˚ test at T=0 month.

Peel		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
PSA	Gr.				Lower Bound	Upper Bound		
2516	A1	0.0522	0.0015	0.0007	0.0503	0.0540	0.0502	0.0536
	A2	0.0609	0.0204	0.0091	0.0356	0.0862	0.0425	0.0947
	A3	0.0149	0.0035	0.0016	0.0106	0.0192	0.0102	0.0193
2852	B1	0.1532	0.0139	0.0062	0.1359	0.1705	0.1389	0.174
	B2	0.1563	0.0276	0.0124	0.1220	0.1906	0.1278	0.1903
	B3	0.0479	0.0077	0.0034	0.0384	0.0575	0.0392	0.0577
4098	C1	0.1268	0.0041	0.0018	0.1217	0.1318	0.1198	0.1300
	C2	0.2991	0.0794	0.0355	0.2005	0.3977	0.2146	0.4229
	C3	0.1130	0.0251	0.0112	0.0819	0.1442	0.0914	0.1474

Table 61. Statistically data of Peel adhesion 180˚ test at T=0 month (Duro-Tak® 87-2516).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	A2	-0.1010	0.0053	0.0128	-0.1125	-0.0896
	A3	0.0373	0.0053	0.0000*	0.0258	0.0488
A2	A1	0.1010	0.0053	0.0128	0.0896	0.1125
	A3	0.1383	0.0053	0.0000*	0.1268	0.1498
A3	A1	-0.0373	0.0053	0.0000*	-0.0488	-0.0258
	A2	-0.1383	0.0053	0.0000*	-0.1498	-0.1268

* The mean difference is significant at the 0.05 level

Table 62. Statistically data of Peel adhesion 180˚ test at T=0 month (Duro-Tak® 87-2582).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
B1	B2	-0.0955	0.0128	0..3336	-0.1234	-0.0675
	B3	0.0129	0.0128	0.0000*	-0.0150	0.0409
B2	B1	0.0955	0.0128	0.3336	0.0675	0.1234
	B3	0.1084	0.0128	0.0000*	0.0804	0.1364
B3	B1	-0.0129	0.0128	0.0000*	-0.0409	0.0150
	B2	-0.1084	0.0128	0.0000*	-0.1364	-0.0804

* The mean difference is significant at the 0.05 level

Table 63. Statistically data of Peel adhesion 180˚ test at T=0 month (Duro-Tak® 87-4098).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
C1	C2	-0.1723	0.0304	0.0001*	-0.2387	-0.1060
	C3	0.0137	0.0304	0.6603	-0.0526	0.0801
C2	C1	0.1723	0.0304	0.0001*	0.1060	0.2387
	C3	0.1860	0.0304	0.0001*	0.1197	0.2524
C3	C1	-0.0137	0.0304	0.6603	-0.0801	0.0526
	C2	-0.1860	0.0304	0.0001*	-0.2524	-0.1197

* The mean difference is significant at the 0.05 level

Table 64. Comparison of descriptive data of Peel adhesion 180˚ test at T=1 month.

Peel		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
PSA	Gr.				Lower Bound	Upper Bound		
2516	A1	0.05	0.00	0.00	0.05	0.06	0.05	0.06
	A2	0.06	0.00	0.00	0.06	0.06	0.06	0.06
	A3	0.12	0.01	0.00	0.10	0.13	0.11	0.13
2852	B1	0.15	0.02	0.01	0.13	0.17	0.14	0.18
	B2	0.15	0.01	0.00	0.14	0.17	0.14	0.17
	B3	0.27	0.03	0.01	0.23	0.30	0.24	0.31
4098	C1	0.02	0.00	0.00	0.01	0.02	0.01	0.02
	C2	0.05	0.01	0.00	0.04	0.06	0.03	0.06
	C3	0.12	0.01	0.01	0.10	0.14	0.10	0.14

Table 65. Statistically data of Peel adhesion 180˚ test at T=1 month (Duro-Tak® 87-2516).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	A2	-0.01	0.00	0.0243*	-0.02	0.00
	A3	-0.06	0.00	0.0000*	-0.07	-0.06
A2	A1	0.01	0.00	0.0243*	0.00	0.02
	A3	-0.06	0.00	0.0000*	-0.06	-0.05
A3	A1	0.06	0.00	0.0000*	0.06	0.07
	A2	0.06	0.00	0.0000*	0.05	0.06

* The mean difference is significant at the 0.05 level

Table 66. Statistically data of Peel adhesion 180˚ test at T=1 month (Duro-Tak® 87-2582).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
B1	B2	0.00	0.01	0.9066	-0.03	0.03
	B3	-0.12	0.01	0.0000*	-0.14	-0.09
B2	B1	0.00	0.01	0.9066	-0.03	0.03
	B3	-0.11	0.01	0.0000*	-0.14	-0.09
B3	B1	0.12	0.01	0.0000*	0.09	0.14
	B2	0.11	0.01	0.0000*	0.09	0.14

* The mean difference is significant at the 0.05 level

Table 67. Statistically data of Peel adhesion 180˚ test at T=1 month (Duro-Tak® 87-4098).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
C1	C2	-0.03	0.01	0.0005*	-0.04	-0.02
	C3	-0.10	0.01	0.0000*	-0.11	-0.09
C2	C1	0.03	0.01	0.0005*	0.02	0.04
	C3	-0.07	0.01	0.0000*	-0.08	-0.06
C3	C1	0.10	0.01	0.0000*	0.09	0.11
	C2	0.07	0.01	0.0000*	0.06	0.08

* The mean difference is significant at the 0.05 level

Table 68. Comparison of descriptive data of Peel adhesion 180˚ test at T=2 month.

Peel		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
PSA	Gr.				Lower Bound	Upper Bound		
2516	A1	0.05	0.00	0.00	0.05	0.05	0.05	0.05
	A2	0.06	0.00	0.00	0.05	0.06	0.05	0.06
	A3	0.11	0.01	0.00	0.10	0.12	0.10	0.12
2852	B1	0.15	0.02	0.01	0.13	0.17	0.13	0.17
	B2	0.15	0.02	0.01	0.12	0.17	0.12	0.17
	B3	0.20	0.05	0.02	0.14	0.26	0.13	0.25
4098	C1	0.02	0.00	0.00	0.01	0.02	0.01	0.02
	C2	0.05	0.01	0.00	0.03	0.06	0.04	0.06
	C3	0.12	0.01	0.01	0.10	0.13	0.10	0.13

Table 69. Statistically data of Peel adhesion 180˚ test at T=2 month (Duro-Tak® 87-2516).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	A2	-0.01	0.00	0.0617	-0.01	0.00
	A3	-0.06	0.00	0.0000*	-0.07	-0.06
A2	A1	0.01	0.00	0.0617	0.00	0.01
	A3	-0.06	0.00	0.0000*	-0.06	-0.05
A3	A1	0.06	0.00	0.0000*	0.06	0.07
	A2	0.06	0.00	0.0000*	0.05	0.06

* The mean difference is significant at the 0.05 level

Table 70. Statistically data of Peel adhesion 180˚ test at T=2 month (Duro-Tak® 87-2582).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
B1	B2	0.00	0.02	0.9896	-0.04	0.04
	B3	-0.05	0.02	0.0219*	-0.09	-0.01
B2	B1	0.00	0.02	0.9896	-0.04	0.04
	B3	-0.05	0.02	0.0214*	-0.09	-0.01
B3	B1	0.05	0.02	0.0219*	0.01	0.09
	B2	0.05	0.02	0.0214*	0.01	0.09

* The mean difference is significant at the 0.05 level

Table 71. Statistically data of Peel adhesion 180˚ test at T=2 month (Duro-Tak® 87-4098).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
C1	C2	-0.03	0.01	0.0002*	-0.04	-0.02
	C3	-0.10	0.01	0.0000*	-0.11	-0.09
C2	C1	0.03	0.01	0.0002*	0.02	0.04
	C3	-0.07	0.01	0.0000*	-0.08	-0.06
C3	C1	0.10	0.01	0.0000*	0.09	0.11
	C2	0.07	0.01	0.0000*	0.06	0.08

* The mean difference is significant at the 0.05 level

Table 72. Comparison of descriptive data of Peel adhesion 180˚ test between T=0 - 2 month. (Formulation A1, A2 and A3)

Peel		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Gr.	T (month)				Lower Bound	Upper Bound		
A1	T=0	0.0522	0.0015	0.0007	0.0503	0.0540	0.0502	0.0536
	T=1	0.0514	0.0037	0.0016	0.0469	0.0560	0.0491	0.0579
	T=2	0.0498	0.0024	0.0011	0.0468	0.0528	0.0465	0.0527
A2	T=0	0.0609	0.0204	0.0091	0.0356	0.0862	0.0425	0.0947
	T=1	0.0606	0.0020	0.0009	0.0582	0.0631	0.0591	0.0638
	T=2	0.0559	0.0033	0.0015	0.0518	0.0601	0.0526	0.0600
A3	T=0	0.1268	0.0041	0.0018	0.1217	0.1318	0.1198	0.1300
	T=1	0.1158	0.0089	0.0040	0.1048	0.1268	0.1053	0.1263
	T=2	0.1130	0.0070	0.0031	0.1043	0.1218	0.1040	0.1204

Table 73. Comparison of descriptive data of Peel adhesion 180˚ test between T=0 - 2 month. (Formulation B1, B2 and B3)

Peel		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Gr.	T (month)				Lower Bound	Upper Bound		
B1	T=0	0.1532	0.0139	0.0062	0.1359	0.1705	0.1389	0.1740
	T=1	0.1520	0.0162	0.0073	0.1319	0.1722	0.1414	0.1797
	T=2	0.1492	0.0188	0.0084	0.1258	0.1726	0.1285	0.1709
B2	T=0	0.1563	0.0276	0.0124	0.1220	0.1906	0.1278	0.1903
	T=1	0.1535	0.0101	0.0045	0.1410	0.1660	0.1413	0.1663
	T=2	0.1489	0.0198	0.0089	0.1243	0.1735	0.1204	0.1728
B3	T=0	0.2991	0.0794	0.0355	0.2005	0.3977	0.2146	0.4229
	T=1	0.2677	0.0279	0.0125	0.2331	0.3024	0.2425	0.3144
	T=2	0.2005	0.0459	0.0205	0.1435	0.2574	0.1275	0.2500

Table 74. Comparison of descriptive data of Peel adhesion 180˚ test between T=0 - 2 month. (Formulation C1, C2 and C3)

Peel		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Gr.	T (month)				Lower Bound	Upper Bound		
C1	T=0	0.0149	0.0035	0.0016	0.0106	0.0192	0.0102	0.0193
	T=1	0.0185	0.0037	0.0017	0.0139	0.0231	0.0139	0.0229
	T=2	0.0161	0.0042	0.0019	0.0109	0.0213	0.0109	0.0219
C2	T=0	0.0479	0.0077	0.0034	0.0384	0.0575	0.0392	0.0577
	T=1	0.0481	0.0099	0.0044	0.0357	0.0604	0.0314	0.0563
	T=2	0.0456	0.0093	0.0041	0.0341	0.0571	0.0350	0.0592
C3	T=0	0.1130	0.0251	0.0112	0.0819	0.1442	0.0914	0.1474
	T=1	0.1191	0.0133	0.0059	0.1025	0.1356	0.1010	0.1375
	T=2	0.1153	0.0117	0.0052	0.1008	0.1298	0.1005	0.1317

Table 75. Statistically data of Peel adhesion 180˚ test between T=0 - 2 month (Formulation A1).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	0.0007	0.0017	0.6698	-0.0029	0.0044
	T=2	0.0024	0.0017	0.1886	-0.0013	0.0060
T=1	T=0	-0.0007	0.0017	0.6698	-0.0044	0.0029
	T=2	0.0016	0.0017	0.3575	-0.0021	0.0053
T=2	T=0	-0.0024	0.0017	0.1886	-0.0060	0.0013
	T=1	-0.0016	0.0017	0.3575	-0.0053	0.0021

* The mean difference is significant at the 0.05 level

Table 76. Statistically data of Peel adhesion 180˚ test between T=0 - 2 month (Formulation A2).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	0.0002	0.0076	0.9752	-0.0163	0.0167
	T=2	0.0049	0.0076	0.5264	-0.0116	0.0214
T=1	T=0	-0.0002	0.0076	0.9752	-0.0167	0.0163
	T=2	0.0047	0.0076	0.5463	-0.0118	0.0212
T=2	T=0	-0.0049	0.0076	0.5264	-0.0214	0.0116
	T=1	-0.0047	0.0076	0.5463	-0.0212	0.0118

* The mean difference is significant at the 0.05 level

Table 77. Statistically data of Peel adhesion 180˚ test between T=0 - 2 month (Formulation A3).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	0.0110	0.0044	0.0280*	0.0014	0.0205
	T=2	0.0137	0.0044	0.0087*	0.0042	0.0233
T=1	T=0	-0.0110	0.0044	0.0280*	-0.0205	-0.0014
	T=2	0.0028	0.0044	0.5411	-0.0068	0.0123
T=2	T=0	-0.0137	0.0044	0.0087*	-0.0233	-0.0042
	T=1	-0.0028	0.0044	0.5411	-0.0123	0.0068

* The mean difference is significant at the 0.05 level

Table 78. Statistically data of Peel adhesion 180˚ test between T=0 - 2 month (Formulation B1).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	0.0012	0.0104	0.9116	-0.0215	0.0238
	T=2	0.0041	0.0104	0.7031	-0.0186	0.0267
T=1	T=0	-0.0012	0.0104	0.9116	-0.0238	0.0215
	T=2	0.0029	0.0104	0.7866	-0.0198	0.0255
T=2	T=0	-0.0041	0.0104	0.7031	-0.0267	0.0186
	T=1	-0.0029	0.0104	0.7866	-0.0255	0.0198

* The mean difference is significant at the 0.05 level

Table 79. Statistically data of Peel adhesion 180˚ test between T=0 - 2 month (Formulation B2).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	0.0028	0.0130	0.8313	-0.0254	0.0310
	T=2	0.0074	0.0130	0.5763	-0.0208	0.0357
T=1	T=0	-0.0028	0.0130	0.8313	-0.0310	0.0254
	T=2	0.0046	0.0130	0.7275	-0.0236	0.0328
T=2	T=0	-0.0074	0.0130	0.5763	-0.0357	0.0208
	T=1	-0.0046	0.0130	0.7275	-0.0328	0.0236

* The mean difference is significant at the 0.05 level

Table 80. Statistically data of Peel adhesion 180˚ test between T=0 - 2 month (Formulation B3).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	0.0313	0.0350	0.3882	-0.0449	0.1076
	T=2	0.0986	0.0350	0.0155*	0.0224	0.1749
T=1	T=0	-0.0313	0.0350	0.3882	-0.1076	0.0449
	T=2	0.0673	0.0350	0.0787	-0.0090	0.1435
T=2	T=0	-0.0986	0.0350	0.0155*	-0.1749	-0.0224
	T=1	-0.0673	0.0350	0.0787	-0.1435	0.0090

* The mean difference is significant at the 0.05 level

Table 81. Statistically data of Peel adhesion 180˚ test between T=0 - 2 month (Formulation C1).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	-0.0036	0.0024	0.1628	-0.0088	0.0017
	T=2	-0.0012	0.0024	0.6271	-0.0064	0.0040
T=1	T=0	0.0036	0.0024	0.1628	-0.0017	0.0088
	T=2	0.0024	0.0024	0.3423	-0.0029	0.0076
T=2	T=0	0.0012	0.0024	0.6271	-0.0040	0.0064
	T=1	-0.0024	0.0024	0.3423	-0.0076	0.0029

* The mean difference is significant at the 0.05 level

Table 82. Statistically data of Peel adhesion 180˚ test between T=0 - 2 month (Formulation C2).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	-0.0001	0.0057	0.9836	-0.0125	0.0123
	T=2	0.0023	0.0057	0.6913	-0.0101	0.0147
T=1	T=0	0.0001	0.0057	0.9836	-0.0123	0.0125
	T=2	0.0024	0.0057	0.6763	-0.0100	0.0149
T=2	T=0	-0.0023	0.0057	0.6913	-0.0147	0.0101
	T=1	-0.0024	0.0057	0.6763	-0.0149	0.0100

* The mean difference is significant at the 0.05 level

Table 83. Statistically data of Peel adhesion 180˚ test between T=0 - 2 month (Formulation C3).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	-0.0060	0.0112	0.6010	-0.0304	0.0184
	T=2	-0.0023	0.0112	0.8436	-0.0267	0.0222
T=1	T=0	0.0060	0.0112	0.6010	-0.0184	0.0304
	T=2	0.0038	0.0112	0.7430	-0.0207	0.0282
T=2	T=0	0.0023	0.0112	0.8436	-0.0222	0.0267
	T=1	-0.0038	0.0112	0.7430	-0.0282	0.0207

* The mean difference is significant at the 0.05 level

Table 84. Comparison of descriptive data of Tack rolling ball test at T=0 month.

Tack		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Conc.	Gr.				Lower Bound	Upper Bound		
30%	A1	6.07	0.07	0.03	5.99	6.15	6.00	6.15
	B1	5.67	0.06	0.03	5.60	5.74	5.60	5.75
	C1	8.42	0.06	0.03	8.35	8.49	8.35	8.50
40%	A2	4.66	0.07	0.03	4.58	4.74	4.60	4.75
	B2	4.13	0.04	0.02	4.07	4.19	4.10	4.20
	C2	6.24	0.11	0.05	6.11	6.37	6.15	6.40
50%	A3	3.29	0.08	0.04	3.19	3.39	3.20	3.40
	B3	2.65	0.05	0.02	2.59	2.71	2.60	2.70
	C3	4.80	0.08	0.04	4.70	4.90	4.70	4.90

Table 85. Statistically data of Tack rolling ball test at T=0 month (30% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	B1	0.40	0.04	0.0000*	0.32	0.48
	C1	-2.35	0.04	0.0000*	-2.43	-2.27
B1	A1	-0.40	0.04	0.0000*	-0.48	-0.32
	C1	-2.75	0.04	0.0000*	-2.83	-2.67
C1	A1	2.35	0.04	0.0000*	2.27	2.43
	B1	2.75	0.04	0.0000*	2.67	2.83

* The mean difference is significant at the 0.05 level

Table 86. Statistically data of Tack rolling ball test at T=0 month (40% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A2	B2	0.53	0.05	0.0000*	0.42	0.64
	C2	-1.58	0.05	0.0000*	-1.69	-1.47
B2	A2	-0.53	0.05	0.0000*	-0.64	-0.42
	C2	-2.11	0.05	0.0000*	-2.22	-2.00
C2	A2	1.58	0.05	0.0000*	1.47	1.69
	B2	2.11	0.05	0.0000*	2.00	2.22

* The mean difference is significant at the 0.05 level

Table 87. Statistically data of Tack rolling ball test at T=0 month (50% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A3	B3	0.64	0.05	0.0000*	0.54	0.74
	C3	-1.51	0.05	0.0000*	-1.61	-1.41
B3	A3	-0.64	0.05	0.0000*	-0.74	-0.54
	C3	-2.15	0.05	0.0000*	-2.25	-2.05
C3	A3	1.51	0.05	0.0000*	1.41	1.61
	B3	2.15	0.05	0.0000*	2.05	2.25

* The mean difference is significant at the 0.05 level

Table 88. Comparison of descriptive data of Tack rolling ball test at T=1 month.

Tack		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Conc.	Gr.				Lower Bound	Upper Bound		
30%	A1	6.04	0.10	0.04	5.92	6.16	5.90	6.15
	B1	5.79	0.11	0.05	5.66	5.92	5.65	5.90
	C1	8.50	0.08	0.04	8.40	8.60	8.40	8.60
40%	A2	4.80	0.12	0.05	4.65	4.95	4.60	4.90
	B2	4.20	0.04	0.02	4.16	4.24	4.15	4.25
	C2	6.31	0.12	0.05	6.16	6.46	6.15	6.45
50%	A3	3.24	0.07	0.03	3.16	3.32	3.15	3.30
	B3	2.72	0.08	0.03	2.63	2.81	2.60	2.80
	C3	4.94	0.10	0.04	4.82	5.06	4.80	5.05

Table 89. Statistically data of Tack rolling ball test at T=1 month (30% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	B1	0.25	0.06	0.0014*	0.12	0.38
	C1	-2.46	0.06	0.0000*	-2.59	-2.33
B1	A1	-0.25	0.06	0.0014*	-0.38	-0.12
	C1	-2.71	0.06	0.0000*	-2.84	-2.58
C1	A1	2.46	0.06	0.0000*	2.33	2.59
	B1	2.71	0.06	0.0000*	2.58	2.84

* The mean difference is significant at the 0.05 level

Table 90. Statistically data of Tack rolling ball test at T=1 month (40% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A2	B2	0.60	0.06	0.0000*	0.46	0.74
	C2	-1.51	0.06	0.0000*	-1.65	-1.37
B2	A2	-0.60	0.06	0.0000*	-0.74	-0.46
	C2	-2.11	0.06	0.0000*	-2.25	-1.97
C2	A2	1.51	0.06	0.0000*	1.37	1.65
	B2	2.11	0.06	0.0000*	1.97	2.25

* The mean difference is significant at the 0.05 level

Table 91. Statistically data of Tack rolling ball test at T=1 month (50% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A3	B3	0.52	0.05	0.0000*	0.41	0.63
	C3	-1.70	0.05	0.0000*	-1.81	-1.59
B3	A3	-0.52	0.05	0.0000*	-0.63	-0.41
	C3	-2.22	0.05	0.0000*	-2.33	-2.11
C3	A3	1.70	0.05	0.0000*	1.59	1.81
	B3	2.22	0.05	0.0000*	2.11	2.33

* The mean difference is significant at the 0.05 level

Table 92. Comparison of descriptive data of Tack rolling ball test at T=2 month.

Tack		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Conc.	Gr.				Lower Bound	Upper Bound		
30%	A1	5.97	0.12	0.05	5.82	6.12	5.80	6.10
	B1	5.77	0.07	0.03	5.69	5.85	5.70	5.85
	C1	8.52	0.10	0.05	8.39	8.65	8.35	8.60
40%	A2	4.74	0.11	0.05	4.60	4.88	4.55	4.85
	B2	4.16	0.11	0.05	4.03	4.29	4.00	4.30
	C2	6.29	0.04	0.02	6.24	6.34	6.25	6.35
50%	A3	3.33	0.10	0.05	3.20	3.46	3.20	3.45
	B3	2.68	0.09	0.04	2.57	2.79	2.55	2.80
	C3	4.88	0.12	0.05	4.74	5.02	4.75	5.05

Table 93. Statistically data of Tack rolling ball test at T=2 month (30% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	B1	0.20	0.06	0.0080*	0.06	0.34
	C1	-2.55	0.06	0.0000*	-2.69	-2.41
B1	A1	-0.20	0.06	0.0080*	-0.34	-0.06
	C1	-2.75	0.06	0.0000*	-2.89	-2.61
C1	A1	2.55	0.06	0.0000*	2.41	2.69
	B1	2.75	0.06	0.0000*	2.61	2.89

* The mean difference is significant at the 0.05 level

Table 94. Statistically data of Tack rolling ball test at T=2 month (40% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A2	B2	0.58	0.06	0.0000*	0.45	0.71
	C2	-1.55	0.06	0.0000*	-1.68	-1.42
B2	A2	-0.58	0.06	0.0000*	-0.71	-0.45
	C2	-2.13	0.06	0.0000*	-2.26	-2.00
C2	A2	1.55	0.06	0.0000*	1.42	1.68
	B2	2.13	0.06	0.0000*	2.00	2.26

* The mean difference is significant at the 0.05 level

Table 95. Statistically data of Tack rolling ball test at T=2 month (50% of acrylic PSA).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A3	B3	0.65	0.07	0.0000*	0.51	0.79
	C3	-1.55	0.07	0.0000*	-1.69	-1.41
B3	A3	-0.65	0.07	0.0000*	-0.79	-0.51
	C3	-2.20	0.07	0.0000*	-2.34	-2.06
C3	A3	1.55	0.07	0.0000*	1.41	1.69
	B3	2.20	0.07	0.0000*	2.06	2.34

* The mean difference is significant at the 0.05 level

Table 96. Comparison of descriptive data of Tack rolling ball test at T=0 month.

Tack		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
PSA	Gr.				Lower Bound	Upper Bound		
2516	A1	6.07	0.07	0.03	5.99	6.15	6.00	6.15
	A2	4.66	0.07	0.03	4.58	4.74	4.60	4.75
	A3	3.29	0.08	0.04	3.19	3.39	3.20	3.40
2852	B1	5.67	0.06	0.03	5.60	5.74	5.60	5.75
	B2	4.13	0.04	0.02	4.07	4.19	4.10	4.20
	B3	2.65	0.05	0.02	2.59	2.71	2.60	2.70
4098	C1	8.42	0.06	0.03	8.35	8.49	8.35	8.50
	C2	6.24	0.11	0.05	6.11	6.37	6.15	6.40
	C3	4.80	0.08	0.04	4.70	4.90	4.70	4.90

Table 97. Statistically data of Tack rolling ball test at T=0 month (Duro-Tak® 87-2516).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	A2	1.41	0.05	0.0000*	1.31	1.51
	A3	2.78	0.05	0.0000*	2.68	2.88
A2	A1	-1.41	0.05	0.0000*	-1.51	-1.31
	A3	1.37	0.05	0.0000*	1.27	1.47
A3	A1	-2.78	0.05	0.0000*	-2.88	-2.68
	A2	-1.37	0.05	0.0000*	-1.47	-1.27

* The mean difference is significant at the 0.05 level

Table 98. Statistically data of Tack rolling ball test at T=0 month (Duro-Tak® 87-2582).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
B1	B2	1.54	0.03	0.0000*	1.47	1.61
	B3	3.02	0.03	0.0000*	2.95	3.09
B2	B1	-1.54	0.03	0.0000*	-1.61	-1.47
	B3	1.48	0.03	0.0000*	1.41	1.55
B3	B1	-3.02	0.03	0.0000*	-3.09	-2.95
	B2	-1.48	0.03	0.0000*	-1.55	-1.41

* The mean difference is significant at the 0.05 level

Table 99. Statistically data of Tack rolling ball test at T=0 month (Duro-Tak® 87-4098).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
C1	C2	2.18	0.05	0.0000*	2.06	2.30
	C3	3.62	0.05	0.0000*	3.50	3.74
C2	C1	-2.18	0.05	0.0000*	-2.30	-2.06
	C3	1.44	0.05	0.0000*	1.32	1.56
C3	C1	-3.62	0.05	0.0000*	-3.74	-3.50
	C2	-1.44	0.05	0.0000*	-1.56	-1.32

* The mean difference is significant at the 0.05 level

Table 100. Comparison of descriptive data of Tack rolling ball test at T=1 month.

Tack		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
PSA	Gr.				Lower Bound	Upper Bound		
2516	A1	6.04	0.10	0.04	5.92	6.16	5.90	6.15
	A2	4.80	0.12	0.05	4.65	4.95	4.60	4.90
	A3	3.24	0.07	0.03	3.16	3.32	3.15	3.30
2852	B1	5.79	0.11	0.05	5.66	5.92	5.65	5.90
	B2	4.20	0.04	0.02	4.16	4.24	4.15	4.25
	B3	2.72	0.08	0.03	2.63	2.81	2.60	2.80
4098	C1	8.50	0.08	0.04	8.40	8.60	8.40	8.60
	C2	6.31	0.12	0.05	6.16	6.46	6.15	6.45
	C3	4.94	0.10	0.04	4.82	5.06	4.80	5.05

Table 101. Statistically data of Tack rolling ball test at T=1 month (Duro-Tak® 87-2516).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	A2	1.24	0.06	0.0000*	1.11	1.37
	A3	2.80	0.06	0.0000*	2.67	2.93
A2	A1	-1.24	0.06	0.0000*	-1.37	-1.11
	A3	1.56	0.06	0.0000*	1.43	1.69
A3	A1	-2.80	0.06	0.0000*	-2.93	-2.67
	A2	-1.56	0.06	0.0000*	-1.69	-1.43

* The mean difference is significant at the 0.05 level

Table 102. Statistically data of Tack rolling ball test at T=1 month (Duro-Tak® 87-2582).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
B1	B2	1.59	0.05	0.0000*	1.48	1.70
	B3	3.07	0.05	0.0000*	2.96	3.18
B2	B1	-1.59	0.05	0.0000*	-1.70	-1.48
	B3	1.48	0.05	0.0000*	1.37	1.59
B3	B1	-3.07	0.05	0.0000*	-3.18	-2.96
	B2	-1.48	0.05	0.0000*	-1.59	-1.37

* The mean difference is significant at the 0.05 level

Table 103. Statistically data of Tack rolling ball test at T=1 month (Duro-Tak® 87-4098).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
C1	C2	2.19	0.06	0.0000*	2.05	2.33
	C3	3.56	0.06	0.0000*	3.42	3.70
C2	C1	-2.19	0.06	0.0000*	-2.33	-2.05
	C3	1.37	0.06	0.0000*	1.23	1.51
C3	C1	-3.56	0.06	0.0000*	-3.70	-3.42
	C2	-1.37	0.06	0.0000*	-1.51	-1.23

* The mean difference is significant at the 0.05 level

Table 104. Comparison of descriptive data of Tack rolling ball test at T=2 month.

Tack		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
PSA	Gr.				Lower Bound	Upper Bound		
2516	A1	5.97	0.12	0.05	5.82	6.12	5.80	6.10
	A2	4.74	0.11	0.05	4.60	4.88	4.55	4.85
	A3	3.33	0.10	0.05	3.20	3.46	3.20	3.45
2852	B1	5.77	0.07	0.03	5.69	5.85	5.70	5.85
	B2	4.16	0.11	0.05	4.03	4.29	4.00	4.30
	B3	2.68	0.09	0.04	2.57	2.79	2.55	2.80
4098	C1	8.52	0.10	0.05	8.39	8.65	8.35	8.60
	C2	6.29	0.04	0.02	6.24	6.34	6.25	6.35
	C3	4.88	0.12	0.05	4.74	5.02	4.75	5.05

Table 105. Statistically data of Tack rolling ball test at T=2 month (Duro-Tak® 87-2516).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
A1	A2	1.23	0.07	0.0000*	1.07	1.39
	A3	2.64	0.07	0.0000*	2.48	2.80
A2	A1	-1.23	0.07	0.0000*	-1.39	-1.07
	A3	1.41	0.07	0.0000*	1.25	1.57
A3	A1	-2.64	0.07	0.0000*	-2.80	-2.48
	A2	-1.41	0.07	0.0000*	-1.57	-1.25

* The mean difference is significant at the 0.05 level

Table 106. Statistically data of Tack rolling ball test at T=2 month (Duro-Tak® 87-2582).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
B1	B2	1.61	0.06	0.0000*	1.49	1.73
	B3	3.09	0.06	0.0000*	2.97	3.21
B2	B1	-1.61	0.06	0.0000*	-1.73	-1.49
	B3	1.48	0.06	0.0000*	1.36	1.60
B3	B1	-3.09	0.06	0.0000*	-3.21	-2.97
	B2	-1.48	0.06	0.0000*	-1.60	-1.36

* The mean difference is significant at the 0.05 level

Table 107. Statistically data of Tack rolling ball test at T=2 month (Duro-Tak® 87-4098).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
C1	C2	2.23	0.06	0.0000*	2.10	2.36
	C3	3.64	0.06	0.0000*	3.51	3.77
C2	C1	-2.23	0.06	0.0000*	-2.36	-2.10
	C3	1.41	0.06	0.0000*	1.28	1.54
C3	C1	-3.64	0.06	0.0000*	-3.77	-3.51
	C2	-1.41	0.06	0.0000*	-1.54	-1.28

* The mean difference is significant at the 0.05 level

Table 108. Comparison of descriptive data of Tack rolling ball test between T=0 - 2 month. (Formulation A1, A2 and A3)

Tack		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Gr.	T (month)				Lower Bound	Upper Bound		
A1	T=0	6.07	0.07	0.03	5.99	6.15	6.00	6.15
	T=1	6.04	0.10	0.04	5.92	6.16	5.90	6.15
	T=2	5.97	0.12	0.05	5.82	6.12	5.80	6.10
A2	T=0	4.66	0.07	0.03	4.58	4.74	4.60	4.75
	T=1	4.80	0.12	0.05	4.65	4.95	4.60	4.90
	T=2	4.74	0.11	0.05	4.60	4.88	4.55	4.85
A3	T=0	3.29	0.08	0.04	3.19	3.39	3.20	3.40
	T=1	3.24	0.07	0.03	3.16	3.32	3.15	3.30
	T=2	3.33	0.10	0.05	3.20	3.46	3.20	3.45

Table 109. Comparison of descriptive data of Tack rolling ball test between T=0 - 2 month. (Formulation B1, B2 and B3)

Tack		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Gr.	T (month)				Lower Bound	Upper Bound		
B1	T=0	5.67	0.06	0.03	5.60	5.74	5.60	5.75
	T=1	5.79	0.11	0.05	5.66	5.92	5.65	5.90
	T=2	5.77	0.07	0.03	5.69	5.85	5.70	5.85
B2	T=0	4.13	0.04	0.02	4.07	4.19	4.10	4.20
	T=1	4.20	0.04	0.02	4.16	4.24	4.15	4.25
	T=2	4.16	0.11	0.05	4.03	4.29	4.00	4.30
B3	T=0	2.65	0.05	0.02	2.59	2.71	2.60	2.70
	T=1	2.72	0.08	0.03	2.63	2.81	2.60	2.80
	T=2	2.68	0.09	0.04	2.57	2.79	2.55	2.80

Table 110. Comparison of descriptive data of Tack rolling ball test between T=0 - 2 month. (Formulation C1, C2 and C3)

Tack		Mean	S.D.	S.E.	95% Confidence Interval for Mean		Min.	Max.
Gr.	T (month)				Lower Bound	Upper Bound		
C1	T=0	8.42	0.06	0.03	8.35	8.49	8.35	8.50
	T=1	8.50	0.08	0.04	8.40	8.60	8.40	8.60
	T=2	8.52	0.10	0.05	8.39	8.65	8.35	8.60
C2	T=0	6.24	0.11	0.05	6.11	6.37	6.15	6.40
	T=1	6.31	0.12	0.05	6.16	6.46	6.15	6.45
	T=2	6.29	0.04	0.02	6.24	6.34	6.25	6.35
C3	T=0	4.80	0.08	0.04	4.70	4.90	4.70	4.90
	T=1	4.94	0.10	0.04	4.82	5.06	4.80	5.05
	T=2	4.88	0.12	0.05	4.74	5.02	4.75	5.05

Table 111. Statistically data of Tack rolling ball test between T=0 - 2 month (Formulation A1).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	0.03	0.06	0.6338	-0.10	0.16
	T=2	0.10	0.06	0.1292	-0.03	0.23
T=1	T=0	-0.03	0.06	0.6338	-0.16	0.10
	T=2	0.07	0.06	0.2763	-0.06	0.20
T=2	T=0	-0.10	0.06	0.1292	-0.23	0.03
	T=1	-0.07	0.06	0.2763	-0.20	0.06

* The mean difference is significant at the 0.05 level

Table 112. Statistically data of Tack rolling ball test between T=0 - 2 month (Formulation A2).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	-0.14	0.07	0.0541	-0.28	0.00
	T=2	-0.08	0.07	0.2459	-0.22	0.06
T=1	T=0	0.14	0.07	0.0541	0.00	0.28
	T=2	0.06	0.07	0.3782	-0.08	0.20
T=2	T=0	0.08	0.07	0.2459	-0.06	0.22
	T=1	-0.06	0.07	0.3782	-0.20	0.08

The mean difference is significant at the .05 level.

Table 113. Statistically data of Tack rolling ball test between T=0 - 2 month (Formulation A3).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	0.05	0.05	0.3715	-0.07	0.17
	T=2	-0.04	0.05	0.4719	-0.16	0.08
T=1	T=0	-0.05	0.05	0.3715	-0.17	0.07
	T=2	-0.09	0.05	0.1205	-0.21	0.03
T=2	T=0	0.04	0.05	0.4719	-0.08	0.16
	T=1	0.09	0.05	0.1205	-0.03	0.21

* The mean difference is significant at the 0.05 level

Table 114. Statistically data of Tack rolling ball test between T=0 - 2 month (Formulation B1).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	-0.12	0.05	0.0365*	-0.23	-0.01
	T=2	-0.10	0.05	0.0735	-0.21	0.01
T=1	T=0	0.12	0.05	0.0365*	0.01	0.23
	T=2	0.02	0.05	0.7018	-0.09	0.13
T=2	T=0	0.10	0.05	0.0735	-0.01	0.21
	T=1	-0.02	0.05	0.7018	-0.13	0.09

* The mean difference is significant at the 0.05 level

Table 115. Statistically data of Tack rolling ball test between T=0 - 2 month (Formulation B2).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	-0.07	0.04	0.1435	-0.17	0.03
	T=2	-0.03	0.04	0.5150	-0.13	0.07
T=1	T=0	0.07	0.04	0.1435	-0.03	0.17
	T=2	0.04	0.04	0.3887	-0.06	0.14
T=2	T=0	0.03	0.04	0.5150	-0.07	0.13
	T=1	-0.04	0.04	0.3887	-0.14	0.06

* The mean difference is significant at the 0.05 level

Table 116. Statistically data of Tack rolling ball test between T=0 - 2 month (Formulation B3).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	-0.07	0.05	0.1614	-0.17	0.03
	T=2	-0.03	0.05	0.5345	-0.13	0.07
T=1	T=0	0.07	0.05	0.1614	-0.03	0.17
	T=2	0.04	0.05	0.4105	-0.06	0.14
T=2	T=0	0.03	0.05	0.5345	-0.07	0.13
	T=1	-0.04	0.05	0.4105	-0.14	0.06

* The mean difference is significant at the 0.05 level

Table 117. Statistically data of Tack rolling ball test between T=0 - 2 month (Formulation C1).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	-0.08	0.05	0.1496	-0.19	0.03
	T=2	-0.10	0.05	0.0783	-0.21	0.01
T=1	T=0	0.08	0.05	0.1496	-0.03	0.19
	T=2	-0.02	0.05	0.7070	-0.13	0.09
T=2	T=0	0.10	0.05	0.0783	-0.01	0.21
	T=1	0.02	0.05	0.7070	-0.09	0.13

* The mean difference is significant at the 0.05 level

Table 118. Statistically data of Tack rolling ball test between T=0 - 2 month (Formulation C2).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	-0.07	0.06	0.2722	-0.20	0.06
	T=2	-0.05	0.06	0.4271	-0.18	0.08
T=1	T=0	0.07	0.06	0.2722	-0.06	0.20
	T=2	0.02	0.06	0.7480	-0.11	0.15
T=2	T=0	0.05	0.06	0.4271	-0.08	0.18
	T=1	-0.02	0.06	0.7480	-0.15	0.11

* The mean difference is significant at the 0.05 level

Table 119. Statistically data of Tack rolling ball test between T=0 - 2 month (Formulation C3).

GROUP	GROUP	Mean Difference	S.E.	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
T=0	T=1	-0.14	0.06	0.0431*	-0.27	-0.01
	T=2	-0.08	0.06	0.2206	-0.21	0.05
T=1	T=0	0.14	0.06	0.0431*	0.01	0.27
	T=2	0.06	0.06	0.3516	-0.07	0.19
T=2	T=0	0.08	0.06	0.2206	-0.05	0.21
	T=1	-0.06	0.06	0.3516	-0.19	0.07

* The mean difference is significant at the 0.05 level

APPENDIX F

Adhesive properties

Table 120. The peel adhesion of 10% w/w Ketoprofen patches (T=0)

n	A1	A2	A3	B1	B2	B3	C1	C2	C3
1	0.0533	0.0508	0.1300	0.1513	0.1410	0.2146	0.0172	0.0469	0.1474
2	0.0528	0.0947	0.1198	0.1740	0.1903	0.2799	0.0141	0.0392	0.0914
3	0.0536	0.0638	0.1286	0.1431	0.1813	0.2559	0.0193	0.0423	0.0942
4	0.0502	0.0425	0.1288	0.1389	0.1413	0.3221	0.0137	0.0577	0.1318
5	0.0510	0.0526	0.1266	0.1588	0.1278	0.4229	0.0102	0.0536	0.1004
Average	0.0522	0.0609	0.1268	0.1532	0.1563	0.2991	0.0149	0.0479	0.1130
S.D.	0.0015	0.0204	0.0041	0.0139	0.0276	0.0794	0.0035	0.0077	0.0251

Table 121. The peel adhesion of 10% w/w Ketoprofen patches (T=1)

n	A1	A2	A3	B1	B2	B3	C1	C2	C3
1	0.0506	0.0638	0.1053	0.1535	0.1529	0.2680	0.0214	0.0550	0.1206
2	0.0579	0.0613	0.1263	0.1414	0.1604	0.3144	0.0229	0.0563	0.1224
3	0.0491	0.0591	0.1229	0.1421	0.1467	0.2425	0.0139	0.0482	0.1138
4	0.0503	0.0595	0.1093	0.1797	0.1663	0.2511	0.0182	0.0494	0.1375
5	0.0493	0.0595	0.1152	0.1435	0.1413	0.2627	0.0160	0.0314	0.1010
Average	0.0514	0.0606	0.1158	0.1520	0.1535	0.2677	0.0185	0.0481	0.1191
S.D.	0.0037	0.0020	0.0089	0.0162	0.0101	0.0279	0.0037	0.0099	0.0133

Table 122. The peel adhesion of 10% w/w Ketoprofen patches (T=2)

n	A1	A2	A3	B1	B2	B3	C1	C2	C3
1	0.0515	0.0600	0.1193	0.1389	0.1410	0.1947	0.0219	0.0417	0.1206
2	0.0496	0.0547	0.1083	0.1709	0.1728	0.2244	0.0143	0.0592	0.1135
3	0.0465	0.0535	0.1204	0.1674	0.1204	0.1275	0.0183	0.0500	0.1317
4	0.0527	0.0526	0.1040	0.1285	0.1502	0.2500	0.0109	0.0422	0.1005
5	0.0488	0.0589	0.1132	0.1401	0.1601	0.2057	0.0151	0.0350	0.1102
Average	0.0498	0.0559	0.1130	0.1492	0.1489	0.2005	0.0161	0.0456	0.1153
S.D.	0.0024	0.0033	0.0070	0.0188	0.0198	0.0459	0.0042	0.0093	0.0117

Table 123. The tack properties of 10% w/w Ketoprofen patches (T=0)

n	A1	A2	A3	B1	B2	B3	C1	C2	C3
1	6.10	4.60	3.35	5.65	4.10	2.70	8.45	6.15	4.75
2	6.00	4.75	3.25	5.60	4.15	2.60	8.40	6.30	4.80
3	6.10	4.65	3.40	5.75	4.10	2.65	8.50	6.40	4.90
4	6.15	4.70	3.20	5.65	4.20	2.60	8.35	6.15	4.85
5	6.00	4.60	3.25	5.70	4.10	2.70	8.40	6.20	4.70
Average	6.07	4.66	3.29	5.67	4.13	2.65	8.42	6.24	4.80
S.D.	0.0671	0.0652	0.0822	0.0570	0.0447	0.0500	0.0570	0.1084	0.0791

Table 124. The tack properties of 10% w/w Ketoprofen patches (T=1)

n	A1	A2	A3	B1	B2	B3	C1	C2	C3
1	6.15	4.80	3.20	5.85	4.20	2.60	8.55	6.40	4.80
2	5.90	4.60	3.30	5.65	4.25	2.70	8.45	6.45	5.05
3	6.10	4.90	3.15	5.90	4.20	2.75	8.60	6.25	5.00
4	6.00	4.90	3.30	5.85	4.15	2.75	8.50	6.30	4.90
5	6.05	4.80	3.25	5.70	4.20	2.80	8.40	6.15	4.95
Average	6.04	4.80	3.24	5.79	4.20	2.72	8.50	6.31	4.94
S.D.	0.0962	0.1225	0.0652	0.1084	0.0354	0.0758	0.0791	0.1194	0.0962

Table 125. The tack properties of 10% w/w Ketoprofen patches (T=2)

n	A1	A2	A3	B1	B2	B3	C1	C2	C3
1	5.90	4.55	3.35	5.80	4.00	2.70	8.55	6.25	5.05
2	6.00	4.75	3.25	5.70	4.15	2.65	8.35	6.35	4.75
3	6.10	4.80	3.45	5.80	4.30	2.70	8.60	6.30	4.90
4	5.80	4.85	3.40	5.85	4.15	2.80	8.50	6.30	4.80
5	6.05	4.75	3.20	5.70	4.20	2.55	8.60	6.25	4.90
Average	5.97	4.74	3.33	5.77	4.16	2.68	8.52	6.29	4.88
S.D.	0.1204	0.1140	0.1037	0.0671	0.1084	0.0908	0.1037	0.0418	0.1151

APPENDIX G

Film thickness

Table 126. The film thickness of 10% w/w Ketoprofen patches (n = 20)

n	Film thickness of ketoprofen patches (cm)								
	A1	A2	A3	B1	B2	B3	C1	C2	C3
1	0.024	0.024	0.025	0.024	0.024	0.024	0.024	0.024	0.024
2	0.025	0.024	0.024	0.024	0.024	0.024	0.024	0.024	0.024
3	0.024	0.024	0.025	0.024	0.024	0.025	0.024	0.024	0.024
4	0.024	0.025	0.024	0.024	0.023	0.024	0.024	0.024	0.024
5	0.024	0.024	0.024	0.024	0.024	0.023	0.024	0.024	0.024
6	0.025	0.025	0.024	0.025	0.024	0.024	0.023	0.024	0.024
7	0.024	0.025	0.025	0.024	0.024	0.024	0.024	0.024	0.025
8	0.024	0.024	0.025	0.024	0.024	0.024	0.024	0.024	0.024
9	0.024	0.024	0.024	0.025	0.024	0.024	0.025	0.025	0.024
10	0.023	0.024	0.024	0.024	0.025	0.025	0.024	0.024	0.024
11	0.024	0.024	0.024	0.024	0.024	0.024	0.024	0.024	0.025
12	0.024	0.024	0.024	0.024	0.024	0.024	0.025	0.024	0.024
13	0.024	0.025	0.024	0.023	0.024	0.025	0.024	0.024	0.024
14	0.025	0.024	0.024	0.024	0.025	0.024	0.025	0.025	0.024
15	0.024	0.023	0.025	0.024	0.024	0.024	0.023	0.024	0.025
16	0.025	0.024	0.024	0.024	0.025	0.024	0.024	0.024	0.024
17	0.025	0.024	0.024	0.025	0.024	0.025	0.024	0.024	0.024
18	0.024	0.025	0.025	0.025	0.024	0.024	0.024	0.024	0.024
19	0.024	0.024	0.024	0.024	0.024	0.024	0.024	0.025	0.024
20	0.024	0.025	0.024	0.023	0.025	0.024	0.024	0.024	0.024
Average	0.0242	0.0243	0.0243	0.0241	0.0242	0.0242	0.0241	0.0242	0.0242
S.D.	0.00052	0.00055	0.00047	0.00055	0.00049	0.00049	0.00051	0.00037	0.00037

APPENDIX H

Content uniformity

Table 127. The content uniformity of 10% w/w Ketoprofen patches (n = 10)

n	Ketoprofen content (% w/w)								
	A1	A2	A3	B1	B2	B3	C1	C2	C3
1	10.15	10.12	10.08	10.11	10.14	10.06	10.23	10.21	10.13
2	10.14	10.09	10.07	10.16	10.07	10.12	10.15	10.02	10.09
3	10.11	10.06	10.04	10.07	10.16	10.11	10.13	10.11	10.13
4	10.15	10.12	10.18	10.14	10.11	10.14	10.01	10.21	10.13
5	10.18	10.16	10.27	10.17	10.14	10.24	10.11	10.06	9.99
6	10.00	10.13	10.06	10.05	9.98	10.10	10.02	10.12	9.95
7	10.02	10.16	10.07	10.07	10.25	10.14	9.99	10.14	10.07
8	10.05	10.15	9.98	10.21	10.21	10.10	10.12	10.22	10.07
9	10.06	10.03	10.13	9.96	10.13	10.08	10.13	10.23	10.03
10	10.09	9.99	10.13	10.17	10.12	10.30	10.12	9.97	10.04
Average	10.09	10.10	10.10	10.11	10.13	10.14	10.10	10.13	10.06
S.D.	0.063	0.057	0.081	0.074	0.073	0.074	0.072	0.090	0.061

APPENDIX I

Preliminary study

Evaluate of appropriate concentration of adhesive in the patches

Adhesive was the essential component in the TDDS. However, it could reduce the permeation rate of drug. Thus, the concentration used should be kept at minimum. The various concentration of adhesive in the formulation at 25%, 50% and 75% w/w was investigated. The procedures were:

1. EtOH, Panasate 800 and ketoprofen were mixed with the ratio of 25:25:10 g (16.67% w/w of ketoprofen).
2. Each type of the adhesives with the different concentrations of 25%, 50% and 75% w/w was added to the mixture in step 1.
3. 3.0 g of the mixture was, then, poured on a backing layer.
4. After 24 hours, each patch was weighted and the concentrations of ketoprofen were calculated.

Table 128. Composition of formulation

Formulation	Adhesive	Concentration of adhesive (% w/w)
1.1	Duro-Tak® 87-2516	25
1.2	Duro-Tak® 87-2516	50
1.3	Duro-Tak® 87-2516	75
2.1	Duro-Tak® 87-2852	25
2.2	Duro-Tak® 87-2852	50
2.3	Duro-Tak® 87-2852	75
3.1	Duro-Tak® 87-4098	25
3.2	Duro-Tak® 87-4098	50
3.3	Duro-Tak® 87-4098	75

Table 129. Concentration of ketoprofen in the preliminary formulation

Formulation	**1.1**					**1.2**					**1.3**				
No.	1	2	3	Average	S.D.	1	2	3	Average	S.D.	1	2	3	Average	S.D.
% KP	19.63	19.95	19.63	19.74	0.1809	14.53	14.62	14.04	14.4	0.3103	7.81	7.62	7.72	7.72	0.0953
Attachment	+					+++					++++				
Precipitation	yes					no					no				
Formulation	**2.1**					**2.2**					**2.3**				
No.	1	2	3	Average	S.D.	1	2	3	Average	S.D.	1	2	3	Average	S.D.
% KP	21.68	22.19	21.93	21.93	0.2565	15.24	15.06	15.43	15.24	0.1859	7.31	7.27	7.23	7.27	0.0423
Attachment	+					+++					++++				
Precipitation	yes					no					no				
Formulation	**3.1**					**3.2**					**3.3**				
No.	1	2	3	Average	S.D.	1	2	3	Average	S.D.	1	2	3	Average	S.D.
% KP	21.68	21.68	22.06	21.8	0.2208	14.04	13.74	13.81	13.86	0.1608	7.23	7.27	7.18	7.23	0.0418
Attachment	+					+++					++++				
Precipitation	yes					no					no				

\+ means Poor adhesion ++ means Fairly good adhesion

\+++ means Good adhesion ++++ means Very good adhesion

The adhesive concentration at 25% and 75% w/w were not appropriate because formulae at 25% showed ketoprofen precipitation and formulae at 75% showed the adhesion which was more than the required level. The variation between 30% to 50% w/w of adhesive were investigated using the same method.

Table 130. Concentration of ketoprofen in the formulation and the calculation of ketoprofen concentration to prepared 10% w/w ketoprofen patches at 30%, 40% and 50% w/w of adhesive.

Formulation	**A1**						**A2**						**A3**					
No.	1	2	3	Average	S.D.	Cal. Conc.*	1	2	3	Average	S.D.	Cal. Conc.*	1	2	3	Average	S.D.	Cal. Conc.*
% KP	18.72	18.52	18.72	18.65	0.11	8.94	16.48	16.67	16.39	16.51	0.14	8.14	14.53	14.62	14.04	14.4	0.31	8.41
Attachment	+						++						+++					
Precipitation	no						No						no					
Formulation	**B1**						**B2**						**B3**					
No.	1	2	3	Average	S.D.	Cal. Conc.*	1	2	3	Average	S.D.	Cal. Conc.*	1	2	3	Average	S.D.	Cal. Conc.*
% KP	20.47	20.35	20.59	20.47	0.12	10.09	17.86	18.07	18.18	18.04	0.16	9.24	15.24	15.06	15.43	15.24	0.18	9.68
Attachment	+						++						+++					
Precipitation	no						No						no					
Formulation	**C1**						**C2**						**C3**					
No.	1	2	3	Average	S.D.	Cal. Conc.*	1	2	3	Average	S.D.	Cal. Conc.*	1	2	3	Average	S.D.	Cal. Conc.*
% KP	19.66	19.89	19.89	19.81	0.13	11.57	17.24	17.34	17.05	17.21	0.15	10.94	14.04	13.74	13.81	13.86	0.16	12.02
Attachment	+						++						+++					
Precipitation	no						No						no					

*, Cal. Conc. = the calculated ketoprofen concentration to prepared 10% w/w ketoprofen patches.

Examples of the calculation: Formulation A1

16.67% w/w of ketoprofen in EtOH:Panasate 800 was mixed with adhesive at 30% w/w; after 24 hr the patch contained **18.65 % w/w** of ketoprofen. **10% w/w** of ketoprofen patch was required. Therefore, concentration of ketoprofen in EtOH:Panasate 800 before mixing with adhesive could be calculated by:

$$\% \text{ w/w of ketoprofen in EtOH:Panasate 800} = \frac{10\% \times 16.67\%}{18.65\%} = 8.94\%$$

Table 131. Confirmation of concentration of ketoprofen in the patches.

Formulation	A1					A2					A3				
No.	1	2	3	Average	S.D.	1	2	3	Average	S.D.	1	2	3	Average	S.D.
% KP	10.13	10.18	10.13	10.14	0.0318	9.96	10.07	10.13	10.05	0.0849	10.10	10.04	10.10	10.08	0.0337
Formulation	B1					B2					B3				
No.	1	2	3	Average	S.D.	1	2	3	Average	S.D.	1	2	3	Average	S.D.
% KP	9.92	10.03	10.09	10.01	0.0890	10.09	9.97	10.03	10.03	0.0604	9.95	9.95	10.08	10.00	0.0705
Formulation	C1					C2					C3				
No.	1	2	3	Average	S.D.	1	2	3	Average	S.D.	1	2	3	Average	S.D.
% KP	9.93	10.10	10.05	10.03	0.0866	10.12	10.12	10.06	10.10	0.0338	10.15	10.09	10.09	10.11	0.0327

APPENDIX J

Appropriate drying condition

Drying condition

Since A1, B1 and C1 contained the highest concentration of vehicle from all formulation. They were chosen to evaluate the appropriate condition for drying the formulation.

Table 132. Test for drying condition

Formulation	Condition					
	60 °C			90 °C		
	10 min	15 min	20 min	10 min	15 min	20 min
Weight at started (g)	3.00	3.00	3.00	3.00	3.00	3.00
A1	**2.06 ± 0.01**	**1.99 ± 0.01**	**1.99 ± 0.02**	**1.87 ± 0.02**	**1.77 ± 0.01**	**1.76 ± 0.02**
B1	2.08 ± 0.01	1.99 ± 0.02	1.99 ± 0.01	1.85 ± 0.01	1.76 ± 0.02	1.75 ± 0.02
C1	2.06 ± 0.01	1.99 ± 0.02	1.98 ± 0.01	1.86 ± 0.02	1.77 ± 0.01	1.77 ± 0.02

From Table 132, the condition of 90 °C for 15 minutes was the suitable condition to prepare the transdermal patches. In formulation A1, ketoprofen weight, adhesive weight and Panasate 800 weight was totally 1.60 g. These components would not evaporate, thus the weight after drying should be close to the total weight, and 1.77 g. was closer to the total weight.

APPENDIX K

Acrylic adhesive properties

Table 133. The adhesive properties of acrylic adhesive in this study.

Adhesive properties	Duro-Tak® 87-2516	Duro-Tak® 87-2852	Duro-Tak® 87-4098
Description	Acrylate-vinylacetate	Acrylic	Acrylate-vinylacetate
Functional group	Hydroxyl group	Carboxyl group	No functional group
Curing	Self-curing	Self-curing	Non-curing
Appearance solution	Clear, slightly yellow liquid	Clear, colorless to slightly yellow liquid	Hazy, colorless liquid
Appearance dry patch	Clear, colorless	Clear, colorless	Clear, colorless
Solid content (%)	41.5	33.5	38.5
Viscosity-Brookfield (mPa·S)	4350	2500	7500
T_g (Theoretical) (°C)	-36	-26	-11
180° test : 20 minutes	10 N/25mm (4 N/cm)	14 N/25mm (5.6 N/cm)	7 N/25mm (2.8 N/cm)
180° test : 24 hours	11 N/25mm (4.4 N/cm)	17 N/25mm (6.8 N/cm)	8 N/25mm (3.2 N/cm)
180° test : 1 week	22 N/25mm (8.8 N/cm)	21 N/25mm (8.4 N/cm)	10 N/25mm (4 N/cm)
Tack (Loop)	8 N/25mm^2	11 N/25mm^2	5 N/25mm^2

BIOGRAPHY

NAME	Rassamee Joradol
DATE OF BIRTH	25 November 1977
PLACE OF BIRTH	Bangkok, Thailand
INSTITUTIONS ATTENDED	Huachiew Chalermprakiet University, 1995-2000: Bachelor of Science in Pharmacy Mahidol University, 2000-2005: Master of Science in Pharmacy (Pharmaceutics)
HOME ADDRESS	38 Romyennives Paknam, Muang, Samutprakarn, 10270