"FORMULATION DEVELOPMENT, OPTIMIZATION AND CHARACTERIZATION OF LIDOCAINE TOPICAL PATCH"

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MASTER OF PHARMACY

IN

PHARMACEUTICAL TECHNOLOGY AND

BIOPHARMACEUTICS

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CERTIFICATE

This is to certify that the dissertation work entitled "Formulation Development, Optimization and Characterization of Lidocaine Topical Patch" submitted by Mr. Rupak jain with Regn. No. (10MPH110) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" is a bonafide research work carried out by the candidate at the Department of pharmaceutics and pharmaceutical technology, Institute of Pharmacy, Nirma University under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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DECLARATION

I hereby declare that the dissertation entitled "Formulation Development, Optimization and Characterization of Lidocaine Topical Patch", is based on the original work carried out by me under the guidance of Dr. Renuka D Mishra, Assistant professor, and Mr. Jigar N shah, Assistant Professor, Department of Pharmaceutics and pharmaceutical technology , Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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A. LIST OF ABBREVIATIONS

Short name	Abbreviation
DMSO	Di-methyl sulphoxide
NMP	N-methyl-2-pyrrolidone
SLS	Sodium Lauryl Sulphate
PSA	Pressure Sensitive Adhesive
EVA	Ethyl Vinyl Acetate
PVC	Poly Vinyl Chloride
TDDS	Topical Drug Delivery System
FDA	Food and Drug Administration
MEGX	Monoethylglycinexylidide
API	Active Pharmaceutical Ingredient
DECS	Drug Excipient Compatibility Study
INDA	Investigational New Drug Application
ANDA	Abbreviated New Drug Application
TGA	Thermo Gravimetric Analysis
PIB	Poly isobutylene
GME	Gelva Multipolymer Emulsion
CSD	Colloidal Silicone Dioxide
HPLC	High performance liquid chromatography
UV	Ultra Violet
SGF	Simulated Gastric Fluid
ICH	International Conference on Harmonisation
µg	Microgram
ml	Milliliter
FTIR	Fourier Transform Infra red
˚C	Degree centigrade
RH	Relative Humidity

B. LIST OF TABLES

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ABSTRACT

The most common chronic complication of herpes zoster (causative agent varicella-zoster virus) is postherpetic neuralgia, in which peripheral neurons discharge spontaneously, having lowered activation thresholds and exhibit an exaggerated response to stimuli. Pain that persists for longer than one to three months after resolution of the rash is generally accepted as the sign of postherpetic neuralgia which occurs mainly in older patients. To overcome the problem of partial pain relief, less patient compliance and tolerability in available traditional treatments, Lidocaine topical patch was formulated by solvent casting method. Absorption study of Lidocaine with various liners and backing films was performed and from the study release liner Saint Gobain 8310 and Backing film EW 9100 was selected due to their less absorption of Lidocaine compared to other release liners and backing films. The topical patches were prepared using Aqueous Gelva as pressure sensitive adhesive, Oleyl Alcohol as a permeation enhancer, talc as a matrix stiffener, Glycerine as a smoothing agent, and Tween 80 as a surfactant.

Optimized batch indicated 99.61% drug content, 1.24±0.11% moisture uptake, 1.42±0.19% moisture content, 4.56±0.17 N/inch Peel adhesion at 180˚ angle, 1.58±0.1 N/18.89mm² Tack property, 43±4.3 min Shear strength, 27.4±1.1 gf/inch Release force, 98±2.3% Drug Release. Cumulative permeation (57.39±10.31µg/cm²) & Skin Flux (5.58±1.00 µg/cm²/hr) of lidocaine topical patch was similar to innovator cumulative permeation (55.72±6.84 µg/cm²) & skin flux (5.42±0.66 µg/cm²/hr) through human cadaver skin after 12 hours ex-vivo permeation study. The selected formulation was found to be stable at 45˚C/75% RH after one month. Thus, it can be concluded that topical patch of Lidocaine was developed with similarity to the innovator and provides better healing compared to marketed oral formulation product.

1. AIM OF THE INVESTIGATION:

The most common chronic complication of herpes zoster is postherpetic neuralgia, in which peripheral neurons discharge spontaneously, have lowered activation thresholds, and exhibit an exaggerated response to stimuli. Pain that persists for longer than one to three months after resolution of the rash is generally accepted as the sign of postherpetic neuralgia which occurs majorly in older patients. Traditional treatments used in an attempt to reduce postherpetic neuralgia include tricyclic antidepressants (e.g. amitriptyline), antiepileptics (e.g. gabapentin) and opioid analgesics, as well as topical treatments such as capsaicin However, adverse systemic effects, partial pain relief, and tolerability are problems in these treatments. Lidocaine is an amide-type local anesthetic and has been known to have analgesic and anti-arrhythmic activity in variable doses. Lidocaine at sub-optimal dose for anesthesia shows analgesic action and thus, can be used for relief of pain associated with post-herpetic neuralgia, but if lidocaine reaches systemic circulations shows some side effects as CNS stimulation, depression, euphoria, tremors, convulsions, unconsciousness, respiratory depression and arrest. Due to these adverse systemic effects and tolerability. Thus, there is a dire need to develop a better dosage form of Lidocaine to treat the postherpetic neuralgia. Hence, the aim of present investigation was to develop a topical lidocaine patch to treat postherpetic neuralgia without systemic toxicity and tolerability.

1.2 OBJECTIVE OF WORK

1. To develop a **drug-in-adhesive topical patch** containing lidocaine to treat post-herpetic neuralgia.
2. To optimize amount of permeation enhancer to give acceptable penetration of drug through skin.
3. To select suitable pressure sensitive adhesive matrix which has sufficiently high drug release and high partitioning of the drug from the resulting patch to skin.
4. To select liner in such way that it will not lock the system i.e. it can be easily removable.

2. INTRODUCTION

Treatment of chronic and acute disease has been accomplished by delivery of drug to patient using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of drug. But recently several technical advancement has been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release.

An ideal controlled drug delivery system is the one which delivers drug at a predetermined rate, locally or systemically, for a specified period of time. An ideal targeted drug delivery system is the one which delivers the drug only to its site of action and not to the non-target organs or tissues. Controlled release is different from sustain release system which simply prolong the drug release and hence plasma drug levels for an extended period of time.[1]

The term-controlled release has a meaning that goes beyond scope of sustained release. The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another.[2] The difference between sustained release and controlled release is shown in **Fig. 2.1**.

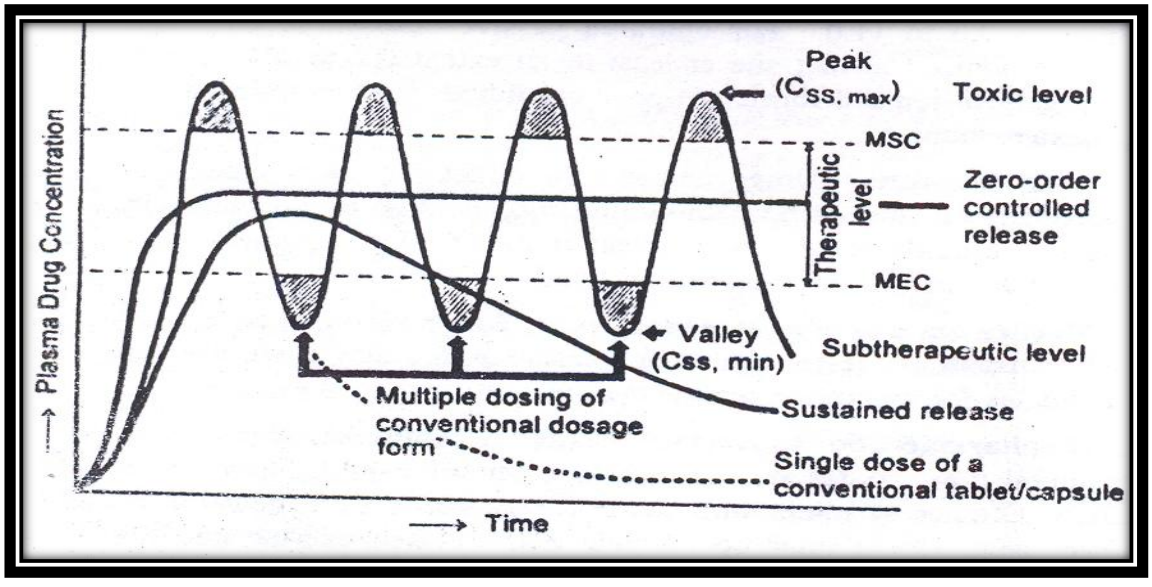


Figure 2.1: Comparative graphs of conventional, sustained and controlled release delivery systems

The classification of controlled drug delivery can be given as follows:

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Out of these classes first class contains new drug delivery systems as transdermal delivery, intra uterine delivery, ocular inserts, and sub dermal implants. The transdermal drug delivery has advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time.

2.1 INTRODUCTION TO TOPICAL DELIVERY

Over the last decades the treatment of illness has been accomplished by administrating drugs to human body via various routes namely oral, sublingual, rectal, parental, topical, inhalation etc.

2.1.1 Definition

Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use[2].

Topical delivery includes two basic types of product:

1. External topicals that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area.
2. Internal topicals that are applied to the mucous membrane orally, vaginally or on anorectal tissues for local activity[3].

For the most part topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or

mucous membranes. Although some unintended drug absorption may occur, it is sub therapeutics in quantities and generally of minor concern[4].

2.1.2 Modes of Delivery to the Skin

2.1.2.1 Topical Delivery

Topical delivery can be defined as the application of a drug-containing formulation to the skin to directly treat cutaneous disorders (e.g., acne) or the cutaneous manifestations of a general disease (e.g., psoriasis), with the intent of confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Although systemic absorption may be unavoidable, it is always unwelcome. Semisolid formulations, in all their diversity, dominate the systems for topical delivery, but foams, sprays, medicated powders, solution, and even medicated adhesive systems are in use[2].

2.1.2.2 Regional Delivery

Regional delivery, in contrast, involves the application of a drug to the skin for the purpose of treating diseases or alleviating disease symptoms in deep tissues beneath the application. Here, the intention is to produce pharmacological actions of the drug within musculature, vasculature, joints, and other, beneath and around the site of application. A selectivity of action over that achieved by systemic administration is sought. Regional activity requires percutaneous absorption and deposition; one is depending on back leakage of drug from the venous drainage of the application site. At best, back diffusion would be an inefficient process; consequently, substantial systemic uptake, although unwelcome, is unavoidable. Nevertheless, regional concentrations are thought to be higher than can be achieved by systemic administration at the same total body exposure to the drug. The focusing of drugs into tissues in this manner has been difficult to prove unequivocally, and thus considerable scepticism exists concerning the validity of regional therapy. Regional delivery is accomplished with traditional ointments and creams as well as large adhesive patches, plasters, poultices and cataplasms[2].

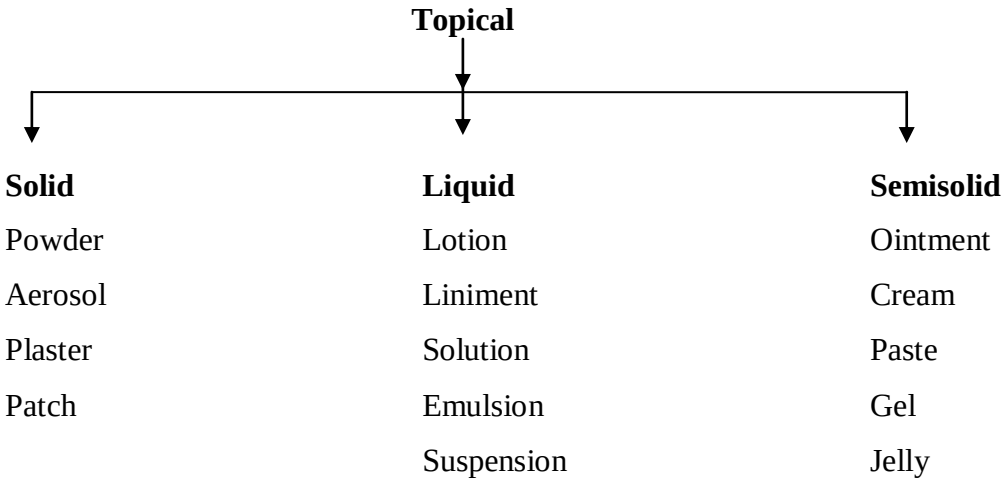
2.1.2.3 Transdermal Delivery

Transdermal delivery involves the application of a drug to the skin to treat systemic disease and is aimed at achieving systemically active levels of the drug. Although such traditional dosage forms as ointments can be employed in this kind of therapy

(e.g., nitro-glycerine ointments), adhesive systems of precisely defined size are the rules. Here, percutaneous absorption with appreciable systemic drug accumulation is absolutely essential. Ideally, there would be no local accumulation of drug, but such accumulation is unavoidable. The drug is forced through the relatively small diffusional window defined by the contact area of the patch. Consequently, high and potentially irritating or sensitizing concentrations of a drug in the viable tissues underlying the patch are preordained by the nature of the delivery process[2].

2.1.3 Classification of Topical Drug Delivery Systems[7]:

Classification of Topical Drug Delivery Systems based on physical state is provided as below:



2.1.4 Advantages of Topical Drug Delivery Systems[3, 5]

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time etc.
- Achievement of efficacy with lower total daily dosage of drug by continuous drug input.
- Avoids fluctuation in drug levels, inter- and intra-patient variations.
- Ability to easily terminate the medications, when needed.

- A relatively large area of application in comparison with buccal or nasal cavity
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.
- Providing utilization of drugs with short biological half-life, narrow therapeutic window.
- Improving physiological and pharmacological response.
- Improve patient compliance.
- Provide suitability for self-medication.

2.1.5 Disadvantages of Topical Drug Delivery Systems[3, 6]

- Skin irritation of contact dermatitis may occur due to the drug and/ or excipients.
- Poor permeability of some drugs through the skin.
- Possibility of allergenic reactions.
- Can be used only for drugs which require very small plasma concentration for action
- Enzyme in epidermis may denature the drugs.
- Drugs of larger particle size not easy to absorb through the skin.

2.1.6 Examples of Dosage Forms Used In Topical Delivery.

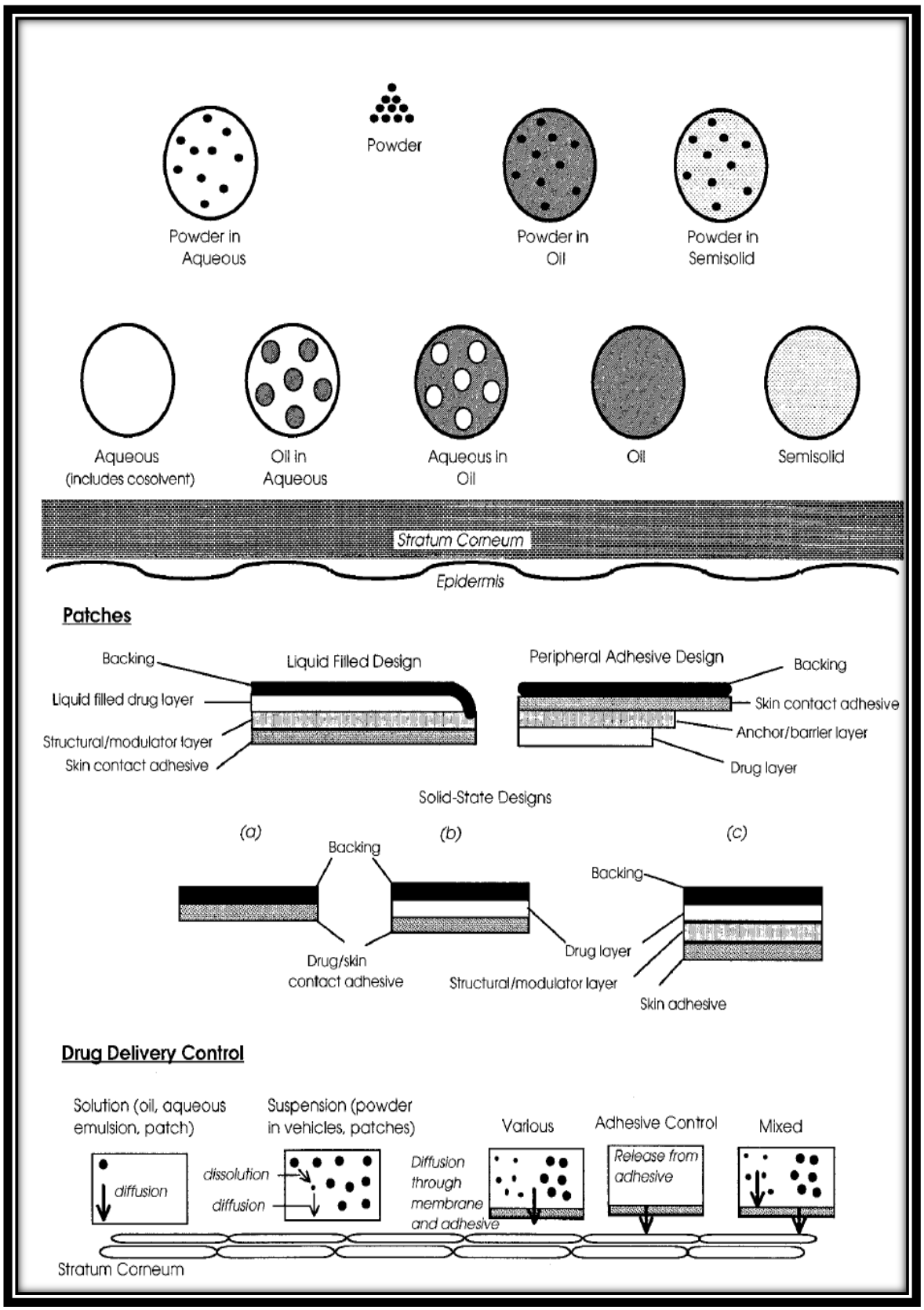


Figure 2.2: Examples of Dosage Forms Used in Topical Delivery[2]

2.2 Anatomy and Physiology of Skin[9,10,11]

The skin, the heaviest single organ of the body, combines with the mucosal lining of the respiratory, digestive and urogenital tracts to form a capsule which separates the internal body structures from external environment. For an average 70 kg human with skin surface area of 1.8 m^2, a typical square centimeter covers 10 hair follicles, 12 nerves, 15 sebaceous glands, 100 sweat glands and 3 blood vessels with 92 cm total length (**Fig. 2.3**).

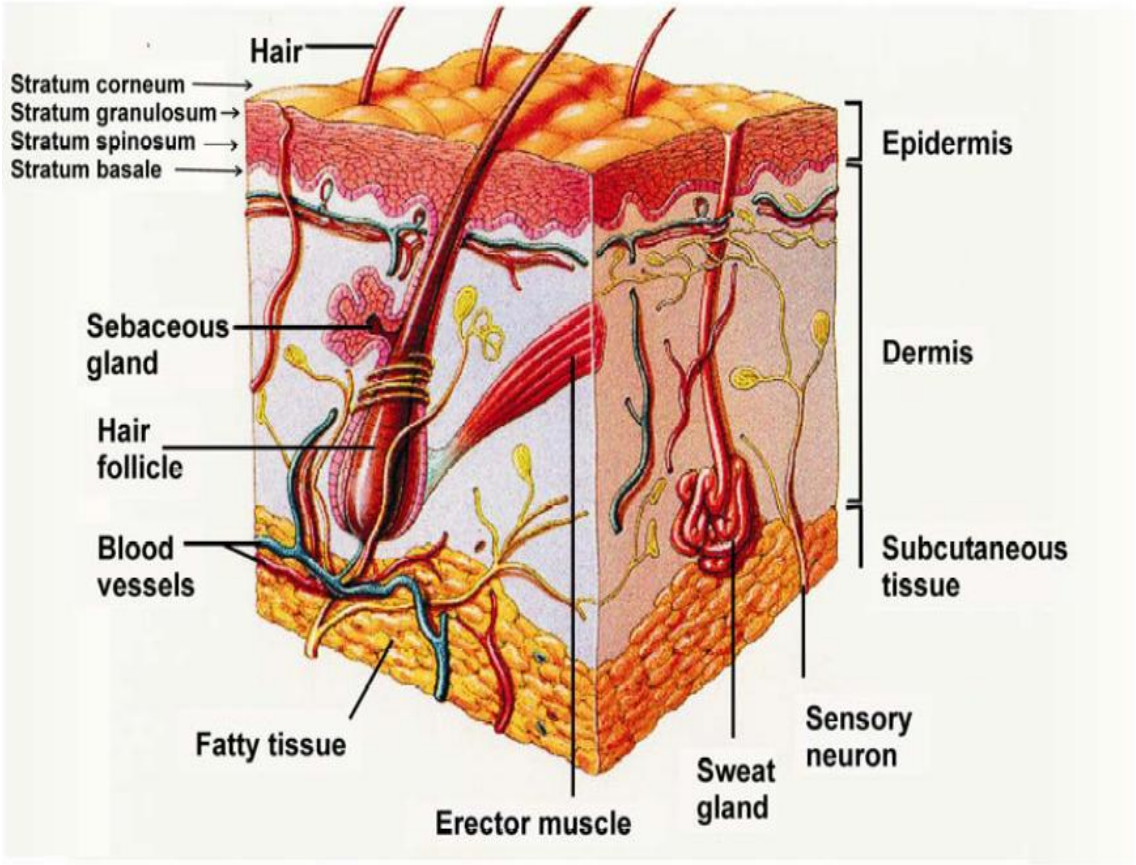


Figure 2.3: Structure of skin

Human skin comprises of three distinct but mutually dependent tissues:-

A. The stratified, a vascular, cellular epidermis
B. Underlying dermis of connective tissues
C. Hypodermis

A. Epidermis

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum and the remainder of the epidermis so called viable epidermis cover a major area of skin.

i) Stratum corneum

This is the outermost layer of skin also called as horny layer. It is approximately 10mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nature of the horny layer depends critically on its constituents: 75-80% proteins, 5-15% lipids on a dry weight basis. Protein fraction predominantly contains alpha-keratin (70%) with some beta keratin (10%) and cell envelope (5%). Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane. The architecture of horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as a protein "bricks" embedded in lipid "mortar." The lipids are arranged in a multiple bilayers and it has been suggested that there is sufficient amphiphilic material in the lipid fraction such as polar free fatty acids and cholesterol to maintain a bilayer form.

ii) Viable epidermis

This is situated beneath the stratum corneum and varies in thickness from 0.06mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horny cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

B. Dermis

Dermis is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature.

It also provides nutrients and oxygen to the skin, while removing toxins and waste products. Capillaries reach to within 0.2mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a very low and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation.

C. Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanic protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

2.2.1 Functions of Skin[9,12]

- Protection – from invasion by microbes, chemicals, physical agents (e.g. mild trauma, UV light) and dehydration.
- Reflex action – due to sensory nerves to stimuli.
- Regulation of body temperature – regulate body temperature about 36.8°C (98.4°F) with variation of 0.5°C to 0.75°C.
- Formation of vitamin D – fatty substance present in skin, 7-dehydrocholesterol, in presence of UV light from sun is converted to vitamin D.
- Absorption – absorbs some drug with low molecular weight as well as toxic chemicals like mercury.
- Excretion – excretes sodium chloride in sweat, urea when kidney function is impaired and aromatic substances (e.g. garlic and other spices).

2.2.2 Fundamentals of Skin Permeation[12]

Until the last century the skin was supposed to be impermeable with exception to gases. However, in the current century the study indicated the permeability to lipid soluble drugs like electrolytes.

Also it was recognized that various layers of skin are not equally permeable i.e. epidermis is less permeable than dermis. After a large controversy, all doubts about stratum corneum permeability were removed and using isotopic tracers, it was suggested that stratum corneum greatly hamper permeation.

A) Stratum corneum as skin permeation barrier

The average human skin have 40-70 hair follicles and 200-250 sweat ducts per square centimetre area. especially water-soluble substances pass faster through these ducts, Therefore stratum corneum acts as a passive route for diffusion of neutral molecules.

Series of steps in sequence:

- Sorption of a penetrant molecule on surface layer of stratum corneum.
- Diffusion through it and viable epidermis.
- The molecule is taken up into the microcirculation for systemic distribution (**Fig. 2.4).**

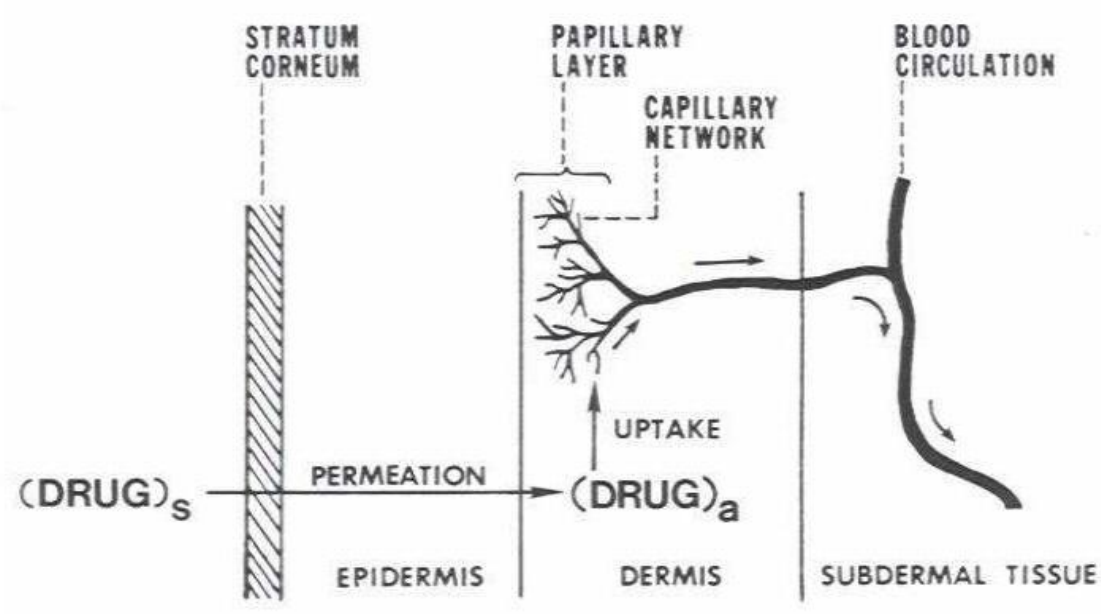


Figure 2.4: A Multilayer skin model showing sequence of transdermal permeation of drug for systemic delivery

Table 2.1: Regional variation in water permeability of stratum corneum

Sr. no.	Skin region	Thickness (µm)	Permeation ($mg/cm^2/hr$)	Diffusivity ($cm^2/sec \times 10^{10}$)
1	Abdomen	15	0.34	6
2	Volar forearm	16	0.31	5.9
3	Back	10.5	0.29	3.5
4	Forehead	13	0.85	12.9
5	Scrotum	5	1.70	7.4
6	Back of hand	49	0.56	32.3
7	Palm	400	1.14	535
8	Plantar	600	3.90	930

B) Intracellular verses transcellular diffusion

Intracellular regions in stratum corneum are filled with lipid rich amorphous material. In dry stratum corneum intracellular volume may be 5% to 1% in fully hydrated stratum corneum.

C) Permeation Pathways[2, 9]

Percutaneous absorption involves passive diffusion of the substances through the skin. A molecule may use two diffusional routes to penetrate normal intact skin, the appendageal route and the epidermal route.

I. Appendageal route

Appendageal route comprises transport via sweat glands and hair follicles with their associated sebaceous glands (**Fig. 2.5**). These routes circumvent penetration through the stratum corneum and are therefore known as "shunt" routes. This route is considered to be of minor importance because of its relatively small area, approximately 0.1 % of the total skin area.

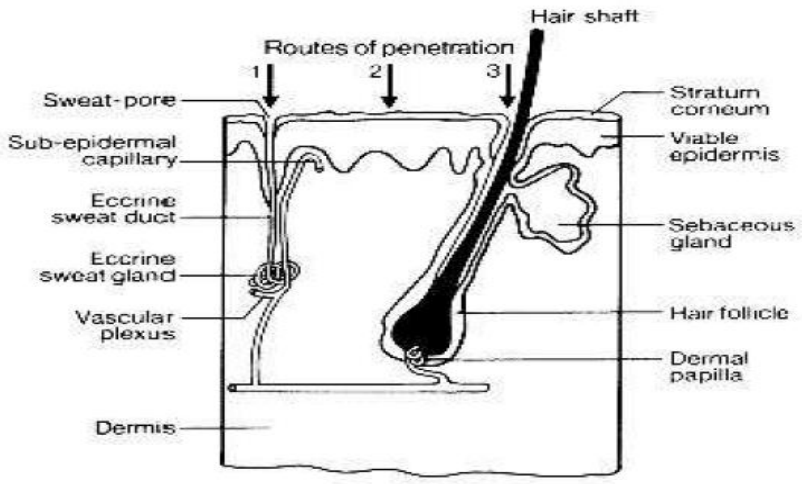


Figure 2.5: Routes for drug permeation

II. Epidermal route

For drugs, which mainly cross-intact horny layer, two potential micro routes exists, the transcellular (intracellular) and intercellular pathways (**Fig. 2.6**).

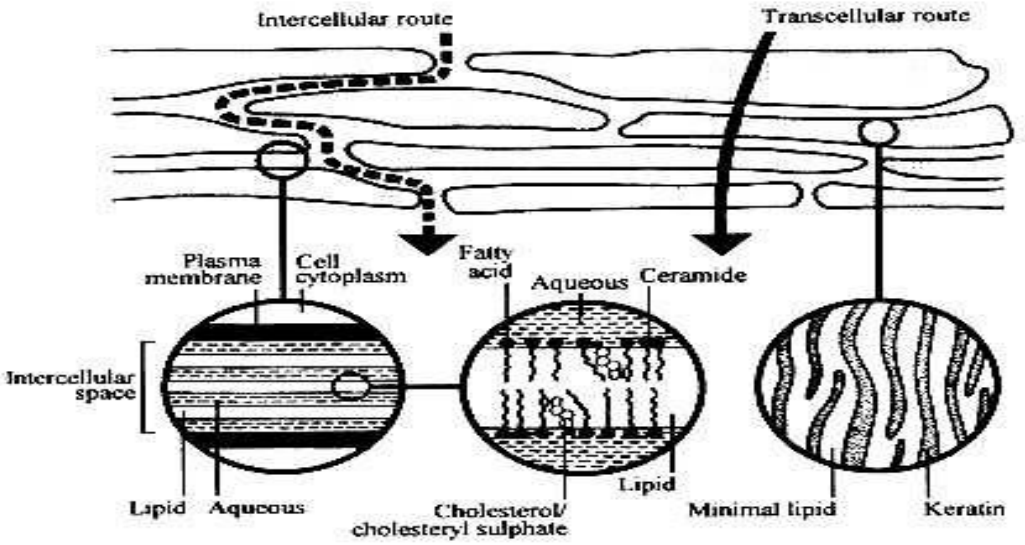


Figure 2.6: Epidermal routes for drug permeation

i) Transcellular

Transcellular pathway means transport of molecules across epithelial cellular membrane. These include passive transport of small molecules, active transport of ionic and polar compounds and endocytosis and transcytosis of macromolecules.

ii) Paracellular

Paracellular pathway means transport of molecules around or between the cells. Tight junctions or similar situations exist between the cells. The principal pathway taken by a permeant is decided mainly by the partition coefficient (log k). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants (o/w log k >2) traverse the stratum corneum via the intercellular route. Most permeants permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs.

2.2.3 KINETICS OF SKIN PERMEATION

Knowledge of skin permeation is vital in the successful development of topical formulation. Permeation of a drug involves the following steps,

- Sorption by stratum corneum,
- Penetration of drug though viable epidermis,
- Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physicochemical properties. The rate of permeation across the skin (dQ/dt) is given by:

$$\frac{\mathbf{dQ}}{\mathbf{dt}} = \mathbf{P}(\mathbf{C_d} - \mathbf{C_r}) - - - - - - (\mathbf{1})$$

Where C_d and C_r are the concentration of the skin penetrant in the donor compartment, i.e., on the surface of stratum corneum and in the receptor compartment, i.e., body respectively. Ps is the overall permeability coefficient of the skin tissue to the penetrant. This permeability coefficient is given by the relationship[13, 14]:

$$\mathbf{P_s} = \frac{\mathbf{K_s} * \mathbf{D_{ss}}}{\mathbf{h_s}} - - - - - - - (\mathbf{2})$$

Where K_s is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum, D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and hs is the overall thickness

of skin tissues. As K_s, D_{ss}, and h_s are constant under given conditions the permeability coefficient P_s for a skin penetrant can be considered to be constant. From equation (1) it is clear that a constant rate of drug permeation can be obtained only when $C_d >> C_r$, i.e., the drug concentration at the surface of the stratum corneum C_d is consistently and substantially greater than the drug concentration in the body C_r. The equation becomes[13, 14]:

$$\frac{dQ}{dt} = P_s * C_d \quad (3)$$

The rate of skin permeation is constant provided the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant the drug should be released from the device at a rate R_r, i.e., either constant or greater than the rate of skin uptake R_a, i.e., $R_r >> R_a$. Since $R_r >> R_a$, the drug concentration on the skin surface C_d is maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum C_s, i.e., $C_d >> C_s$. Therefore a maximum rate of skin permeation is obtained and is given by the equation:

$$\frac{dQ}{dt} = P_s * C_s \quad (4)$$

From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient P_s and is equilibrium solubility in the stratum corneum C_s. Thus skin permeation appears to be stratum corneum limited[13. 14].

2.2.4 FACTOR AFFECTING TOPICAL PERMEATION[15, 16]

There are various factors that affect the topical permeation of drug, these are:

1. Physicochemical properties of drug molecule

a. Partition co-efficient of drug molecule
b. pH of drug
c. Permeant concentration

2. Physicochemical properties of drug delivery system

a. Release characteristics
b. Composition of drug delivery system
c. Enhancement of transdermal permeation.

3. Physiological and pathological conditions of skin

a. Skin hydration
b. Skin temperature
c. Reservoir effect of homogeneous system
d. Lipid layer
e. Regional variation
f. Pathological injury

4. Drug metabolism and drug loss while permeation through skin

a. Drug metabolism
b. Drug reaching to localized site of action
c. Drug binding to the contents of epidermis.

2.3 TOPICAL PATCH

Topical patch is a device for delivering the therapeutic substances through the skin for topical effect at predetermined and controlled rate; comprising of backing membrane, drug incorporated into matrix, release liner and with/without rate controlling membrane.

2.3.1 Topical Patch Design

Flynn and Cleary provided reviews on the design, properties, characteristics and manufacturing costs of a variety of patch configurations. Briefly, all adhesive transdermal systems exist as polymeric laminates. They minimally have three layers, a backing layer, an adhesive layer and a protective release layer. The outer surface of the patch is the top of the backing layer and contains product particulars. The backing layer itself is made from sheets of polymer and must adhere strongly to the adhesive layer below it. The "peel- off" protective or release liner lies below the adhesive layer and is also made from polymeric sheets and must have minimal ability to bind to the adhesive layer. This is required since just before attachment to skin, the release liner has to be peeled off and therefore should pull away freely from the rest of the patch. Such lack of adherence is achieved by coating the release liner with a fluorocarbon or other non-stick material[17].

2.3.2 Basic Components of Topical Patch

The component of topical patch includes:

A. Polymer matrix or matrices

B. The drug (active pharmaceutical ingredient)

C. Permeation enhancers

D. Pressure sensitive adhesives

E. Backing membrane and release liner

F. Microporous or semipermeable membrane

A. POLYMER MATRIX

The Polymer controls the release of the drug from the device. Possible useful polymers for topical devices are:

1. **Natural Polymers**
   Cellulose Derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums And Their Derivatives, Natural Rubber, Starch, Etc.
2. **Synthetic Elastomers**
   Polybutadieine, Terpene Rubber, Polysiloxane, Silicone Rubber, Nitrile, Acrylonitrile, Butyl Rubber, Styrenebutadieine Rubber, Neoprene, Etc.
3. **Synthetic polymers**
   Polyvinyl Alcohol, Polyvinyl Chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy, Etc.

B. DRUG

To develop a successful transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

i. Biological properties

1. Drug flux should be in between 10 -20µg/cm2/hr range from saturated solution of drug
2. Drug should have short half life. (10hr or less)
3. Oral dose of drug should be minimum.
4. There should be no skin toxicity of drug to be delivered.

ii. Physicochemical properties

1. The drug should have a molecular weight less than approximately 1000 Daltons
2. The drug should have affinity for both, lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin
3. The drug should have short biological half-life
4. Concentration gradient across the membrane is directly proportional to the log solubility of drug in lipid phase which is reciprocal of its melting point so ideal drug candidate should have melting point below 200˚C
5. The compound having log P value in-between 1 and 4 is good candidate for transdermal delivery.

C. PERMEATION ENHANCERS

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrate. (Table 2.2)

i) Water

One long-standing approach to improve transdermal and topical delivery of medicaments is to use water. The water content of human stratum corneum is typically around 15.20% of the tissue dry weight, although clearly this varies depending on the external environment such as humidity. Soaking the skin in water, exposing the membrane to high humidity or, as is more usual under clinical conditions, occluding the tissue so preventing transepidermal water loss can allow the stratum corneum to reach water contents in equilibrium with that of the underlying epidermal skin cells. Typically, from thermal analysis and spectroscopic methodologies, some 25.35% of the water present in stratum corneum can be assessed as bound, i.e., associated with some structural elements within the tissue. The remaining water within the tissue is free and is available to act as a solvent within the membrane for polar permeants[17].

ii) Sulphoxide and similar chemical

Dimethylsulphoxide (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful aprotic solvent which hydrogen bonds with itself rather than with water; it is colorless, odourless and is hygroscopic and is often used in many areas of pharmaceutical sciences as a “universal solvent”.

Despite the evidence that DMF irreversibly damage human skin membranes, this penetration enhancer has been used in vivo and promoted the bioavailability of betamethasone-17- benzoate as judged by the vasoconstrictor assay[18, 19].

iii) Azones®

Azone® (1-dodecylazacycloheptan-2-one or Lauracapram®) was the first molecule specifically designed as a skin penetration enhancer. Chemically it may be considered to be a hybrid of a cyclic amide, as with pyrrolidone structures. Surprisingly, Azone is most effective at low concentrations, being employed typically between 0.1% and 5%, often between 1% and 3%.

It is expected that this enhancer partitions into the bilayer lipids of epidermis to disrupt their packing arrangement; integration into the lipids is unlikely to be homogeneous considering the variety of compositional and packing domains within stratum corneum lipid bilayers[18, 19].

iv) Fatty acids

From the extensive experiments, it appears that saturated alkyl chain lengths of around C_{10}-C_{12} attached to a polar head group yields a potent enhancer. These acids disrupt the lipidic arrangement of skin[18, 19].

v) Alcohol, fatty alcohol and glycols

Alcohol is a polar solvent it inserts into the polar head group region of the lipid structure and cause “fluidization” by loosening of packing structure of lipid and drug molecule easily penetrates into the skin. A further potential mechanism of action arising as a consequence of rapid ethanol permeation across the skin has been reported; solvent “drag” may carry Permeant into the tissue as ethanol traverses. Propylene glycol may partition into the tissue facilitating uptake of the drug into skin and there may be some minor disturbance to intercellular lipid packing within the stratum corneum bilayers[18, 19].

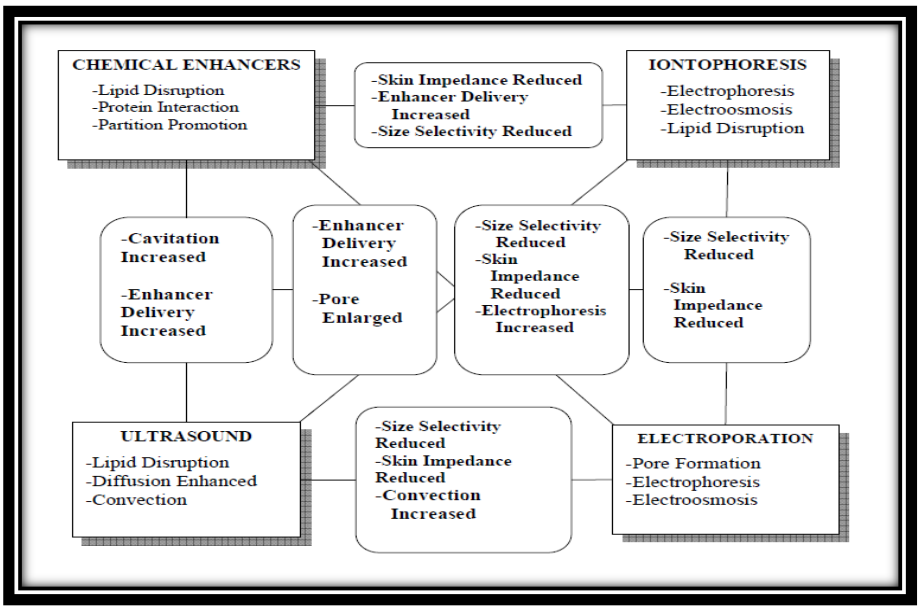


Figure 2.7: Mechanisms for the actions of topical penetration enhancers (in main rectangular boxes) and possible synergistic actions between methods as illustrated in connecting boxes (rounded rectangles)[18]

vi) Pyrrolidones

N-methyl-2-pyrrolidone (NMP) and 2-pyrrolidone (2P) are the most widely studied enhancers of this group. The mechanisms of the sulphoxide penetration enhancers and DMSO in particular, are complex.

DMSO is widely used to denature proteins and on application to human skin has been shown to change the intercellular keratin confirmation, from á helical to an â sheet. As well as an effect on the proteins, DMSO has also been shown to interact with the intercellular lipid domains of human stratum corneum. Considering the small highly polar nature of this molecule it is feasible that DMSO interacts with the head groups of some bilayer lipids to distort to the packing geometry. Further, DMSO within skin membranes may facilitate drug partitioning from a formulation into this "universal solvent" within the tissue[18, 19].

vii) Fatty alcohols (or Alkanols)

These may also have penetration enhancing activity. These molecules are typically applied to the skin in a co-solvent often PG at concentrations between 1% to 10%[18, 19].

viii) Surfactant

Anionic surfactants include sodium lauryl sulphate (SLS), cationic surfactants include tyltrimethyl ammonium bromide, the nonoxynol surfactants are non-ionic surfactants and zwitterionic surfactants include dodecyl betaine. Anionic and cationic surfactants have potential to damage human skin; SLS is a powerful irritant and increased the trans epidermal water loss in human volunteers in vivo and both anionic and cationic surfactants swell the stratum corneum and interact with intercellular keratin. Non-ionic surfactants tend to be widely regarded as safe. Surfactants generally have low chronic toxicity and most have been shown to enhance the flux of materials permeating through biological membranes[18, 19].

ix) Urea

Urea is a hydrating agent (a hydrotrope) used in the treatment of scaling conditions such as psoriasis, ichthyosis and other hyper-keratotic skin conditions. Applied in water in oil vehicle, urea alone or in combination with ammonium lactate produced significant stratum corneum hydration and improved barrier function when compared to the vehicle alone in human volunteers in vivo. Urea also has keratolytic properties, usually when used in combination[19].

x) Essential oils, terpene and terpenoids

Limonene, menthol, the essential oils of eucalyptus and chenopodium were effective penetration enhancers for flouorouracil traversing in human skin in vivo. Hydrocarbon or the non-polar group containing terpenes, such as limonene provide better enhancement for lipophilic permeants than do the polar terpenes. Relationship tends to imply that one mechanism by which these agents operate is to modify the solvent nature of the stratum corneum, improving drug partitioning into the tissue. Many terpens permeate human skin well, and large amounts of terpenes (up to 1.5 µg/cm2) were found in the epidermis after application from a matrix type patch. With loss of terpenes, which are generally good solvents, from a formulation there could be an alteration to the thermodynamic activity of the Permeant in the formulation as was described for ethanol. Terpenes may also modify drug diffusivity through the membrane. During steady state permeation experiments using Terpenes as penetration enhancers, the lag time for permeation is usually reduced.

Table 2.2: Different classes of Permeation enhancers[15]

Sr. no.	Types of Permeation Enhancers	Examples of Permeation Enhancers
1	Sulfoxide and similar Compounds	Dimethylsulfoxide, Dimethylacetamide, Dimethylformamide, N-methylformamide
2	Pyrrolidones	2-Pyrrolidone 1-methyl 2-pyrrolidone, 5-methyl 2-pyrrolidone, 1,5 dimethyl, 2-pyrrolidone, 1-ethyl 2 pyrrolidone
3	Fatty acids	Oleic acid, Lauric acid, Linolic acid, Myristic acid
4	Azone or Lauracapram and its derivatives	1-dodecylazacycloheptan-2-one
5	Urea	Urea
6	Anionic, cationic, non-ionic Surfactants	Sodium laurayl sulphate, Trimethyl ammonium bromide, Synperonic NP series
7	Solvents	Ethanol, Lauryl alcohol, Linolenyl alcohol, Octanol
8	Glycols	Propylene glycol, Polyethylene glycol 400
9	Terpenes and terpenoids	Limonene, menthol, camphor

D. PRESSURE SENSITIVE ADHESIVES (PSA)

For transdermal patch, pressure-sensitive adhesives (PSAs) play a major role, serving as the matrix that carries everything active (such as additives and permeation enhancers) and the means for making the patch stick to the skin. There are several classes of PSA (Table 2.3) and each one is used for a very specific reason. The PSA must stick to the skin immediately and stay there for as long as it is needed. The correct choice of PSA has a critical effect on the stability of the system, the release of the active, the dermatotoxicity potential, and the accurate administration of the drug. There are three major families of PSAs: rubber-based PSAs, acrylic PSAs in the form of acrylic solutions, emulsion polymers or hot melts, and silicon PSAs[18, 20].

Table 2.3: Adhesive used in transdermal patch[20]

Sr. no.	Type of Adhesive	Advantages	Limitations
1	**Polyisobutylenes** Vistanex® LM-MS, LM-MH , LM-H (Exxon) Oppanol® B10, B15, B30, B50, B100 (BASF) Durotak 608A	Good adherence to low and high energy surfaces, relatively inert, high initial adhesion, useful in broad temperature range, flexibility	Low tack and adhesion without additives, low shear and irradiation resistance, molecular weight variability, poor ageing, moderate cost
2	**Polysiloxanes** BioPSA 7-4100, 4200, 4300, 4400, 4500, 4600	Good UV, solvent and hydrolysis resistance, excellent adhesion build-up, easy to apply, good service life	Fair initial adhesion
3	**Polyacrylate copolymers** Durotak 2052, 2287, 2516 Gelva 737,788, 4098	Chemical and biological inertness, extremely low toxicity, sensitization and irritation, retaining of mechanical and physiochemical properties on the skin	Highest cost, no aggressive behaviour

1. Desirable feature of pressure sensitive adhesive[18]

- It should adhere to the skin aggressively, should be easily removed.
- It should not leave an unwashable residue on the skin.
- It should not irritate or sensitize the skin.
- It should be physically and chemical compatible with the drug, excipients and enhancers of the device of which it is a part.
- Permeation of drug should not be affected.
- The delivery of simple or blended permeation enhancers should not be affected.

E. BACKING MEMBRANE

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin, e.g., EVA co-polymer, metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc), etc[20].

F. RELEASE LINER

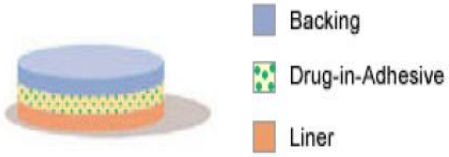
It gives protection to drug matrix and it is removed before application. Siliconized PVC, polyethylene are generally used as release liner[17].

2.3.3 Desirable features for Patches

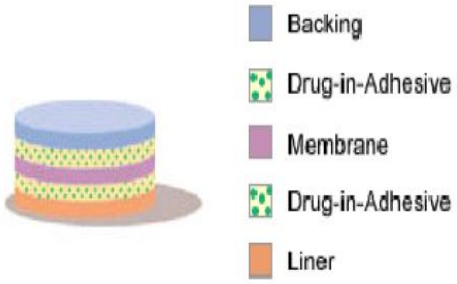
- Reasonable system size.
- Easy removal of release liner (e.g., for children and elderly patients).
- Adequate skin adhesion (i.e., should not fall off during the dosing interval and easy removal without skin trauma)
- Defined site for application.
- No acceptable dermal reaction (i.e., contact dermatitis, skin sensitization, erythema and itching).
- Delivery should be (typically) zero order.

2.3.4 Types of Patches

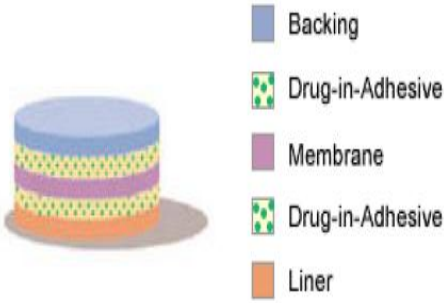
A. Single-layer Drug-in-Adhesive



B. Single-layer Drug-in-Adhesive



C. Drug Reservoir-in-Adhesive



D. Drug Matrix-in-Adhesive

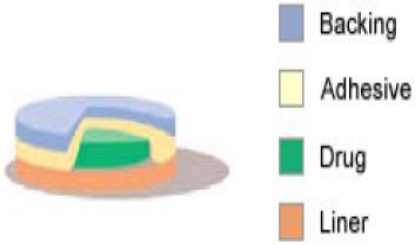


Figure 2.8: Diagrammatic presentation of various types of transdermal patches[21]

A. Single-layer Drug-in-Adhesive

The single-layer drug-in-adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin. The intrinsic rate of drug release from this type of drug delivery system is defined by following equation:-

$$\frac{dQ}{dt} = \frac{C_r}{\frac{1}{P_m} + \frac{1}{P_a}} \quad \text{--------(5)}$$

Where C_r is the drug concentration in the reservoir compartment and P_a and P_m are the permeability coefficients of the adhesive layer and the rate controlling membrane, P_m is the sum of permeability coefficients across the pores and the polymeric material. P_m and P_a respectively are defined as follows.

$$P_m = \frac{K_{m/r} * D_m}{h_m} \quad \text{--------(6)}$$

$$\mathbf{P_a = \frac{K_{a/r} * D_a}{h_a}} \quad \mathbf{(7)}$$

Where $K_{m/r}$ and $K_{a/r}$ are the partition coefficients for the interfacial partitioning of drug from the reservoir to the membrane and from the membrane to adhesive respectively; D_m and D_a are the diffusion coefficients in the rate controlling membrane and adhesive layer, respectively; and h_m and ha are the thicknesses of the rate controlling membrane and adhesive layer, respectively[21].

B. Multi-layer Drug-in-Adhesive

The multi-layer drug-in-adhesive is similar to the single-layer drug-in-adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film. The rate of drug release in this system is defined by:

$$\mathbf{\frac{dQ}{dt} = \frac{K_{a/r} * D_a}{h_a} C_a} \quad \mathbf{(8)}$$

Where $K_{a/r}$ is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer[21].

C. Drug Reservoir-in-Adhesive

The reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane. The rate of drug release from this drug reservoir gradient controlled system is given by:-

$$\mathbf{\frac{dQ}{dt} = \frac{K_{a/r} * D_a}{h_a(t)} A * (h_a)} \quad \mathbf{(9)}$$

In the above equation, the thickness of the adhesive layer increases with time ha (t). To compensate for this time dependent increase in the diffusion path due to the depletion of drug dose by release, the drug loading level is also increased with increase in thickness of diffusional path A (ha).The rate of drug release from this type of system is defined as:

$$\frac{dQ}{dt} = \frac{\sqrt{AC_0D_0}}{2t} - - - - - - - (10)$$

Where A is the initial drug loading dose dispersed in the polymer matrix and C_0 and D_0 are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release, Cp is essentially equal to C_r, where C_r is the drug concentration in the reservoir compartment[17].

2.3.5 Various Methods for Preparation of TDDS

A) Asymmetric TPX membrane method[22]

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane and sealed by an adhesive.

[(**Asymmetric TPX membrane preparation):** These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is evaporated at 50°C for 30 sec then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs].

B) Circular Teflon mould method[23]

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs.

The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

***C)* Mercury substrate method**[24]

In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

***D)* By using "IPM membranes" method**[25]

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

***E)* By using "EVAC membranes" method**[26]

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes.

If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

***F)* Aluminium backed adhesive film method**[27]

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved.

A custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

G) **Preparation of TDDS by using Proliposomes**[28,29]

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

H) **By using free film method**[30]

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. 5 ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petridish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petridish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

2.4 Patch: Market Overview

The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. The table 2.4 gives detail information of the different drugs which are administered as transdermal patch and the common names by which they are marketed; it also gives the conditions for which the individual system is used.

Table 2.4: Examples of marketed transdermal drug delivery system[31]

Sr. No.	Product Name	Drug	Manufacturer	Indication
1.	Alora	Estradiol	Thera Tech/proctol & Gamble	Postmenstrual syndrome
2.	Climaderm	Estradiol	Ethical Holdings /Wyeth -Ayerest	Postmenstrual syndrome
3.	Climara	Estradiol	3M Pharmaceuticals/ Berlex Labs	Postmenstrual syndrome
4.	Estraderm	Estradiol	Alza/Norvatis .	Postmenstrual syndrome
5.	Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare Ltd.	Postmenstrual syndrome
6.	FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
7.	CombiPatch	Estradiol/Norethindrone	Noven , Inc./Aventis	Hormone replacement therapy
8.	Nuvelle	Estrogen/Progesterone	TS Ethical Holdings/Schering	Hormone replacement therapy
9.	Ortho-Evra	Norelgestromin/estradiol	Ortho-McNeil Pharmaceuticals	Birth control
10.	Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism (males)
11.	Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension

12.	Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
13.	Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
14.	Nitrodur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
15.	Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
16.	Transderm-Nitro	Nitroglycerin	Alza/Norvatis	Angina pectoris
17.	Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
18.	Duragesic	Fentanyl	Alza/Janssen Pharmaceutica	Pharmaceutical moderate/severe pain
19.	Habitraol	Nicotine	Novartis	Smoking cessation
20.	Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
21	Nicotrol	Nicotine	Cygnus Inc./McNeil Consumer Products, Ltd.	Smoking cessation
22.	Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
23.	Nupatch	Diclofenac	Zydus Cadila	Pain relief

2.5 Innovation in Transdermal Technology

More recently, transdermal dosage forms have been developed and/or modified in order to enhance the driving force of drug diffusion (thermodynamic activity) and/or increase the permeability of the skin. These so-called 'active' transdermal technologies include iontophoresis, electroporation, microneedles, abrasion, needle-less injection, suction, stretching, ultrasound, magnetophoresis, radio frequency, LASERs, photomechanical waves, and temperature manipulation. Some most commonly employed techniques include the following.

A. Iontophoresis

This method involves the application of a low level electric current either directly to the skin or indirectly via the dosage form in order to enhance permeation of a topically applied therapeutic agent. FDA approved a pre-filled, pre-programmed iontophoric device for sale in the United States, e.g., Lidosite® delivers lidocaine and

epinephrine to intact skin to provide local anesthesia for superficial dermatological procedures[32, 33].

B. Electroporation

This method involves the application of high voltage pulses (100 V) for short durations (milliseconds) to the skin which has been suggested to induce the formation of transient pores. Other electrical parameters that affect delivery include pulse properties such as waveform, rate and number[32, 33].

C. Microneedle-based devices

A new area of intense transdermal research and development is the development of devices that create micropores in the stratum corneum, the top most layer of the skin that serves as the greatest barrier to drug diffusion. Such devices include microstructured arrays, sometimes called microneedles, when applied to the skin, painlessly create micropores in the stratum corneum without causing bleeding. These micropores offer lower resistance to drug diffusion than normal skin without micropores[32, 33].

D. Skin abrasion

The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments.

Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing (e.g., micro-abrasion) which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes[32, 33].

E. Needle-less injection

This is reported to involve a pain-free method of administering drugs to the skin. Over the years, there have been numerous examples of both liquid (Ped-O-Jet, Iject, Biojector2000, Medi-jector and Intraject) and powder (PMED device formerly known as Powderject injector) systems. The latter device has been reported to successfully deliver testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin[32, 33].

F. Ultrasound (sonophoresis and phonophoresis)

This technique involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment and is frequently

referred to as sonophoresis or phonophoresis. The Sonoprep device (Sontra Medical Corp.) uses low frequency ultrasound (55 kHz) for an average duration of 15 seconds to enhance skin permeability. This battery-operated, hand held device consists of a control unit, ultrasonic horn with control panel, a disposable coupling medium cartridge, and a return electrode[32, 33].

G. LASER Radiation

This method involves direct and controlled exposure of a LASER to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs42. A hand held portable LASER device has been developed by Norwood Abbey Ltd. (Victoria, Australia), which, in a study involving human volunteers, was found to reduce the onset of action of lidocaine to 3 to 5 minutes, while 60 minutes was required to attain a similar effect in the control group[32, 33].

2.6 INTRODUCTION TO LIDOCAINE {USP, BP, DRUG BANK}[37]

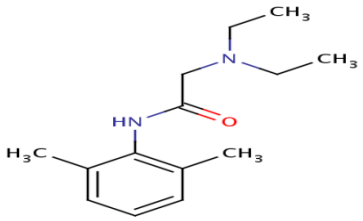
2.6.1 PHYSICO CHEMICAL PARAMETERS:

Molecular weight: 234.33 g/mol

Empirical formula: $C_{14}H_{22}N_2O$

Chemical name: 2-(Diethyl amino)-*N*-(2, 6-dimethylphenyl) acetamide

Structure:



Description: White or almost white, crystalline powder

Solubility: Practically insoluble in water, very soluble in ethanol (96 per cent) and in methylene chloride

Storage: Preserve in well-closed containers.

2.6.2 PHARMACOLOGY

Category: Local anaesthetic; Class I antiarrhythmic.

Mechanism of Action:

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses thereby effecting local anaesthetic action. Lidocaine alters signal conduction in neurons by blocking the fast voltage gated sodium (Na+) channels in the neuronal cell membrane that are responsible for signal propagation. With sufficient blockage the membrane of the postsynaptic neuron will not depolarize and will thus fail to transmit an action potential. This creates the anaesthetic effect by not merely preventing pain signals from propagating to the brain but by aborting their birth in the first place.

2.6.3 Pharmacokinetics parameters of Lidocaine

Absorption:

Lidocaine is rapidly absorbed from the GIT and respiratory tract. It is not effective orally due to high first-pass effect. It is rapidly absorbed following parenteral administration. It has onset of action of two minutes and duration of action 10 to 20 minutes following intravenous bolus. Therapeutic levels may not be reached for an hour if constant intravenous infusion given without an initial bolus. Intramuscular injections may be used in dogs if intravenous infusion is not possible (every 1.5 hours). Absorption through intact skin occurs for the eutectic mixture of lidocaine and prilocaine, EMLA (Astra).

Distribution:

Good tissue penetration, Rapid distribution into highly perfused organs such as kidney, liver, lungs, heart, Distributed widely throughout body tissues, High affinity for fat and adipose tissue, Distributed into milk.

As a local anaesthetic:

Greater spread through the tissues than with procaine; more effective penetration from injections made in the neighbourhood of a nerve trunk. In cattle following injection into a hind limb vein at 10 mg/kg for intravenous regional anaestheseia, concentrations in the distal limb veins were high in the first five to ten minutes following injection (e.g.140 to 4,666µg/ml) and then decreased rapidly.

In the systemic circulation (jugular vein samples) prior to release of the tourniquet trace amounts were present for example 0.03 µg/mL, but always less than 0.1 µg/mL. Following release of the tourniquet 60 minutes after injection, the highest concentration one minute after tourniquet release was 0.37 µg/mL and three minutes after release the highest concentration reached was 1.48 µg/mL, after this time concentrations in the systemic circulation decreased.

Metabolism

Lidocaine is approximately 95% metabolized (dealkylated) in the liver by CYP3A4 to the pharmacologically-active metabolites monoethylglycinexylidide (MEGX) and then subsequently to the inactive glycine xylidide. MEGX has a longer half life than lidocaine but also is a less potent sodium channel blocker.

Excretion

The elimination half-life of lidocaine is approximately 90–120 minutes in most patients. This may be prolonged in patients with hepatic impairment (average 343 minutes) or congestive heart failure (average 136 minutes).

Table 2.5: Pharmacokinetic parameters of Lidocaine

Pharmacokinetic Parameters	Values	
Bioavailability (%)	Oral	35 %
	Topical	3 %
Time to peak plasma concentration (hours)	-	
Peak plasma concentration (mcg/ml)	2-5	
Half-life (hours)	1.5-2	
Protein binding (%)	60-80%	
Volume of distribution (L/kg)	0.7 to 2.7	
Clearance(L/min)	0.64 +/- 0.18	
Urine unchanged	<10%	
Metabolized	90%	

2.7 INDRODUCTION TO EXCIPIENTS

2.7.1 Oleyl Alcohol[38]

1. **Non-proprietary Names**

   BP: Oleyl Alcohol

   PhEur: Oleyl Alcohol

   USP-NF: Oleyl Alcohol

2. **Synonyms**

   Alcohol oleicus; HD-Eutanol V PH; Novol; Ocenol; cis-9- octadecen-1-ol; oleic alcohol; oleo alcohol; oleol.

3. **Chemical Name:** (Z)-9-Octadecen-1-ol

4. **Empirical Formula:** $C_{18}H_{36}O$

5. **Structural Formula:**

6. **Functional Category**

   Antifoaming agent; dissolution enhancer; emollient; emulsifying agent; skin penetrant, sustained-release agent

7. **Method of Manufacture**

   Oleyl alcohol occurs naturally in fish oils. Synthetically, it can be prepared from butyl oleate by a Bouveault–Blanc reduction with sodium and butyl alcohol. An alternative method of manufacture is by the hydrogenation of triolein in the presence of zinc chromite.

8. **Description**

   Oleyl alcohol occurs as a pale yellow oily liquid that gives off acrid fumes when heated.

9. **Typical Properties**

   Boiling point 182–184˚C at 0.152 mPa (1.5 atm)

   Density 0.850 g/cm^3 at 208 ˚C

   Flash point 170 ˚C

   Melting point 13–19˚C

Partition coefficient Log P (octanol : water) = 7.50

Refractive index 1.4582

Solubility Soluble in ethanol (95%), and ether; practically insoluble in water.

10. Safety and storage

The bulk material should be stored in a well-closed container in a cool, dry, place.

11. Regulatory Status

It is included in the FDA inactive ingredients database (topical emulsions and ointments), nonparenteral medicines licensed in the UK and the Canadian list of acceptable non-medicinal ingredients.

2.7.2 Talc[38]

1. Non-proprietary Names

- BP: Purified Talc
- JP: Talc
- PhEur: Talc
- USP: Talc

2. Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.

3. Empirical Formula

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg6\ (Si2O5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

4. Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

5. Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

6. Typical Properties

- Acidity/alkalinity pH = 7–10 for a 20% w/v aqueous dispersion.
- Hardness (Mohs) 1.0–1.5
- Moisture content: Talc absorbs insignificant amounts of water at 258C and relative humidities up to about 90%.
- Particle size distribution Varies with the source and grade of material. Two typical grades are 599% through a 74 mm (#200 mesh) or 599% through a 44 mm (#325 mesh).
- Refractive index 1.54–1.59
- Solubility Practically insoluble in dilute acids and alkalis, organic solvents, and water.
- Specific gravity 2.7–2.8
- Specific surface area 2.41–2.42m^2/g

7. Safety and storage

Talc is a stable material and may be sterilized by heating at 160˚C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

8. Regulatory Status

It is accepted for use as a food additive in Europe, included in the FDA inactive ingredients database (buccal tablets; oral capsules and tablets; rectal and topical preparations), nonparenteral medicines licensed in the UK, the Canadian list of acceptable non-medicinal Ingredients.

2.7.3 Glycerin[38]

1. **Non-proprietary Names**

   BP: Glycerol

   JP: Concentrated Glycerin

   PhEur: Glycerol

   USP: Glycerin

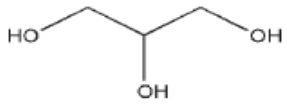
2. **Synonyms**

   Croderol; E422; glicerol; glycerine; glycerolum; Glycon G-100; Kemstrene; Optim; Pricerine; 1,2,3-propanetriol; trihydroxypropane Glycerol

3. **Chemical Name:** Propane-1,2,3-triol

4. **Empirical Formula:** $C_3H_8O_3$

5. **Structural Formula**



6. **Functional Category**

   Antimicrobial preservative; cosolvent; emollient; humectant; plasticizer; solvent; sweetening agent; tonicity agent.

7. **Description**

   Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose.

8. **Typical Properties**

   - Boiling point 290˚C (with decomposition)
   - Density: 1.2656 g/cm^3 at 15˚C, 1.2636 g/cm^3 at 20˚C, 1.2620 g/cm^3 at 25˚C
   - Flash point 176˚C (open cup)
   - Hygroscopic.
   - Melting point 17.8˚C

9. **Safety and storage**

   Glycerin is hygroscopic. Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions, but it decomposes on heating with the evolution of toxic acrolein. Mixtures of glycerin with water, ethanol (95%), and propylene glycol are chemically stable.

3. LITERATURE REVIEW:

3.1 LITERATURE REVIEW ON TOPICAL AND TRANSDERMAL DRUG DELIVERY SYSTEM

Gendy et al.[39] (2009) prepared and evaluated gentamicin sulphate patches for topical application and studied the effect of different bioadhesive polymers on diverse characteristics of prepared patches. Drug patches were evaluated for weight and thickness uniformity, moisture absorption capacity, tensile strength and percentage elongation. *In vitro* release patterns of these patches were studied and analyzed. Tensile strength of the patches prepared using HPMC as bioadhesive polymer were the lowest compared to the other patches. Patches formulated using HPMC gave the most superior results as compared to other compositions.

Sang-Cheol Chi et al.[40] (2008) prepared and evaluated Benztropine drug-in adhesive (DIA) patches. The effects of the formulation factors including pressure-sensitive adhesive (PSA), enhancer, the loading amount of the drug and patch thickness on the skin permeation of the drug were evaluated using excised rat skin. The optimized patch contained 10% Benztropine in Duro-Tak® 2525 as a PSA at a thickness of 100 µm. The pharmacokinetic characteristics of the optimized DIA patch were determined after the transdermal application to rabbits. The calculated relative bioavailability of BZ in the DIA patch was 54% compared to the oral administration of BZ mesylate. This suggests that the transdermal application of BZ in a DIA patch may be used for the treatment of Parkinson disease.

Bharkatiya et al.[41] (2010) studied the effect of different plasticizers on physicochemical properties of the patches to explore their feasibility for transdermal application. Polyethylene glycol (PEG 400), Dibutylphthalate (DBP) and Propylene glycol (PG) were used as plasticizers at a concentration of 40 % w/w of dry polymer weight. Tensile strength and folding endurance of the patches prepared with DBP as plasticizer was high compared to patches plasticized with PG and PEG.

Patrizia Santi [42] (2007) prepared water-based and vapor permeable film using Eudragit E100 intended for dermal and/ortransdermal delivery. The effect of drug loading, of film-forming polymer type and content, of adhesive and plasticizer on lidocaine transport across the skin was evaluated. The film-forming polymer molecular weight had a negligible effect on drug penetration, while its content was more effective. In particular, the presence of lauric acid combined with a basic drug, such as lidocaine, can produce a relevant improvement in

permeation, because of the formation of an ion pair. Concerning the kinetics, drug depletion is responsible for the declining permeation rates observed in the late times of permeation.

Yogesh et al.[43] (2011) selected Eudragit RL 100: Eudragit RS: drug (7:3:1, 7:2:1) and Ethyl cellulose: PVP: drug (7:3:1, 7:2:1) for transdermal administration based on evaluation studies. These polymeric films were prepared by mercury substrate method employing PEG-400 as plasticizer. Two different penetration enhancers Urea and Dimethyl sulphoxide (DMSO) were employed in the study.

Meenakshi et al.[44] (2010) prepared matrix type transdermal patches containing Metoprolol tartrate were by solvent casting method employing a mercury substrate by using the combinations of EC-PVP and Eudragit RL100-PVP in different proportions. The transdermal patches were evaluated for their physicochemical properties like thickness, weight variation, flatness, tensile strength, hardness, folding endurance, drug content, swellability, surface pH, water vapour transmission, in vitro permeation and skin irritation studies. The permeability of Metoprolol tartrate was increased with increase in PVP content.

Sanjay et al.[45] (2010) carried out preparation of carvedilol transdermal patch and the effect of propylene glycol on permeation. Transdermal patches were prepared by using hydroxyl propyl methyl cellulose (HPMC) and Eudragit RS100 polymers by incorporating dibutyl phthalate and propylene glycol as plasticizer and permeation enhancer, respectively.The *invitro* permeation studies indicated that matrix patches containing hydroxyl propyl methyl cellulose and Eudragit RS100 in the ratio of 1:4 shown better release. Propylene glycol was incorporated at different concentration to enhance the permeation of drug. The formulation containing 30% w/w propylene glycol has exhibited better enhancement for the permeation of carvedilol.

Mi-Kyeong Kim.[46] (2001) prepared reservoir-type transdermal delivery system of testosterone (TS) using an ethanol/water (70:30) cosolvent system as the vehicle. The maximum permeation rate achieved by 70% (v/v) of ethanol was further increased with the addition of 1.0% dodecylamine as the skin permeation enhancer. Addition of 1.0% (w/w) gelling agent, hydroxypropyl methylcellulose (HPMC), in the reservoir formulation resulted in desirable rheological properties with an insignificant effect on the skin permeation rate of TS. Thus, a new transdermal delivery system for TS was formulated using EVA membrane coated with a pressure-sensitive adhesive (Duro-Tak 87-2510) and HPMC as a gelling agent.

Ting li et al.[47] (2007) used indomethacin, MASCOS 10 (polyacrylic acid type) pressure sensitive adhesive to prepare a drug-in-adhesive type patch containing a variety of permeation enhancers (*i.e.* azone, *L*-menthol, 2-isopropyl-5-methylcyclohexyl heptanoate (M-HEP), isopropyl myristate (IPM), Tween-80 and oleic acid). It was notable that the presence of IPM, oleic acid and Tween 80 did not increase indomethacin permeation from the transdermal patches compared with the transdermal patches containing azone and *L*-menthol ($P > 0.05$). 5% azone and 5% *L*-menthol were the permeation enhancers of choice for the percutaneous absorption of indomethacin.

Rajan et al.[48] (2008) designed matrix patch formulations for long-acting permeation of diclofenac potassium (DP). Ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) were used as a matrix for the formation of transdermal DP patches with either dibutyl phthalate (DBP) or propylene glycol (PG) as the plasticizer. It was found that most of the release profiles followed Fickian diffusion except for two formulations with DBP following Higuchi release.

Abdul et al.[49] (2010) developed matrix-moderated transdermal systems of Diltiazem HCl using various proportions of *Ficus reticuleta* fruit mucilage. Physical evaluation and *In-vitro* penetration studies were performed. The non-ionic surfactants Span 80, Glycerin, Propylene glycol in the formulation played a role as permeability enhancer. The experimental results shows that the release of drug from the patch delayed in controlled manner as the proportion of *Ficus reticuleta* increased.

Farsiya et al.[50] (2011) formulated and Evaluated Matrix-Type Transdermal Delivery System of Ondansetron Hydrochloride (OSH) Using Solvent Casting Technique. Ondansetron hydrochloride (OSH) with different ratios of hydrophilic and hydrophobic polymeric systems by the solvent evaporation technique by using 25 % w/w of di-butyl phthalate to the polymer weight, incorporated as plasticizer. 5% menthol was used to enhance the Transdermal permeation of OSH. Formulation prepared with combination of hydrophilic polymers containing permeation enhancer showed best *ex vivo* skin permeation through rat skin (Wistar albino rat) as compared to all other formulations.

Aqil M. et al.[51] (2005) have prepared monolithic matrix type transdermal patch of pinacidil monohydrate (PM) by film casting technique on mercury substrate using polymers; eudragit RL 100 and polyvinyl pyrrolidone K-30 (in 8:2, 4:6, 2:8 and 6:4 ratios in formulations B-1, B-2, B-3 and B-4, respectively), along with 20 % w/w of drug- pinacidil monohydrate, 5%

w/w of plasticizer- polyethylene glycol-400 and 5% w/w of penetration enhancer- dimethyl sulfoxide (based on total polymer weight). The amount of drug released in 48 hours from formulations B-1, B-2, B-3 and B-4 were found to be 63.96 %, 55.95 % 52.26%, 92.18 %, respectively. B-4 was the most effective with 37.96% reduction in BP (160.33±4.96 v/s 99.44±4.46 mm Hg). It was concluded that a single patch application of pinacidil TDDS (B-4) can effectively control hypertension in rats for two days.

Rakesh et al.[52] (2009) developed a matrix-type transdermal therapeutic system containing drug Aceclofenac with different ratios of hydrophilic (hydroxyl propyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems by the solvent evaporation technique by using 15 % w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer. Different concentrations of oleic acid and isopropyl myristate were used to enhance the transdermal permeation of Aceclofenac.

Venkateswara Rao J. et al.[53] (2010) have developed matrix type transdermal patch of lercanidipin hydrochloride (LRDP) by solvent evaporation technique. Formulations A1, A2, A3, A4, A5 and A6 were composed of eudragit RL100 (ERL) and hydroxypropyl methyl cellulose (HPMC) in 1.5:8.5, 3:7, 4:6, 6:4, 7:3 and 8.5:1.5 ratios respectively and 8 % v/w of d-limonene as a penetration enhancer, 20 % v/w of propylene glycol as plasticizer. The prepared TDDS were evaluated for physicochemical characteristics, in-vitro release, ex-vivo permeation and skin irritation. By fitting the data into zero order, first order and Higuchi model, it was concluded that drug release from matrix films followed Higuchi model and the mechanism of the drug release was diffusion mediated. The patches composed of ERL, HPMC (1.5:8.5) with 8 % v/w limonene as penetration enhancer was selected for the development of TDDS of LRDP for potential therapeutic use by using a suitable adhesive layer and backing membrane.

Shashikant et al.[54] (2009) studied ketoprofen transdermal patches were prepared by mercury substrate method using polymer Eudragit RS100, Eudragit RL100, HPMC K100M, HPMC E5 and HPMC K4M. Propylene glycol and oleic acid used as a skin permeation enhancer and dibutyl phthalate and polyethylene glycol-400 used as a plasticizer. It was observed that the formulation containing HPMC E5 showed ideal zero-order release kinetics.

Vijaya V. et al.[55] (2010) have developed reservoir type transdermal patches of losartan potassium by solvent evaporation method using HPMC, methyl cellulose and sodium CMC

as hydrophilic polymer and ethyl cellulose and edragit RS100 as hydrophobic polymer and PEG(30%) and tween 80 (1%) as plasticizer and penetration enhancer respectively. The prepared patches showed satisfactory physiochemical characteristics of weight variation, thickness, folding endurances, moisture absorption and drug content. Based on the kinetic studies, the patch containing both HPMC and eudragit RS100 showed satisfactory drug release patterns.

S. Ramkanth et al.[56] (2010) have developed and evaluated matrix-type transdermal therapeutic system containing Metoprolol tartarate by solvent evaporation method using HPMC (M-I (1%), M-II (2%)), PVP (M-III (1%), M-IV (2%)) and HPMC-PVP combination (M-V (1% HPMC & 1% PVP), M-VI (2% HPMC & 2% PVP)) and propylene glycol (30% v/v) as a plasticizer. Based on the *In-vitro* maximum drug release, formulation M-VI (2% HPMC & 2% PVP) was concluded as an optimized formulation, which shows its higher percentage of drug release in concentration independent manner.

Amit L. Shinde et al.[57] (2010) have developed and evaluated matrix type transdermal drug delivery systems (TDDS) of gliclazide by solvent evaporation technique using eudragit RL 100 ,HPMC and chitosan and 5% (w/w) triethyl citrate as permeation enhancer. Attempt was made to increase permeation rate of drug by preparing an inclusion complex with hydroxyl propyl β-cyclodextrin (HP β-CD) and also the effect of chemical penetration enhancer (CPE) (PG or oleic acid) on transdermal transport of drug was studied. In vitro drug release profile indicate that drug release was sustained with increasing amount of edragit RL100 in patch and the inclusion complex of drug showed higher permeation flux compared with patches containing plain drug. It was reported that cyclodextrin alone is less effective than combination with fatty acid and propylene glycol.

Jayprakash et al.[58] (2010) prepared Celecoxib Transdermal patches were prepared by using different polymers such as hydroxylpropylmethylcellulose (HPMC), methylcellulose (MC), Polyvinylpyrolidone (PVP).The *in-vitro* release of the drug from the formulations were studied using commercial semi permeable membrane.

Priyanka et al.[59] (2002) studied matrix-type transdermal patches containing diclofenac diethylamine were prepared using different ratios of polyvinylpyrrolidone (PVP) and ethylcellulose (EC) by solvent evaporation technique. The drug matrix film of PVP and EC was casted on a polyvinylalcohol backing membrane. It concluded that diclofenac

diethylamine can be formulated into the transdermal matrix type patches to sustain its release characteristics and the polymeric composition (PVP/EC, 1:2) was found to be the best choice for manufacturing transdermal patches of diclofenac diethylamine among the formulations studied.

Roongnapa et al.[60] (2008) studied to develop a transdermal patch for selective controlled delivery of the active S-enantiomer from racemic propranolol, and to evaluate its performance in vivo using Wistar rats. The effect of gel reservoir (poloxamer and chitosan) on enantioselective delivery was investigated. The chitosan gel allowed excellent selectivity for delivery of the S-propranolol enantiomer, whilst the more rheologically structured poloxamer gel formulation provided no selective release of S-propranolol. The chitosan gel exhibited high flux and had the ability to enantioselective deliver S-propranolol across excised rat skin.

Iman et al.[61] (2010) studied to formulate an antihistaminic drug-chorpheniramine maleate (CPM) as transdermal patch using different bioadhesive polymer such as ethyl cellulose, cellulose acetate and polyvinyl pyrrolidon with different plasticizers such as propylene glycol and polypropylene glycol 400. Patch was prepared though solvent evaporation method, evaluated for their physical and mechanical properties and subjected to stability study to select the best formulae to be evaluated in vitro and in vivo.

Shashikant D. Barhate et al.[62] (2009) have developed transdermal patch by mercury substrate method using polymer eudragit RS100, eudragit RL100, HPMC K100M, HPMC E5 and HPMC K4M. Propylene glycol and oleic acid used as a skin permeation enhancer and dibutyl phthalate and polyethylene glycol-400 used as a plasticizer. The formulated transdermal patch by using eudragit RS100, eudragit RL100, HPMC K100M, HPMC E5 and HPMC K4M showed good physical properties. It was observed that the formulation containing HPMC E5 showed ideal zero-order release kinetics.

Talasila et al.[63] (2008) used cellulose acetate, ethyl cellulose and Eudragit RS-100 films and evaluated as rate controlling membrane for transdermal drug delivery system. Acetone-methanol (8:2), chloroform- methanol (8:2), dichloromethane-methanol (8:2) and ethyl acetate-methanol (8:2) were used as solvent in the preparation of films. Polymer and solvent showed significant influence on WVT, drug diffusion and permeability of films.

3.2 PATENT REVIEW ON TOPICAL AND TRANSDERMAL DRUG DELIVEY SYSYTEM

US Patent no. 5 411 738: Harry et al.[65] take patent for treating pain associated with herpes zoster and post herpetic neuralgia by topical application of lidocaine. Methods and compositions are offered for reducing nerve injury pain associated with shingles (herpes zoster and post-herpetic neuralgia), where intradermal delivery of lidocaine is maintained for a predetermined period of time.

US Patent no. 20030152616: Rod Lawson et al.[66] Investigated methods for making transdermal drug delivery system capable of achieving substantially zero oder kinetics for delivery of active agent over a period.

US Patent no. 5985317: Srinivasan et al.[67] Given method of transdermally or transmucosally delivering a hydrophic salt form of a drug with water base pressure sensitive hydrophobic adhesive matrix patch optionally containing a permeation enhancer.

US Patent no. 6465004 B1: Sylvala et al.[68] Given composion and method for the continuous and controlled transdermal delivery of an active agent comprising a pharmaceutically acceptable active agent carrier and cellulose derivative which provides a solubilising and stabilizing effect on the active agent incorporated therine.

4.1 MATERIALS AND EQUIPMENTS USED

4.1.1 Materials used

Table 4.1: List of Materials

Sr. no.	Materials	Company
1	Lidocaine USP	Gufic Biosciences Ltd, Navsari, India
2	Ethanol AR	Merck, Germany
3	Propylene Glycol USP	Panreco, USA
4	Ethyl acetate NF	Merck, Germany
5	Acetone AR	Merck, Germany
6	Talc USP	Sinnety (Luzenac)
7	Scotchpak 1109	3M India
8	Aqueous Gelva	Cytex Industries Inc
9	Oleyl Alcohol NF	Croda, USA
10	Triacetin	Croda, USA
11	Oleic Acid NF	Croda, USA
12	Potassium dihydrogen Phosphate	S. D. Fine Chemicals Ltd Mumbai, India
13	Glycerine USP	Procter & Gamble Chemicls
14	Bio-PSA 4102	Mascot Engineering Company
15	Colloidal Silicone Dioxide	Merck
16	Durotak 2510	National Starch
17	Gelva 737	Cytec Industries
18	MD-153	Mascot Engineering Company
19	Bio-PSA 4302	Mascot Engineering Company
20	Saint Gobain 8310	Grindwell Norton Ltd.
21	EW 9100	Japan Vilene
22	Durotak-4287	National Starch
23	Durotak-608 A	National Starch
25	Gelva-9073	Cytec Industries Inc

4.1.2 Equipments

Table 4.2: List of Equipments

Sr. no.	Equipment Name	Company
1	HPLC system Dionex®	Agilent Technologies
2	Thermo-gravimetric analysis Q500	TA instrument
3	Shimadzu® 8400-S FTIR	Shimadzu Corporation, Kyoto, Japan
4	UV/Visible spectrophotometer (Shimadzu® 160A)	Shimadzu Corporation, Kyoto, Japan
5	Mechanical stirrer	Leica
6	Magnetic stirrer	Remi Sales & Engg. Ltd.
7	Lab Coater LTE-SM(1 zone)	Waener Mathis AG, Switzerland
8	Franz® Diffusion cell	Sabar Scientific
9	Weighing Balance Metteler®	Metteler Toledo India Private Ltd.
10	Hot Air Oven	Thermolab Scientific Equipments Ltd
11	Microscope	Mettler Toledo India Private Ltd
12	Temperature gun	Raytek
13	Thermometer	Scientific Trading Corporation
14	Dissolution Apparatus V	Electrolab, India
15	pH meter	Lab India
16	Stability Chamber	Thermolab Scientific Equipments Ltd
17	Helogen moisture Analyser	Mettler Toledo India Private Ltd
18	Brookfield Viscometer Brookfield LV DVII + pro viscometer	Brookfield Engineering Laboratories, USA
19	Universal tester	LLOYD (AMETEX)
20	Shear tester	Cheminstruments®, Fairfield
21	Micrometer MI-1000	Cheminstruments®, Fairfield
22	Manual Patch Cutter	TA Instrument

4.2 PREFORMULATION STUDY OF LIDOCAINE

A Preformulation study is the first step in rational development of dosage form of a drug substance. The objectives of preformulation studies are to develop a basic knowledge or portfolio of information about drug substance, so that this information would be useful to develop formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients[69].

Preformulation studies were designed to identify those physicochemical properties of Lidocaine and excipients that may influence formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of resulting product. Following tests were performed for preformulation study.

4.2.1 Drug characterization

4.2.1.1 I.R. Spectrum

Lidocaine powder was compressed into a pellet along with KBr (KBr pallet technique) using shimadzu hydraulic press. The I.R. spectrum of drug was recorded in the wave number region of 400-4000 cm^{-1} on a Shimadzu® 8400-S FTIR spectrophotometer and shown in Figure 4.1. The interpretation of their spectrum bands is given in Table 4.3.

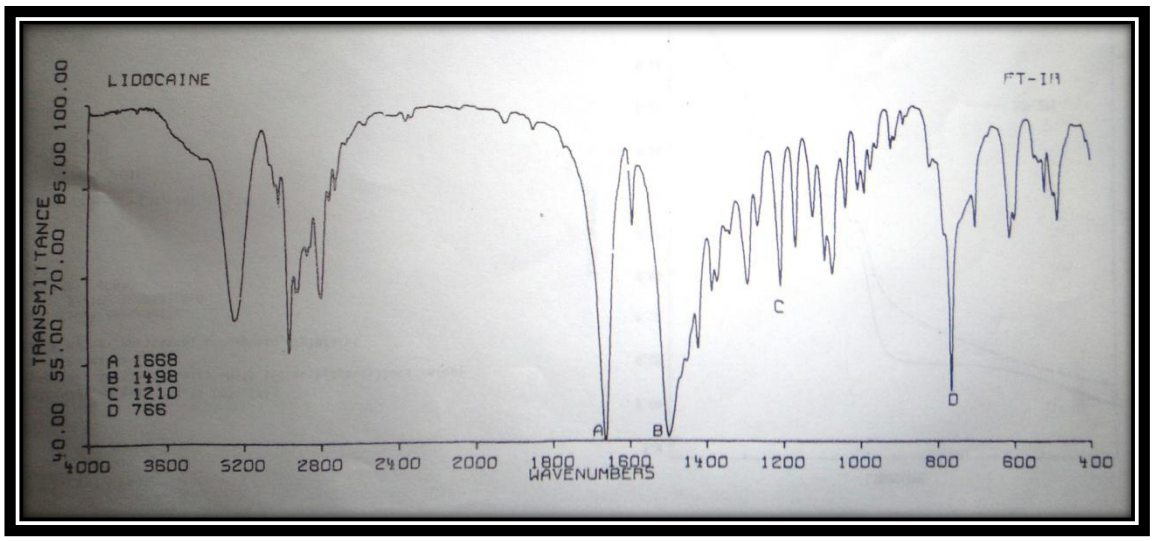


Figure 4.1(a): REPORTED FTIR SPECTRA OF LIDOCAINE

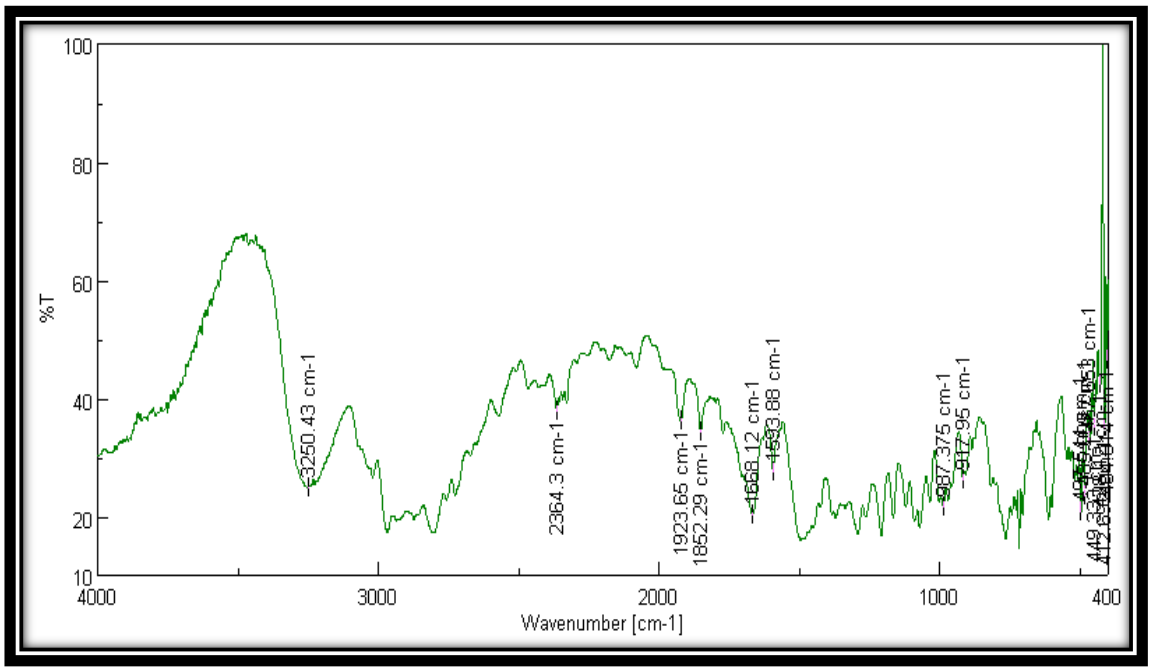


Figure 4.1(b): OBSERVED FTIR SPECTRA OF LIDOCAINE

Table 4.3: Interpretation of infrared spectrum bands of Lidocaine sample[70]

Sr. no.	Wave No.(cm^{-1})	Interpretations
1.	3250	N-H stretching
2.	2690	C-H stretching
3.	2790	C-H stretching
4.	1668	Amide -I stretching
5.	1593	C=C stretching
6.	1498	Amide –II stretching
7.	766	C-H stretching (aromatic)

Result: The FTIR spectrum of lidocaine have identical peaks as reported in references sample of Lidocaine[70].

4.2.1.2 Retention Time of HPLC

Chromatographic Conditions

HPLC system	-	Agilent®
Supporting software	-	Chromeleon®
Detector	-	U V
Mobile phase	-	n-Hexane: Ethanol (90:10)v/v
Column specifications	Type	- Inertsil Silica
	Length	- 250 mm
	Internal diameter	- 4.6 mm
	Particle Size	- 5µm
Detecting wavelength	-	210 nm
Flow rate	-	1.0 ml/min.
Run time	-	10 min.
Sample volume	-	5µl
Diluent	-	Ethyl Acetate

Assay methodology of Lidocaine

Preparation of mobile phase:

Mix about 9 volumes n-Hexane with 1 volume of ethanol in one liter vessel.

Standard Preparation:

Dissolve about 45mg of Lidocaine USP, accurately weighed in 10 ml of ethyl acetate in a 250 ml volumetric flask, and makeup the volume with ethyl acetate to obtain a standard preparation having a known concentration of about 0.18mg/ml of Lidocaine.

Assay Preparation:

Dissolve about 45mg of Lidocaine accurately weighed in 10 ml of ethyl acetate in a 250 ml volumetric flask, and makeup the volume with ethyl acetate to obtain a standard preparation having a known concentration of about 0.18mg/ml of Lidocaine.

Procedure:

Separately inject equal volume (10 micro liters) of a diluent, standard preparation and assay preparation into a HPLC system, record a chromatogram and measure responses for a major peaks and also the retention time of the major peaks.

Calculation:

Drug content in patch was calculated by using following formula,

$$\% \textbf{ Assay} = \frac{\textbf{Area of test}}{\textbf{Area of Standard}} * \frac{\textbf{Weight of Standard}}{\textbf{Standard Dilution}} * \frac{\textbf{Test Dilution}}{\textbf{Weight of test}} * \frac{\textbf{Potency}}{\textbf{100}} * \textbf{100}$$

Chromatograms:

Observation:

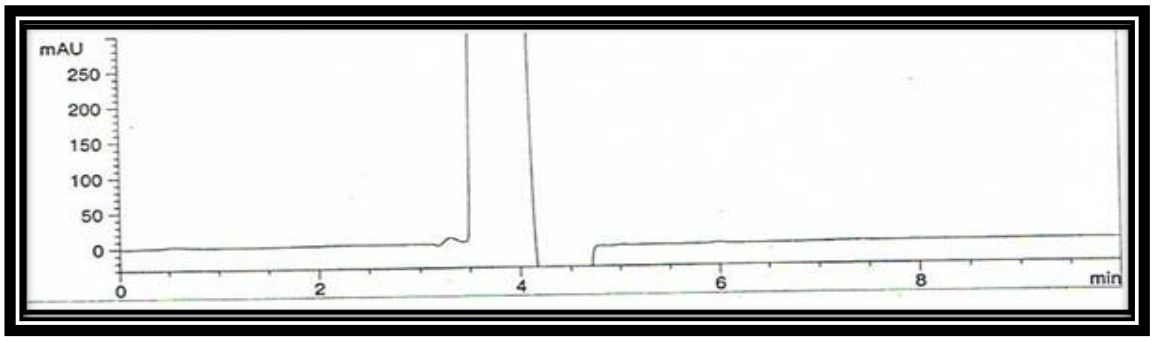


Figure 4.2: Chromatograph of Diluent

Diluent RT: 3.905

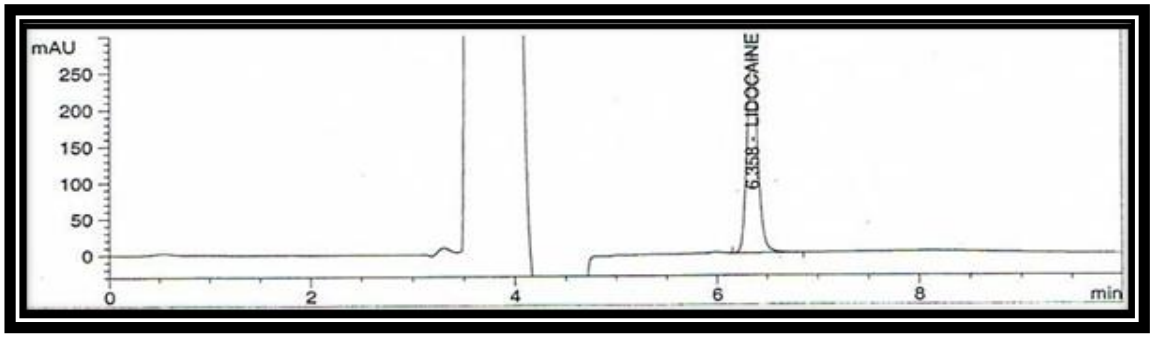


Figure 4.3: Chromatograph of Standard

Standard RT: 6.358

Standard Peak Area: 2046.52686

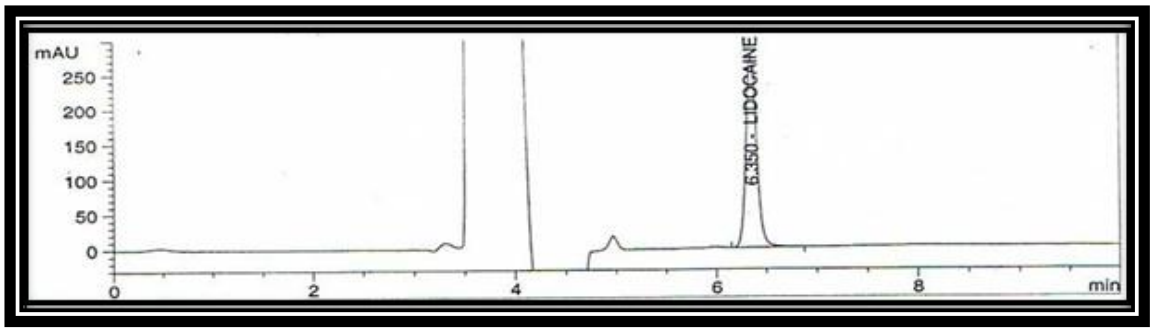


Figure 4.4: Chromatograph of Sample

Sample API RT: 6.350

Sample API Peak Area: 2020.5842

Result: Retention time of lidocaine peak was found to be 6.350 min which was similar to the RT (6.358) of standard drug (Lidocaine USP) and % assay was found to be 99.87.

4.2.1.3 U.V. Spectrum

100 mg lidocaine was weighed accurately and transferred to a 100 ml volumetric flask and ethanol was added and final volume was made up to 100 ml to obtain stock solution. From this stock solution, solution of 100µg/ml was prepared with ethanol, and the sample was scanned between 200 nm to 400 nm on a double beam UV/Visible spectrophotometer (Shimadzu® 1800). The UV spectrum of lidocaine is shown in Figure 4.5[70].

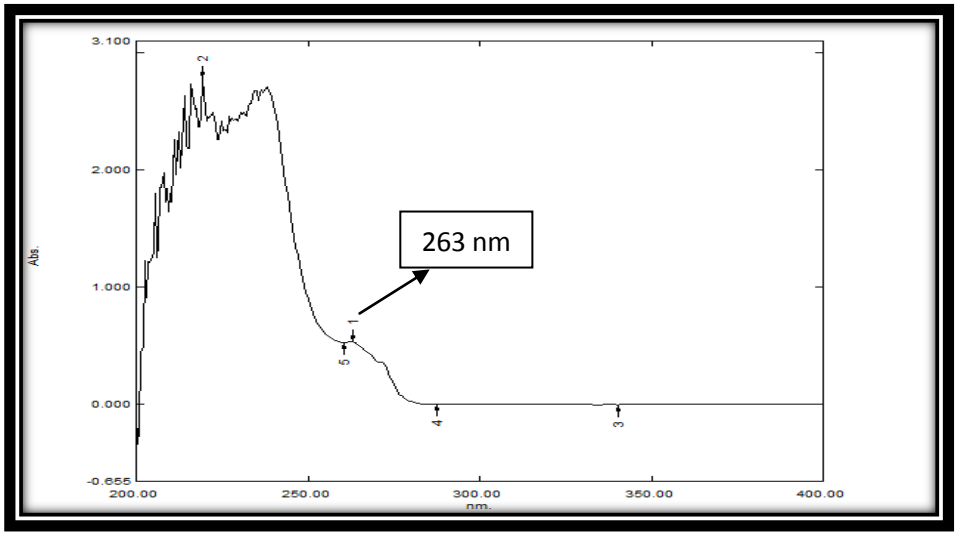


Figure 4.5: U.V. Spectrum of Lidocaine In Ethanol

Result: Sample Lidocaine exhibited λ_{max} at 263 nm. This λ_{max} is same as reported in literature[70].

4.2.1.4 Melting Point

Melting point is the temperature at which the pure liquid and solid exist in the equilibrium. In the practice it is taken as equilibrium mixture at an external pressure of 1 atmosphere; this is sometime known as normal melting point. The thiel's tube method of melting point determination in liquid paraffin was used in the present study.

Actual melting point	66 to 69˚C
Observed melting point	68 ˚C

Inference

The procured sample of lidocaine was characterized by I.R., UV, HPLC and Melting point studies. All the observed data were matching with the reported data of the lidocaine. Hence it was inferred that the procured drug sample was of pure lidocaine and hence used for further studies.

4.2.2 Drug Solubility Study

4.2.2.1 Introduction

Solubility: Quantitatively it is defined as concentration of solute in a saturated solution at a certain temperature. Qualitatively it is defined as the spontaneous interaction of two or more substances (solute & solvent) to form a homogeneous molecular dispersion[71].

4.2.2.2 Objective

To select the best penetration enhancer/ solvent for Lidocaine and to overcome problems arising during preparation of topical patch[72].

4.2.2.3 Preparation of Calibration Curves of Lidocaine

Initially 100 mg of lidocaine was weighed accurately and transferred to 100 ml volumetric flask. To this 10 ml of ethanol was added in order to dissolve the drug and the volume was made up to 100 ml with the respective medium so as to obtain stock solution of 1000 µg/ml. Appropriate dilutions from the stock solution were made with the respective medium in concentration range of 100µg/ml to 700µg/ml. The absorbance of the resulting drug solutions were read on a double beam UV/VIS spectrophotometer (Shimadzu® 1800) at 263 nm against the blank.

The data are recorded and graphically represented in Figure 4.6. The obtained absorbance data for various concentration data were also subjected to linear regression analysis.

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance	Standard Deviation
		1	2	3		
1	0	0	0	0	0	0
2	100	0.136	0.13	0.14	0.136	0.00600
3	200	0.262	0.28	0.28	0.273	0.01060
4	300	0.404	0.42	0.43	0.418	0.01193
5	400	0.533	0.57	0.54	0.548	0.01747
6	500	0.676	0.69	0.65	0.672	0.01779
7	600	0.82	0.81	0.83	0.821	0.00902
8	700	0.953	0.93	0.94	0.943	0.01002

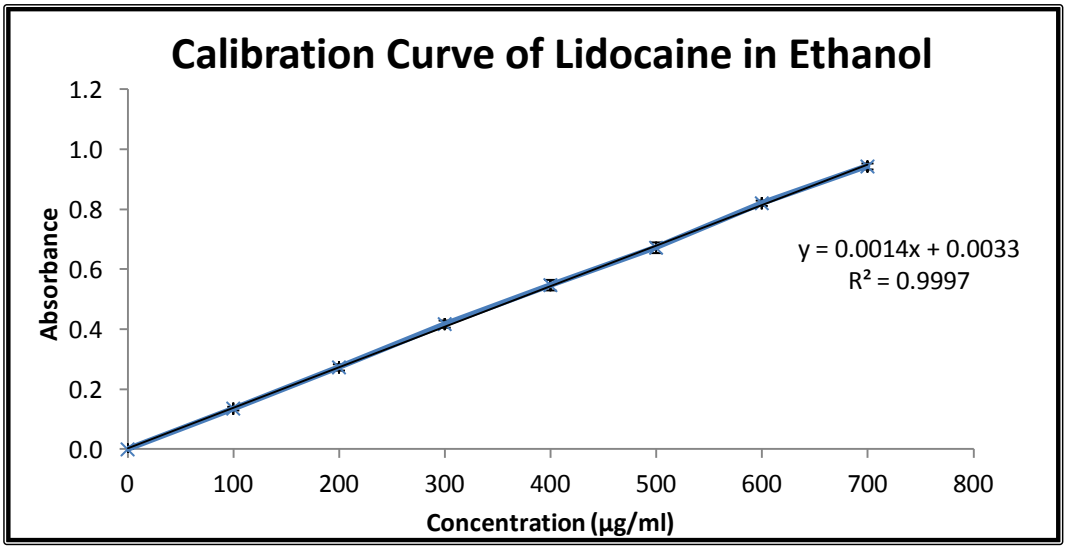


Figure 4.6: Calibration Curves of Lidocaine in Ethanol

Regression Analysis:

Regression parameter	Value
Correlation coefficient	0.9997
Slope	0.0014
Intercept	0.0033

Result: The correlation coefficient of calibration curves of lidocaine (Figure 4.6) in 99% ethanol 0.9997 and was very close to 1. The linear graph obtained and the values of correlation coefficient showed that the Beer- Lambert's law was obeyed in the drug concentration range of 100-700µg/ml.

4.2.2.4 Solubility Determination of Lidocaine in Permeation Enhancers

Solubility studies in different permeation enhancers were carried out by preparing saturated solution of drug in different permeation enhancers. The screw capped tubes containing the solutions were kept on a magnetic stirrer for 24 hr at 25 °C. After 24 hr, the solutions were transferred into other test tubes and centrifuged at about 2000 rpm for 30 min at room temperature. Supernatant liquid from each test tube was taken and filtered through Whatman® filter paper.

The absorbance of solutions was measured at 263 nm on a double beam UV spectrophotometer (Shimadzu® 1800) using the respective medium as the blank. The amount of drug dissolved was quantified from the calibration curve.

Table 4.4: Solubility of Lidocaine in different penetration enhancers

Sr. no.	Penetration Enhancers	Solubility(mg/ml)
1	Mineral oil	77.5
2	Propylene Glycol	281
3	CCT	343
4	**Oleyl Alcohol**	**361.5**
5	Triacetin	226
6	Oleic Acid	276
7	Isopropyl Marystate	285
8	Glycerine	23.5
9	Ethyl oleate	263.5
10	Butylenes Glycol	282.5

4.2.2.5 Solubility Determination of Lidocaine in Solvents

Solubility studies in different solvents were carried out by preparing saturated solution of drug in the respective solvents. The screw capped tubes containing the solutions were kept on a magnetic stirrer for 24 hr at 25 °C. After 24 hr, the solutions were transferred into other test tubes and centrifuged at about 2000 rpm for 30 min at room temperature. Supernatant liquid from each test tube was taken and filtered through Whatman® filter paper. The absorbance of solutions was measured at 263 nm on a double beam UV spectrophotometer (Shimadzu® 1800) using the respective medium as the blank. The amount of drug dissolved was quantified from the calibration curve.

Table 4.5: Solubility of Lidocaine in different solvents

Sr. no.	Solvents	Solubility(mg/ml)
1	Ethanol	1994
2	Phosphate buffer pH 7.4	20
3	1.4 pH SGF buffer	60
4	Water	0.255
5	0.1N HCL	45
6	Toluene	1755.5
7	Heptane	520
8	n-Hexane	1121
9	Ethyl acetate	2070

Results: Lidocaine was found to be very soluble in various permeation enhancers and Solvents. The highest solubility of lidocaine in Oleyl Alcohol is **361.5 mg/ml.**

4.2.3 Partition Coefficient Determination Study

Partition coefficient is a measurement of drug's lipophilicity and its ability to cross the cell membrane. Partition of lidocaine was determined at 37±0.5°C by taking 20 ml of octanol which was saturated with 20 ml of phosphate buffer (7.4 pH) by stirring with externally driven magnetic stirrer for 6 hr. After stirring, the system remained undisturbed for half an hour. About 100 mg of drug was added to this solution and was moderately shaken on wrist action mechanical stirrer for about 3 hr.

Two layers were separated through separating funnel and filtered through whatman grade 41 filter and the amount of lidocaine solubilised in each phase, was determined by measuring the absorbance at 263 nm against blank reagent on a double beam UV spectrophotometer. Partition coefficient was determined as ration of concentration of drug in octanol to concentration of drug in phosphate buffer (7.4pH) and its logarithm value was taken for log P.

Results: Partition coefficient of lidocaine was found to be 2.4 (octanol and phosphate buffer 7.4 pH) which showed that lidocaine is sufficient lipophilic which is necessary for its permeation through skin.

4.2.4 Drug-Excipient compatibility study (DECS)

4.2.4.1 Introduction

When we mix two or more API and / or excipient with each other & if they are antagonistic & affect adversely the safety, therapeutic efficacy, appearance or elegance of product then they are said to be incompatible.

4.2.4.2 Objective

To maximize stability of dosage form and to determine DECS, essential for IND and ANDA submission as USFDA has made it compulsory to submit DECS data for any new formulation approval.

4.2.4.3 Procedure

The drug was mixed with various excipients in 1:1 ratio. This mixture was kept in glass vials than properly capped and sealed with Teflon tape. Two vials of each mixture were kept at room temperature (25˚C) and in the oven at 40ºC for one month period. After every week till one month, the vials were withdrawn and sample mixture was assayed for drug content/related substances.

4.2.4.4 Compatibility study with Permeation Enhancers

Table 4.7: Result of compatibility study with penetration enhancers

Compatible penetration enhancer	Incompatible penetration enhancer
Oleyl alcohol	Ethanol
Triacetin	PEG 400
Propylene Glycol	N-methyl pyrollidone
Oleic acid	Ethyl oleate
	Mineral oil

Results and discussion: The results shown in Table 4.7 indicate Lidocaine was found to be compatible with Oleyl alcohol, Triacetin, Propylene Glycol and Oleic acid. So this permeation enhancer was used for further study.

4.2.4.5 Compatibility study with monomers of acrylate polymers

Solution of polyacrylate adhesives are one type of PSA that are used in transdermal drug delivery patches. Such polyacrylates are made by copolymerizing one or more soft monomers (2-ethylhexyl acrylate, butyl acrylate), one or more hard monomers (Vinyl acetate, methyl acrylate) and one or more functional group-containing monomers (Acrylic acid, 2-hydroxyethyl acrylate) in an organic solvent solution. Modified monomers are typically included to alter the glass transition temperature (Tg) of the polymer. The functional group containing monomer provides sites for cross linking. In the polyacrylate, the functional group(s) will normally be carboxyl, hydroxyl, or combinations thereof [6.] Compatibility study was conducted with monomers of acrylate monomers and any increase in related substances (degradation products) was detected. Temperature should be maintain 40˚C.

- The limit of various related substances are

  A: Single Known degradation product (NMT 0.2%)

  B: Single Unknown degradation product (NMT 0.2%)

  C: Total degradation products (NMT 1.00%)

4.2.4.6 Compatibility study with different PSA polymers

Compatibility studies with polymers were conducted with previously selected acrylate polymers from compatibility study with monomers. the study was also conducted with other polymers such as polyisobutylene PSAs (Durotak 608A) and silicone adhesives (BioPSA 4302) etc. Two temperature condition 25˚C and 40˚C used for this study.

4.2.4.7 Compatibility study with different fillers (Matrix stiffeners)

An essential component of the transdermal patch is filler. The term "filler" signifies a 2 to 10% w/v aqueous dispersion of the filler that exhibits a pH of more than 5. Fillers include a number of inert filler components such as metal oxides (zinc oxide), inorganic salts (sodium carbonate), synthetic polymers (methacrylic resin), clays (Talc, Bentonite, Colloidal silicone dioxide). temperature conditions used for compatibility study were 25˚C and 40˚C.[73]

4.2.5 Absorption study with Backing films and Release liners

4.2.5.1 Objective

Absorption study is critical in selection of the backing and liner. this study was done in order to check the percentage drug absorbed by backing and liner. If the drug is absorbed through any of these it may cause formulation error and drug content in final formulation may decrease. The following backing films and release liners were selected for the Absorption based on literature review and various marketed products.

Backing Films:

- Scotchpak 9730 (Aluminium vapour coated polyester, polyethylene and EVA heat seal)
- Scotchpak 1109 (Polyester film with vapour coated polyester and pigmented polyethylene layer) and
- EW 9100 (Non woven, Polyester film)
- Cotran 9720 (Polyethylene film)

Release Liners:

- Silicon Coated (Loparex 75µm)
- Fluoropolymer coated polyester release liners (Scotchpak 1022)

- Saint Gobain 8310 (polyester and polypropylene)
- Paper liner

4.2.5.2 Procedure

A saturated solution of Lidocaine was prepared in Oleyl Alcohol. Several 140cm² pieces of backing films/release liners were cut and immersed in Lidocaine-Oleyl Alcohol solution and stored at 40°C/75% RH and 25°C/60% RH. The backing film/release liner was sampled at the interval of initial, 1, 2, 3, and 4 weeks. The sample was wiped carefully and analyzed for Lidocaine.

Results and Discussion:

The results of lidocaine absorption studies demonstrate that Scotchpak 9730, Cotran 9720 and Scotchpak 1109 showed a higher absorption 0.010 µg, 0.054 µg and 0.023 µg respectively compared to EW 9100 (0.008µg) at 40°C/75% RH. At room temperature, all four films showed negligible lidocaine absorption.

The results of lidocaine absorption studies demonstrate that Saint Gobain 8310 showed 0.0065 µg which was lower compared to other release liners at both temperature conditions.

Selection: From the above results, Saint Gobain 8310 and EW 9100 were selected as Release liner and Backing film respectively.

4.2.6 Thermo gravimetric analysis[74]

4.2.6.1 Specification

Temperature : Ambient to 1000ºC
Isothermal Temperature Accuracy : 1ºC
Isothermal Temperature Precision : 0.1ºC
Continuous Weighing Capacity : 1.0 gm
Sensitivity : 0.1 gm
Weighing Precision : 0.1 gm
Heating Rate : 20 ºC/ min

Figure 4.7: TA Instruments TGA Q500[67]

4.2.6.2 Procedure[74]

Place an empty sample pan on the platform and Tare from the TGA control menu. With the help of brass tweezers, load the SRM on sample pan. Press the Load key on the control menu touch screen. Press the Furnace key on the control menu. start the temperature calibration. Slowly raise the magnet under the furnace until a weight gain (<2%) is. The magnet should be positioned so as to maintain a magnetic field around the sample and the pan inside the furnace. TGA curve of lidocaine are reported in Figure 4.8.

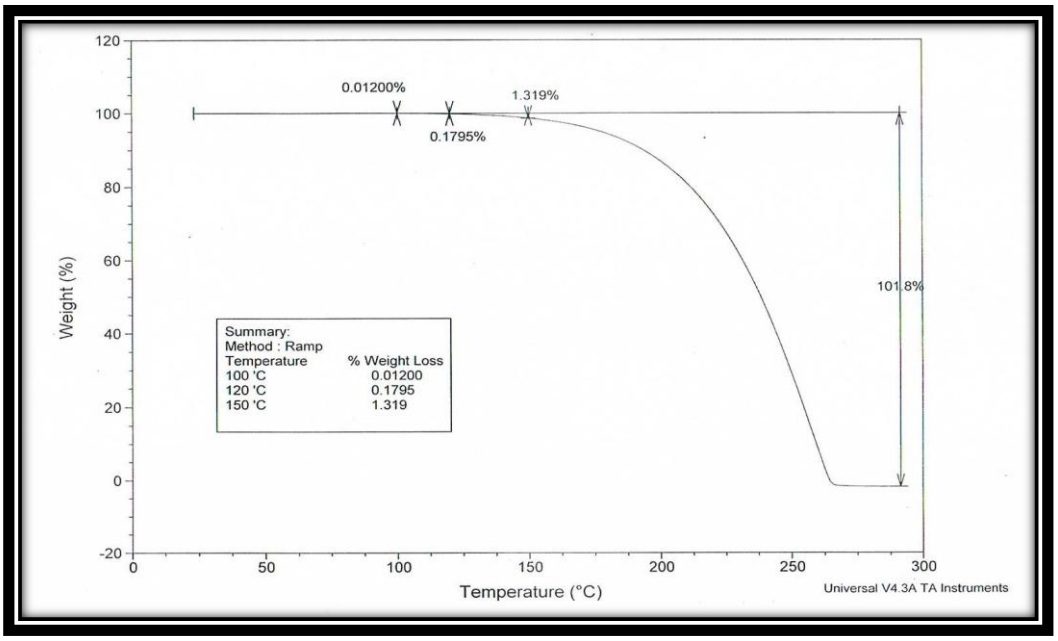


Figure 4.8: TGA Curve of Lidocaine

Results:

Thermo gravimetric analysis of Lidocaine (Figure 4.8) showed that till 150^{o} C, the % weight loss of lidocaine was found to be 1.319%. Further increase in temperature increased % weight loss of lidocaine Hence, it was concluded that the drying temperature of the lidocaine during formulation and development should be less than 150 ^{o} C.

4.3 FORMULATION DEVELOPMENT

4.3.1 Selection of Pressure Sensitive Adhesive.

4.3.1.1 Based on Saturated Solubility Study of Lidocaine in PSA Polymers (Crystallization Study)

Introduction

Solubility of drug molecules in polymer is a critical issue for development of transdermal patch. A patch should be given in such a way that patch has drug loading above the solubility limit in order to obtain zero order release kinetics[75].

Objective

The objective of this study was to determine the saturation solubility of lidocaine in acrylate and polyisobutylene (PIB) pressure sensitive adhesives (PSA) using crystallization studies. The PSAs used for the crystallization study are as in Table 4.15[76].

Table 4.15: Characteristics of PSA polymers

Sr. no.	Polymers	Solvent Composition
1	Durotak-608 A	Heptane
2	Gelva-737	Ethyl acetate, Ethanol, Toluene
3	Gelva-9073	Ethyl acetate, Hexane, Ethanol, Isopropyl alcohol
4	Aqueous Gelva	Water
5	Durotak-4287	Ethyl acetate
6	Durotak-2510	Ethyl acetate
7	Bio-PSA-4102	Heptane
8	Bio-PSA-4302	Ethyl acetate
9	MD-153	-

Procedure:

Lidocaine and adhesive were mixed using stirrer to achieve drug concentration of 2.5, 5, and 10% in dry matrix. The prepared blend was used to make patches using the following coating conditions. Knife gap, Temperature and time condition were maintained at 600µm, 60°C and 50 min respectively. Patches were cut in 10cm^2 size.

The prepared patches were observed for crystallization under light microscope (10X) for one month at different time intervals and observations are as in Table 4.16.

The concentration at which no crystals were observed was considered as the lidocaine's saturation Solubility in the respective adhesive. Results of the crystallization study are as in Table 4.17.

Table 4.17: Crystallization study results of lidocaine in PSA polymer

Sr. no.	PSA Polymers	
	Crystals not found	**Crystals observed**
1	Aqueous Gelva	Durotak-608 A
2	Gelva-737	Gelva-9073
3	MD-153	Durotak-4287
4	-	Durotak-2510
5	-	Bio-PSA-4302
6	-	Bio-PSA-4302

Selection

Based on the above results following PSA polymers and 5% of lidocaine concentration were selected for the further study.

- Gelva- 737
- Aqueous Gelva
- MD-153

4.3.1.2 Based on Adhesion Study

Adhesion test include peel strength, tack property, shear strength and release force.

Introduction[17, 77]

Peel strength: Peel adhesion is the force required to remove a patch from a test substrate. It is important in transdermal patch because adhesive should provide adequate contact of patch with the skin and should not damage the skin on removal.

Tack property: It is the force required to pull a probe away from an adhesive at a fixed rate.

Shear strength: It is the measurement of cohesive strength of an adhesive polymer. Adequate cohesive shear strength will mean that the patch will not slip on application and will leave no residue on removal.

Release force: It is the force required to detach or remove release liner prior to use of patch.

Procedure:

Lidocaine and adhesive were mixed well using stirrer to achieve drug concentration of 5% in dry matrix. Patches were prepared using the following coating conditions. Knife gap, Temperature and time condition were maintained at 600µm, 60°C and 50 min respectively. Patches were cut in 10cm^2 size. The prepared patches were studied for the following adhesion parameters.

Peel strength[78]

- Instrument: LLOYD(AMETEX)
- No. of patches required : 5.
- Attach the test patch on the steel plate.
- Adhere patch on the steel plate in such way that about 1 inch portion of the patch should not adhere.
- Now, roll the roller on it for two-three times.
- Allow it to stand for 1 minute.
- Fix the steel plate on instrument and attach the 1 inch portion on upper jaw.
- Peel at 180˚ using following parameters
    1. Cross head speed -300 mm/min
    2. Load cell-50 Newton.

Tack properties[78]

- Instrument: LLOYD (AMETEX Figure 4.9)
- No. of patches required : 5
- Take one patch and cut it to size of 1 inch square.
- Remove liner and apply on test panel such way that adhesion side remain upward direction towards hole.

- Load the cell on instrument and start machine at speed of 610 mm/min to bring contact of probe to adhesive site of patch.
- After 1 second contact time, remove probe from adhesive at same speed.
- Note down force (maximum) required for removing the probe from patch.
- Repeat same the procedure for other patch.

Figure 4.9: FRICTION TESTER (AMETEX)[78]

(Source:http://indonetwork.co.id/lloydinstruments/964019/friction-testerftplus.htm)

Shear strength:

Instrument: CHEMINSTRUMENT (10 bank shear tester) shown in Figure 4.10 5 patches were required for the study. all the patches were Cut of 0.5 inch width. Then Remove liner from one end and apply the patch on the test panel with 0.5*0.5 inch area. Roll the roller on it and allow it to stand for 15 min. The other end was attached with hook and was applied weight on the hook. Measure time required to fall down the patch.

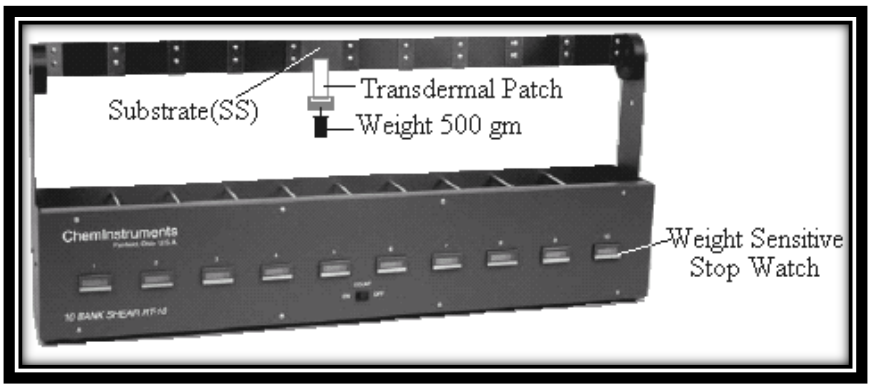


Figure 4.10: Cheminstruments 10 Bank Shear Tester

Release Force:

- Instrument: FRICTION TESTER (AMETEX)
- No. of patches required: 5
- Attach double-sided adhesive tape to the surface of steel panel.
- Adhere test patch on double-sided adhesive tape in such way liner remains outside.
- Attach the liner with movable jaw using cello tape.
- Peel at 180˚ using following parameters
    1. Cross head speed -300 mm/min
    2. Load cell-50 Newton.

Table 4.18: Peel strength and Tack property data

Adhesion study	Peel at 180˚ (N/inch)			Tack property (N/18.89mm²)		
	Aqueous Gelva	Gelva-737	MD-153	Aqueous Gelva	Gelva-737	MD-153
1	4.4	3.4	1.2	1.5	1.2	0.4
2	4.3	3.6	1.7	1.4	1.3	0.6
3	4.2	3.2	1.1	1.4	1.4	0.5
4	4.5	3.4	1.3	1.5	1.5	0.3
5	4.4	3.3	1.2	1.7	1.2	0.7
Average	4.36±0.11	3.38±0.15	1.3±0.23	1.5±0.12	1.32±0.13	0.5±0.16

Table 4.19: Shear strength and Release force data

Adhesion study	Shear strength(min)			Release force (gf/inch)		
	Aqueous Gelva	Gelva-737	MD-153	Aqueous Gelva	Gelva-737	MD-153
1	41	33	12	28	25	7.4
2	37	36	14	34	24	7.2
3	44	31	16	29	28	6.6
4	47	37	8	33	29	5.4
5	42	35	11	26	27	4.7
Average	42.2±3.7	34.4±2.4	12.2±3.0	30±3.4	26.6±2.1	6.26±1.2

Result and discussion

From the above observations it was found that there were no significant differences in adhesion parameters among the patches which were prepared using Aqueous Gelva and Gelva-737 But patches prepared from the PSA adhesive MD-153 showed poor adhesion property, so this polymer was not selected for further study.

4.3.1.3 *Ex-vivo* permeation of lidocaine for selection of pressure sensitive adhesive

A. Objective

The objective of this study was to investigate the effects of various PSAs like aqueous Gelva and Gelva 737 on the *ex-vivo* permeation of Lidocaine across the skin from the patch using Franz diffusion cells at 32±0.5 ˚C.

B. Skin Preparation

Preparation of skin for permeation studies: Hairless human cadaver skin are used for permeation studies. Human cadaver skin may be a logical choice as the skin model because final product will be used on human's skin[79, 80].

Intact Full thickness skin: Hair on dorsal skin were removed with hair clipper, subcutaneous tissue was surgically removed and dermis side was wiped with isopropyl alcohol to remove residual adhering fat. The skin is washed with distilled water. The skin so prepared is wrapped in aluminum foil and stored in a freezer at -20°C till further use. The skin is defrosted at room temperature when required[79, 80].

Separation of epidermis from full thickness skin: The prepared full thickness skin was treated with 2M sodium bromide solution in water for 6 h. The epidermis was separated by using a cotton swab moistened with distilled water. Then epidermis sheet was cleaned by washing with distilled water and dried under vacuum. Dried sheets were stored in desiccators until further use[79, 80].

C. Experimental conditions

Diffusion cell	: Franz diffusion cell
Diffusion medium	: Phosphate buffer (pH 7.4)
Volume of diffusion cell	: 13.2 ml (A), 13.4ml (B), 13.4ml (C)

Sampling volume	: 1.0 ml
Patch size	: 12.56cm²
Label claim	: 15.7mg/12.56cm²
Temperature	: 32±0.5˚C
Area of diffusion cell	: 1.23 cm² (A), 1.27 cm² (B), 0.94 cm² (C)
Sampling time interval	: 3, 6, 9, 12 hour

(A,B,C were different diffusion cell used during study)

D. Procedure

The *Ex vivo* drug release experiment was carried out using Franz diffusion cell. The excised human cadaver skin was cut into desired size of 12.56cm² and clamped between the receptor and donor compartments so that the dermal side of the skin faced the receiver fluid. The release liner was removed from the patch (12.56 cm² size) and the drug releasing surface was pressed on the skin with the adhesive side facing the stratum corneum. The receptor compartment was filled with specified volume of the diffusion medium (phosphate buffer pH 7.4) through sampling port taking care to remove all the air bubbles. The contents were stirred by small magnetic beads continuously at 600 RPM to keep them well mixed. At suitable time intervals, 1ml aliquots of diffusion medium were collected at and filtered through Whatman® filter grade 41. It was suitably diluted and the amount of Lidocaine diffused through the skin membrane was then determined by HPLC. Fresh diffusion medium of the same volume (1ml), which was pre-warmed at 32±0.5 ºC, was replaced into the diffusion cell after each withdrawal to maintain sink condition. The study was continued up to 12 hours. Each study was performed in triplicate (n=3) and mean value was used to calculate the permeability of drug through skin.

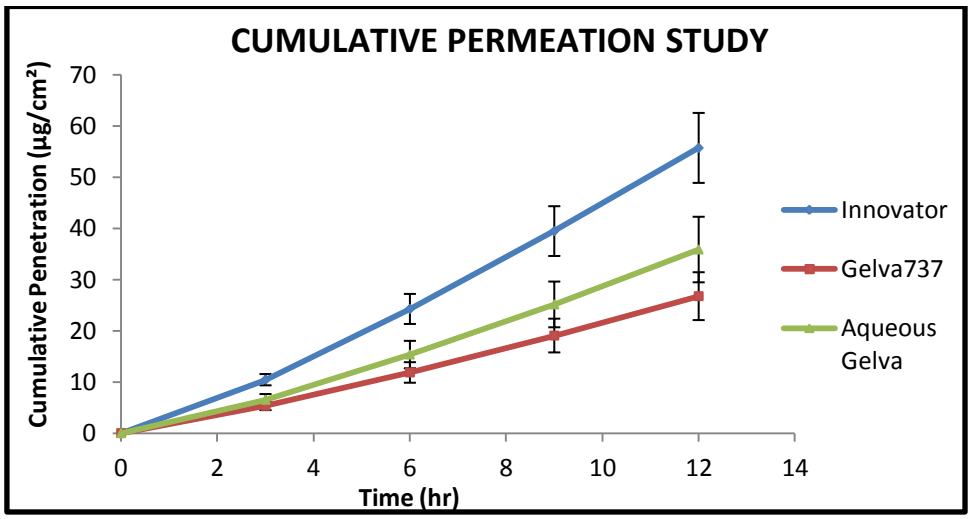


Figure 4.11: Comparison of cumulative permeation between Innovator, Gelva-737 and Aqueous Gelva

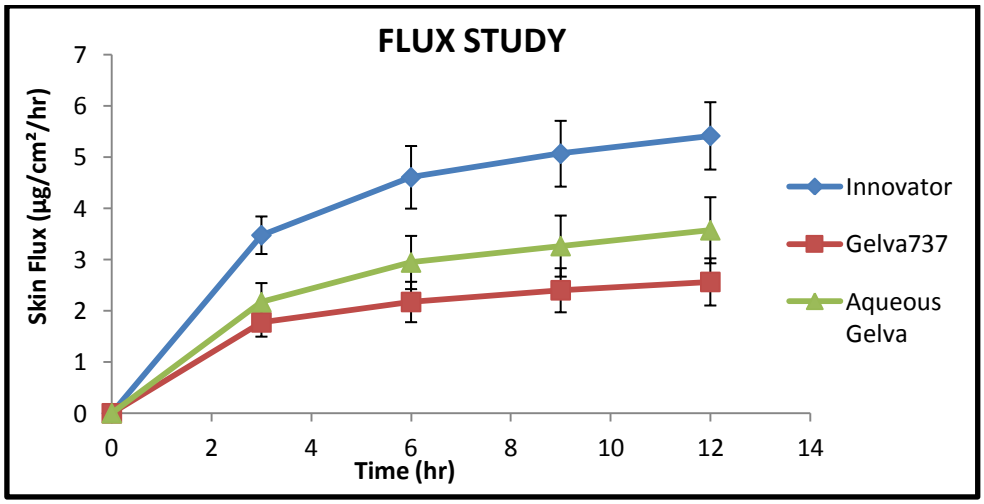


Figure 4.12: Comparison of skin flux between Innovator, Gelva-737 and Aqueous Gelva

Results and Discussion

After 12 hrs, the cumulative permeation of Lidocaine from patch of GMS 737 and Aqueous Gelva was found to be 26.76µg/cm² and 35.87µg/cm² respectively. The skin flux for Lidocaine from patch of GMS 737 and Aqueous Gelva was found to be 2.57µg/cm²/hr and 3.58µg/cm²/hr respectively. From these results, it was concluded that lidocaine in aqueous polymer shows more cumulative permeation and skin flux compared to gelva-737. So this polymer was selected as pressure sensitive adhesive for further study.

4.3.2 Preparation of premix

4.3.2.1 Introduction

Premix usually refers to a substance or object which is mixed in an early stage in the manufacturing and distribution process.

4.3.2.2 Problem

Aqueous Gelva was chosen as adhesive polymer but drug was not completely dissolved in adhesive polymer.

Table 4.22: Formulation of Batch F1

Sr.no.	Ingredients	%Solid (%w/w)	%Liquid (w/v)
		F1	F1
1	Lidocaine	5	3.39
2	Oleyl Alcohol	5	3.39
3	Aqueous Gelva	90	93.21
Total		100	100
Solid content of Aqueous Gelva : 65.5			

4.3.2.3 Procedure

Add 5% Oleyl Alcohol in the clean beaker. Heat it on hot plate at 40˚C. Stir it with low speed. Add drug when temperature reached at 40˚C. When the solution became clear then stopped heating and stirring.

Discussion: Aqueous Gelva was choosen as adhesive polymer. But drug was not completely dissolved in adhesive polymer, so it was required to make drug in dissolve form by preparing the premix of drug in oil. Here 5% Oleyl Alcohol was used.

4.3.4 Addition of surfactant

Surface-active agent (surfactant) is a chemical that stabilizes mixtures of oil and water by reducing the surface tension at the interface between the oil and water molecules. Because water and oil do not dissolve in each other a surfactant has to be added to the mixture to keep it from separating into layers. Surfactants are usually organic compounds that are amphiphilic, meaning they contain both hydrophobic groups (their tails) and hydrophilic groups (their heads).

Therefore, a surfactant molecule contains either a water insoluble (or oil soluble component) and a water soluble component. Surfactant molecules will migrate to the water surface, where the insoluble hydrophobic group may extend out of the bulk water phase, either into the air or, if water is mixed with oil, into the oil phase, while the water soluble head group remains in the water phase. This alignment and aggregation of surfactant molecules at the surface acts to alter the surface properties of water at the water/air or water/oil interface.[82]

Problem

Aqueous Gelva is Gelva Multi-polymer Emulsion (GME). When we added premix in this polymer, polymer became separated due to change in oil concentration.

Discussion: Aqueous Gelva is Gelva Multi-polymer Emulsion (GME). When we added premix in this polymer, polymer became separated due to change in oil concentration. So we required to add some surfactant to stabilize the system. From the literature, 1.5% Tween 80 was selected as surface active agent.

4.3.5 Selection of Matrix Stiffening Agent

4.3.5.1 Introduction

An essential component of the transdermal patch is filler. The term "filler" in connection with this application signifies filler such that a 2 to 10% w/v aqueous dispersion of the filler exhibits a pH of more than 5. Thus, such fillers include a number of inert filler components including metal oxides (zinc oxide, magnesium oxide, titanium oxide, and calcium oxide), inorganic salts (calcium, magnesium and sodium carbonate, calcium and magnesium sulfate, calcium phosphate), synthetic polymers (methacrylic resin, nylon, polyethylene), clays (talc, bentonite, CSD and kaolin) [73].

4.3.5.2 Problem

When patches were prepared by using above formula it was found that matrix was not sufficient hard and lagging was observed in all patches.

4.3.5.3 Objective

To use matrix stiffening agent to make patch sufficient hard and remove lagging.

4.3.5.4 Selection of Matrix Stiffener From CSD and Talc

Table 4.23: Formulation of Batch F2 and F3

Sr.no.	Ingredients	%Solid (%w/w)		%Liquid(w/v)	
		F2	F3	F2	F3
1	Lidocaine	5	5	3.53	3.53
2	Oleyl Alcohol	5	5	3.53	3.53
3	Tween 80	1.5	1.5	1.06	1.06
4	Talc	-	10	-	7.07
5	CSD	10	-	7.07	-
6	Aqueous Gelva	78.5	78.5	84.78	84.78
Total		100	100	100	100
Solid content of Aqueous Gelva : 65.5					

Procedure:

Add required quantity of Aqueous Gelva in the beaker. Stir it at 500 rpm for 2 min. Then add Tween 80 slowly and stir it at 500 rpm for 2 min. Now, add the prepared premix in the beaker and stir it for 2 min at 500rpm. Lastly add talc with high speed stirring rate at 1200 rpm. The blend was stir for 5min at 1200 rpm and to prepare a patch of size 10 cm^2. the blend was then coat on mathis-1 coater, Knife gap was set to 600µm and coated blend was dried at 60°C temperature for 50 min.

Table 4.24: Sequence of Adding Ingredients

Sr.no.	Ingredients	Addition time(min)	Stirring time(min)	Speed (RPM)
1	Gelva	0	2	500
2	Tween 80	2	2	500
3	Premix	2	2	500
4	Talc	5	10	1200

Results and discussion

It was observed that up to 2.3% CSD can add in the polymer. Above 2.5% it chokes the blend and the blend has not good flow property. Thus Talc was used for further study.

4.3.5.5 Optimization of Talc concentration.

A. Preparation of Patches Contain 10, 20, 30 and 40 % Talc.

Table 4.25: Formulation of Batch F3 to F6

Sr.no.	Ingredients	%Solid (%w/w)				%Liquid(w/v)			
		F3	F4	F5	F6	F3	F4	F5	F6
1	Lidocaine	5	5	5	5	3.53	3.67	3.82	3.98
2	Oleyl Alcohol	5	5	5	5	3.53	3.67	3.82	3.98
3	Tween 80	1.5	1.5	1.5	1.5	1.06	1.10	1.14	1.19
4	Talc	**10**	**20**	**30**	**40**	7.07	14.69	22.93	31.86
5	Aqueous Gelva	78.5	68.5	58.5	48.5	84.78	76.85	68.27	58.97
Total		100	100	100	100	100	100	100	100
Solid content of Aqueous Gelva : 65.5									

Procedure

Patches were prepared using above formula and evaluated for their physical appearance.

Results and discussion

From the above observation, it can be concluded that in Batch no. F3 lagging was observed and matrix was not sufficient hard. In Batch no. F4, we were found good adhesion but somewhat lagging was observed. The lagging was absent in the patches of Batch no. F5 but adhesion was not found. So Talc concentration between 20% to 30% was selected for further study.

B. Preparation of Patches Contain 22, 24, 26 and 28% Talc.

Table 4.27: Formulation of Batch F7 to F10

Sr.no.	Ingredients	%Solid (%w/w)			
		F7	**F8**	**F9**	**F10**
1	Lidocaine	5	5	5	5
2	**Oleyl Alcohol**	5	5	5	5
3	Tween 80	1.5	1.5	1.5	1.5
4	Talc	**22**	**24**	**26**	**28**
5	Aqueous Gelva	66.5	64.5	62.5	60.5
Total		100	100	100	100
Solid content of Aqueous Gelva : 65.5					

Procedure

Patches were prepared using above formula and evaluated for their physical appearance.

Results and discussion

From the observation, it can be concluded that in batch no. F7 and F8 lagging was found while in batch no. F10 adhesion and pourability problem was observed. Patches were prepared from 26% Talc (batch no. F9) showed good adhesion, pourable and also lagging was absent. Thus 26% Talc concentration was selected.

4.3.6 Selection of Permeation Enhancer (Base on *Ex-vivo* permeation)

4.3.6.1 Objective

The objective of this study was to investigate the effects of various permeation enhancers like Oleyl Alcohol, Triacetin, Oleic Acid and Propylene Glycol on the *Ex vivo* permeation of Lidocaine across the skin membrane using Franz diffusion cells at 32±0.5˚C.

Table 4.29: Formulation of Batch F9, F11, F12 and F13

Sr.no.	Ingredients	%Solid (%w/w)			
		F9	F11	F12	F13
1	Lidocaine	5	5	5	5
2	**Oleyl Alcohol**	**5**	-	-	-
3	**Triacetin**	-	**5**	-	-
4	**Propylene Glycol**	-	-	**5**	-
5	**Oleic Acid**	-	-	-	**5**
6	Tween 80	1.5	1.5	1.5	1.5
7	Talc	**26**	**26**	**26**	**26**
8	Aqueous Gelva	62.5	62.5	62.5	62.5
Total		100	100	100	100
Solid content of Aqueous Gelva : 65.5					

4.3.6.2 Procedure

By using the above Formulations, patches were made containing penetration enhancer, *Ex-vivo* permeation study of these patches was performed and results are reported in Table 4.30, 4.31 and Figure 4.10, 4.11.

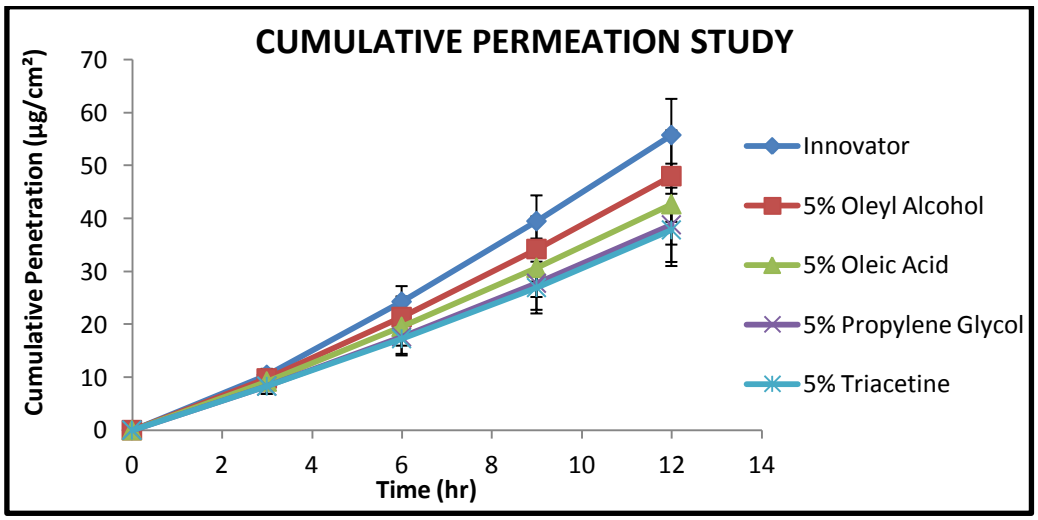


Figure 4.13: Comparison of cumulative permeation from different permeation enhancers

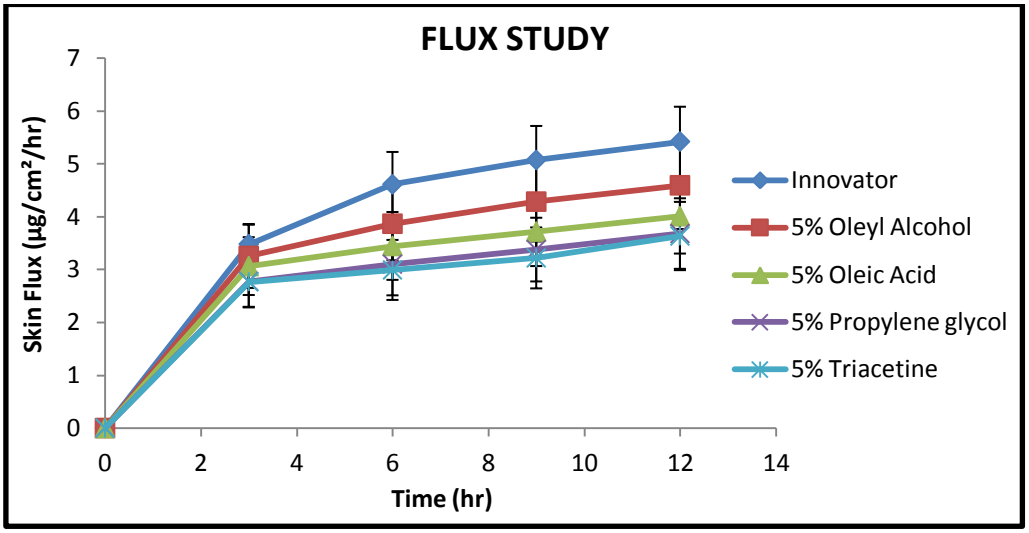


Figure 4.14: Comparison of skin flux from different permeation enhances.

Results and Discussion:

After 12 hrs, the cumulative permeation of Lidocaine from patch of 5% Oleyl Alcohol, 5% Oleic Acid, 5% Propylene Glycol, and 5% Triacetin was found to be 47.97µg/cm², 42.68µg/cm², 38.77 µg/cm² and 37.81µg/cm² respectively.

The skin flux for Lidocaine from patch of 5% Oleyl Alcohol, 5% Oleic Acid, 5% Propylene Glycol and 5% Triacetin was found to be 4.59µg/cm², 4.01µg/cm², 3.68µg/cm², and 3.63µg/cm² respectively. From the results, it was concluded that lidocaine in 5% Oleyl Alcohol shows nearest value of cumulative permeation and skin flux to innovator compared to other permeation enhancers, So Oleyl alcohal was selected as permeation enhancer for further study.

4.3.7 Concentration optimization of Permeation Enhancer (Base on *Ex-vivo* permeation study)

4.3.7.1 Objective

The objective of this study was to see the effects of different concentration of permeation enhancer (Oleyl Alcohol) on the Ex vivo permeation of Lidocaine across the skin membrane using Franz diffusion cells at 32±0.5˚C and select concentration of Oleyl Alcohol in such way that it gives the skin permeation similar to innovator.

Table 4.32: Formulation of Batch F9, F14, and F15

Sr.no.	Ingredients	%Solid (%w/w)		
		F9	F14	F15
1	Lidocaine	5	5	5
2	Oleyl Alcohol	5	7.5	10
3	Tween 80	1.5	1.5	1.5
4	Talc	26	26	26
5	Aqueous Gelva	62.5	60	57.5
Total		100	100	100
Solid content of Aqueous Gelva : 65.5				

4.3.7.2 Procedure

By using the above Formulations, patches were made which contained different concentration of Oleyl Alcohol. *Ex-vivo* permeation study of these patches was performed and results are reported in Table 4.33, 4.34 and in Figure 4.12, 4.13.

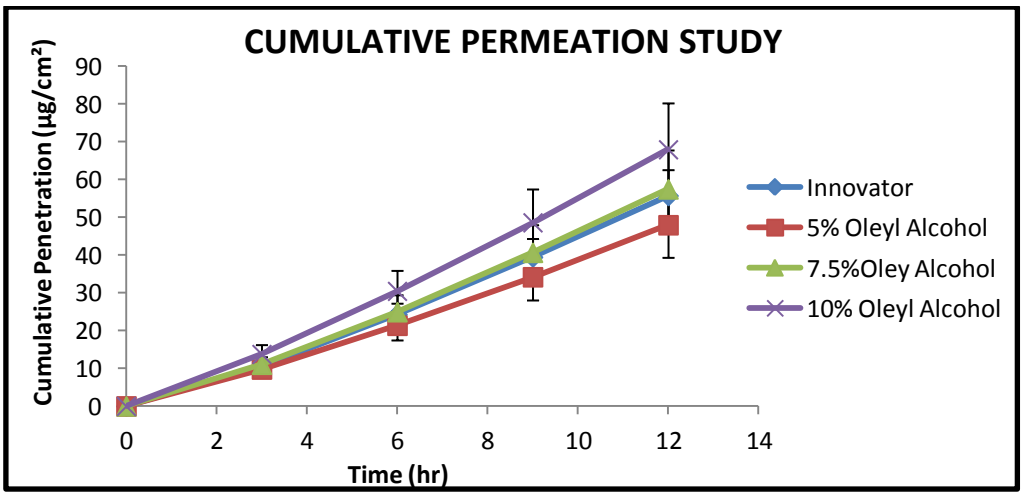


Figure 4.15: Comparison of Cumulative Permeation from different concentrations of Oleyl Alcohol

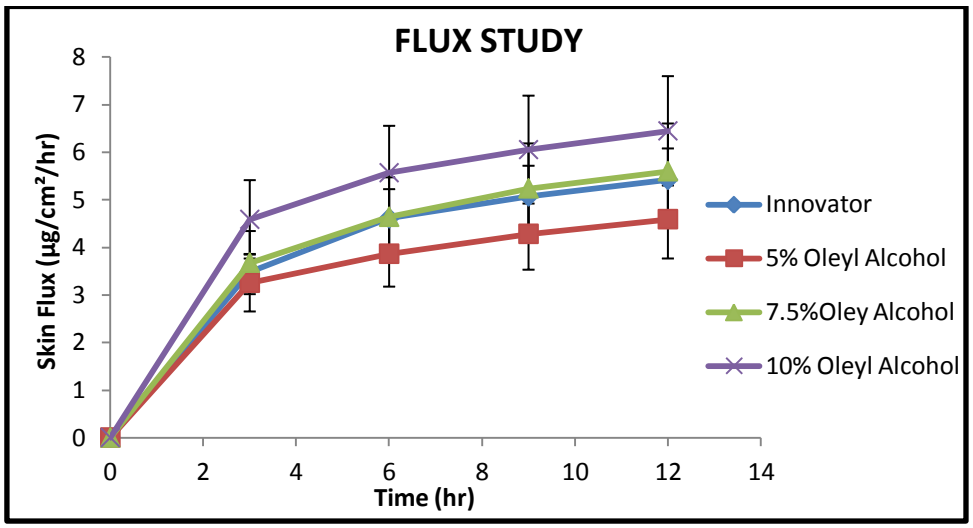


Figure 4.16: Comparison of skin flux from different concentrations of Oleyl Alcohol

Results

After 12 hrs, the cumulative permeation of Lidocaine from patch of 5% Oleyl Alcohol, 7.5% Oleyl Alcohol and 10% Oleyl Alcohol was found to be 47.97µg/cm², 57.46µg/cm² and 67.95µg/cm² respectively. The skin flux for Lidocaine from patch of 5% Oleyl Alcohol, 7.5% Oleyl Alcohol and 10% Oleyl Alcohol was found to be 4.59µg/cm², 5.60µg/cm² and 6.45µg/cm² respectively. From the results, it was concluded that lidocaine in 7.5% Oleyl Alcohol shows comparative cumulative permeation and skin flux with Innovator. So this concentration of permeation enhancer was optimized.

4.3.8 Addition of smoothing agent

4.3.8.1 Problem

When more than 5% of oil was added, the blend became thick which was difficult to coat.

Discussion: due to difficulty in coating smoothing agent was required to be added From the literature 5% glycerine was selected as smoothing agent.

4.4 FABRICATION OF OPTIMIZED PATCH

4.4.1 Procedural Steps for fabrication of Lidocaine Topical patch

The procedural steps followed for fabrication of topical patches are mentioned below:

A. Blending and de-aeration

Procedure:

a. Preparation of Premix

Add 7.5% Oleyl Alcohol in a beaker. Heat it on hot plate at 40˚C and stir it at low speed. Drug was added when temperature reached to 40˚C. When the solution became clear heating was stopped and stirring was done

b. **Preparation of blend**

Aqueous Gelva was taken in beaker and Stir it at 600 r.p.m for 5 min. Then added Tween 80 slowly and stirred it at 600 rpm for 5 min. Than add the glycerin slowly and stirred it at 10 rpm for 2 min. Now add the prepared premix in the beaker and stir it for 5 min at 600 rpm. Lastly added talc with high speed stirring rate at 1200 rpm. The blend was stir for 10 min at 1200 rpm. Resulting drug matrix was carefully sealed and kept aside for 30 minutes to remove the air bubbles. Now, Blend was ready for coating over release liner.

B. Coating and drying of drug matrix to release liner[83]

The prepared drug matrix was coated on to the release liner using Mathis (1 zone) Labcoater (Figure 4.17) and dryer instrument. The required knife gap i.e. coating thickness was adjusted in the instrument. The drug matrix was poured onto the silicone coated side of release liner (18" x 12") into the slot between stainless steel coating roller and knife.

The knife was moved automatically to coat blend on liner. After coating knife was removed and the sheet of liner was dried at 60°C for 50 min.

Figure 4.17: Labcoater type LTS-S[83]

C**. Lamination and cutting**

When coated release liner sheets were properly dried they were subjected to lamination with specified backing membrane using manual laminator instrument.The topical patches so formed were cut-out using die-cutter of size 140 cm^2 and were properly labelled and packed in air tight containers. These topical patches were subjected to further evaluation studies.

4.4.2 Optimization of coating parameters

The prepared blend of topical patch was casted on the release liner using Mathis (1 zone) coater and dryer. The critical parameters for successful development of any topical patch are coating parameters such as coating thickness, drying temperature to cast blend on the liner and drying time. Optimization of these parameters is required to get the best effective topical patch.

4.4.2.1 Optimization of Coating Thickness

Six coating trials were performed to optimize the coating thickness of patch to achieve the target matrix weight of 250 mg in 10 cm^2 patch. Results are reported in Table 4.37.

Table 4.37: Optimization of Coating Thickness

Sr. no.	Knife gap thickness (µm)	Target wt (mg)	Wt obtained (mg)	
			Left	Right
1	400	250	214.18	216.28
2	500		266.41	268.04
3	490		260.87	262.14
4	480		254.66	255.83
5	470		247.59	248.08
6	**475**		**250.1**	**252.2**

Results and Discussion: From the above result, Coating thickness 475 µm was selected. At this thickness we can achieve target weight 250 mg of 10 cm² patch.

4.4.2.2 Optimization of drying temperature and drying time

Drying temperature and drying time were used 60°C and 50 minutes. But the aim was to dry at optimum temperature and time so that good physical appearance of prepared patch was obtained. Here, three different temperature (50, 60 and 70°C) and time conditions (30, 40 and 50 mins) were studied for optimization.

Table 4.38: Optimization of drying temperature and drying time

Sr. no.	Drying temp. (°C)	Drying time (min)
1	50	30
2	50	40
3	50	50
4	60	30
5	60	40
6	60	50
7	70	30
8	70	40
9	70	50
10	80	60

Results and Discussion: From the above result, drying time 50 min and drying temperature 70˚C was chosen because at this condition patch showed good physical appearance and adhesion.

4.5 EVALUATION OF OPTIMIZED PATCH

4.5.1Physicochemical Evaluation of Fabricated Topical Patch

4.5.1.1Thickness

The thickness of the drug-containing adhesive matrix was determined by measuring the thickness of the whole patch (adhesive matrix with the drug plus the backing membrane and release liner) and subtracting the thickness of the backing membrane and release liner. The average thickness was determined using a digital calliper (Micrometer MI-1000, Cheminstruments® Figure 4.6)[15]. The observations are shown in Table 4.39.

Figure 4.18: MI-1000 Micrometer[71]

Table 4.39: Thickness of drug matrix of fabricated topical patches

Sr.no.	Thickness(µm)			
	Whole patch (H_p)	Backing film (H_b)	Release liner (H_r)	Matrix $H_p-(H_b - H_r)$
1	315	70±5	80±5	165
2	320			170
3	325			175
4	320			170
5	330			180

Average	**322±5.70**		**172±5.70**

Result: The thickness of matrix in batch no. F16 was found to be **172±5.70µm.**

4.5.1.2 Uniformity of Weight:

Weight variation was studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight. The observations are shown in Table 4.40.

Table 4.40: Weight Variation Of Fabricated Topical Patches

Sr.no.	Weight(gm)	Sr.no.	Weight(gm)
1	3.559	6	3.529
2	3.529	7	3.565
3	3.584	8	3.528
4	3.529	9	3.529
5	3.459	10	3.459

Results

- Total weight of 10 Patches: **35.271 gm**.
- Theoretical weight of Patches: **3.500 gm**.
- Average weight of Patches: **3.527 gm**.
- % difference: **5 %**
- Lower limit of tolerance**: 3.350 gm.**
- Higher limit of tolerance**: 3.703 gm.**
- No. of Patches deviates from the limit: **0.**
- No. of Patches deviate from double the % limit: **0.**

4.5.1.3 Drug Content Determination

Chromatographic Conditions

HPLC system	-	Agilent®
Supporting software	-	Chromeleon®
Detector	-	U V
Mobile phase	-	n-Hexane: Ethanol (90:10)v/v
Column specifications-	Type	- Inertsil Silica
	Length	- 250 mm
	Internal diameter	- 4.6 mm
	Particle Size	- 5µm
Detecting wavelength	-	210 nm
Flow rate	-	1.0 ml/min.
Run time	-	10 min.
Sample volume	-	5µl
Diluent	-	Ethyl Acetate

Assay methodology of Lidocaine

Preparation of mobile phase

Mix about 9 volumes n-Hexane with 1 volume of ethanol in one liter vessel.

Standard Preparation

Dissolve about 45 mg of Lidocaine USP, accurately weighed in 10 mL of ethyl acetate in a 250 mL volumetric flask, and makeup the volume with ethyl acetate to obtain a standard preparation having a known concentration of about 0.18mg/ml of Lidocaine.

Sample Preparation

The release liner of the patch was removed and the patch was placed into a 500 ml glass beaker such that matrix side faced upwardly. 250 ml of Ethyl acetate was added to the beaker and tightly covered and shaken for 1 hr on a mechanical shaker. Solution was filtered and 5 ml filtrate was diluted with 20 ml of ethyl acetate to obtain preparation having a known concentration of about 0.175mg/ml of Lidocaine.

Procedure

Separately inject equal volume (10 micro liters) of a diluent, standard preparation and sample preparation into a HPLC system, record a chromatogram and measure responses for a major peaks and also the retention time of the major peaks.

Calculation

Drug content in patch was calculated by using following formula,

$$\% \textbf{ Assay} = \frac{\textbf{Area of test}}{\textbf{Area of Standard}} * \frac{\textbf{Weight of Standard}}{\textbf{Standard Dilution}} * \frac{\textbf{Test Dilution}}{\textbf{Weight of test}} * \frac{\textbf{Potency}}{\textbf{100}} * \textbf{100}$$

Chromatograms:

Observation:

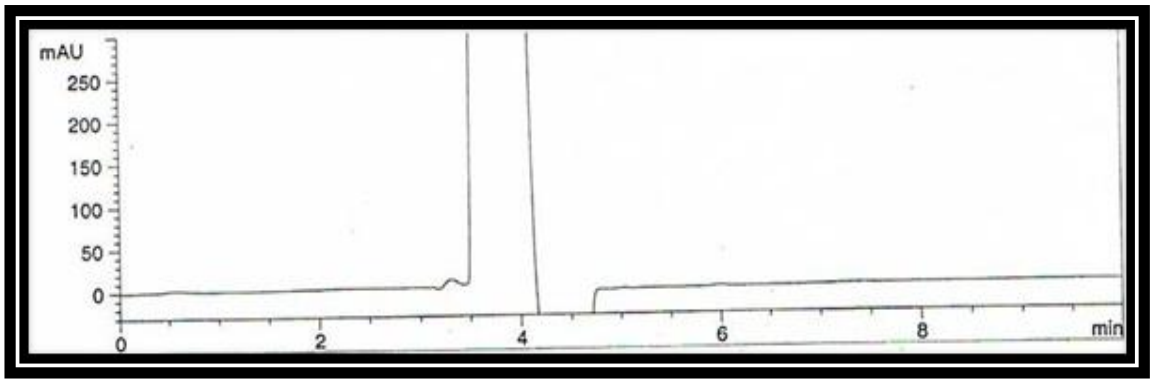


Figure 4.19: Chromatograph of Diluent

Diluent RT: 3.905

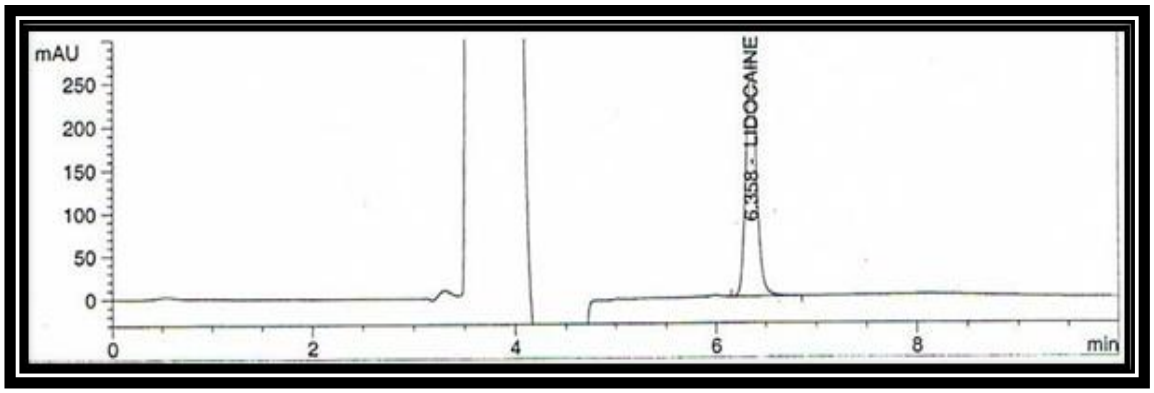


Figure 4.20: Chromatograph of Standard

Standard RT: 6.358

Standard Peak Area: 2046.52686

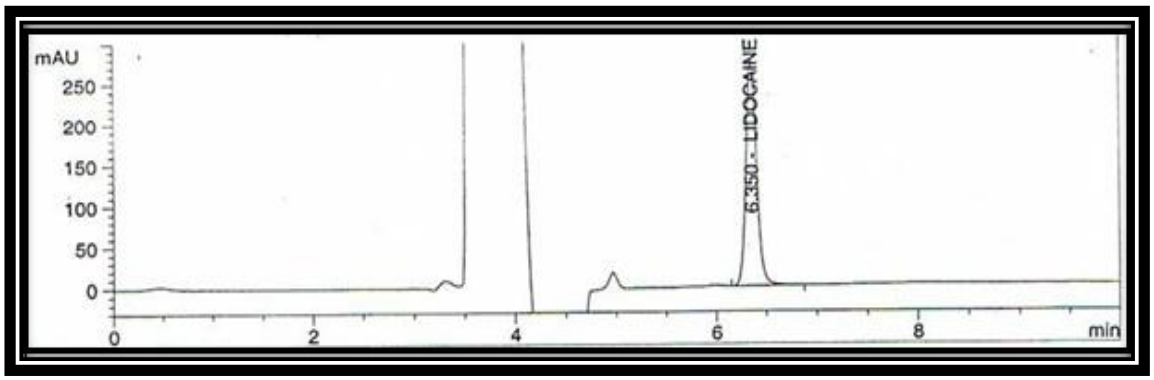


Figure 4.21: Chromatograph of Sample Patch

Sample Patch RT: 6.350

Sample Patch Peak Area: 2038.6343

Result: % Assay of lidocaine topical patch was found to be 99.61% w/w.

4.5.1.4 Content Uniformity Test:

10 patches were selected and content was determined for individual patches as per above method. The results are shown in Table 4.41.

Table 4.41: The results of Content Uniformity Test

Sr.no.	Drug Content(% w/w)	Inference
1	100.98	Pass
2	101.30	Pass
3	99.75	Pass
4	98.83	Pass
5	100.32	Pass
6	99.49	Pass
7	101.34	Pass
8	101.27	Pass
9	98.97	Pass
10	99.96	Pass

Results: Assay of all 10 randomly selected patches was found in between 85-115% w/w range. Thus prepared patches comply content uniformity test.

4.5.1.5 Moisture Uptake Study

This study can predict the moisture-uptake capacity of fabricated patch at various humidity levels. It also helps to determine the effect of sweating and bathing on adhesiveness of patch when applied to skin. Less moisture uptake indicates the stability of the formulation. More moisture uptake on the other hand, indicates bulkiness of the formulation and the chances of microbial growth. To determine moisture uptake , the pre-weighed patches were placed in a desiccator maintained at 85% RH using saturated solution of potassium chloride. Patches were withdrawn after 24 hr and % moisture uptake was calculated using following formula[15, 17].

$$\%\text{Moisture uptake} = \frac{\text{Weight of moisture absorbed by transdermal patch}}{\text{Initial weight of transdermal patch}} \times 100$$

Table 4.42: Moisture absorption by fabricated topical patches

Sr.no.	% Moisture absorption
1	1.2
2	1.4
3	1.1
4	1.2
5	1.3
Average	1.24±0.11

Results: % Moisture absorption by Final Patch was found to be **1.24±0.11**.

4.5.1.6 Moisture Content

A small amount of moisture in patch-type formulations helps to maintain stability and prevents the formation of a dried and brittle film. A greater amount, however, can lead to microbial contamination during storage. It also affects the rate of drug diffuse from the patch. moisture content of the transdermal patches was determined by individually weighing and keeping in a desiccator containing activated silica114 at room temperature for 24 hr. The patches were again weighed individually until they showed a constant weight. Percent moisture content is determined as follows.[15, 17]

$$\%\textbf{Moisture Content} = \frac{\textbf{Weight of water in transdermal patch}}{\textbf{Initial weight of transdermal patch}} \times \mathbf{100}$$

Table 4.43: Moisture content of fabricated topical patches

Sr.no.	% Moisture Content
1	1.4
2	1.3
3	1.2
4	1.5
5	1.7
Average	1.42±0.19

Results: % Moisture content by Final Patch was found to be **1.42±0.19**.

4.5.2 Adhesion Study

Adhesion test include peel strength, tack property, shear strength and release force.

Procedure

Adhesion study of prepared final patches was performed by using procedure given in section 4.3.1.2 and results are reported in Table 4.44.

Result and discussion: From above results, it can be concluded that prepared final patches shown good adhesion value. This adhesion value was sufficient to keep patch 12 hr on skin and easily remove from the skin without leaving residue on skin.

4.5.3 In-Vitro Dissolution Study

4.5.3.1 Introduction

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms. The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug. There are various methods available for determination of drug release rate of TDDS. But this test was performed as only quality parameter test[15, 17].

The Paddle over Disc: (USP apparatus 5/ PhEur 2.9.4.1)

This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C.

The Cylinder modified USP Basket: (USP apparatus 6 / PhEur 2.9.4.3)

This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5°C.

The reciprocating disc: (USP apparatus 7)

In this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method (PhEur 2.9.4.2) may be used.

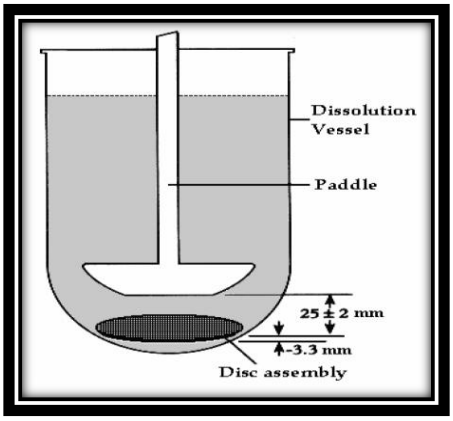


Figure 4.22: USP Dissolution Apparatus 5[15]

4.5.3.2 Procedure

The dissolution study was conducted using USP dissolution apparatus 5/ PhEur 2.9.4.1, Electrolab® TDT-06P (paddle-type dissolution apparatus) with addition of a disc (watch glass fitted with mesh). The fabricated patch was placed against a glass disc (delivery side up) retained with the stainless-steel screen and exposed to 1.4 pH SGF buffer. All dissolution studies were carried out at 32 ± 0.5 °C and 100 ± 5 rpm, with each dissolution jar carrying 900 ml of the 1.4 pH SGF buffer. 5 ml aliquots of dissolution medium sample was withdrawn at various time intervals and replaced with 5 ml of the 1.4 pH SGF buffer.

Withdrawn were appropriate diluted and analyzed by HPLC. The mean cumulative percentage of drug dissolved from the patch was plotted against time. Dissolution data are shown in Table 4.45, 4.46 and graphically represented in Figure 4.23.

4.5.3.3 Dissolution Condition

Dissolution Apparatus	: USP dissolution Apparatus 5
Dissolution medium	: 1.4 pH SGF buffer
Volume of dissolution medium	: 900 ml
Sampling volume	: 5 ml
Patch size	: 12.56cm²
Label claim	: 15.7mg/12.56cm²
Temperature	: 32±0.5˚C
Sampling time interval	: 30 min, 3 hr, 12 hr

Dissolution study of Final Patch was performed using USP dissolution apparatus 5/ PhEur 2.9.4.1. The acceptance criteria for dissolution are given Table 4.45.

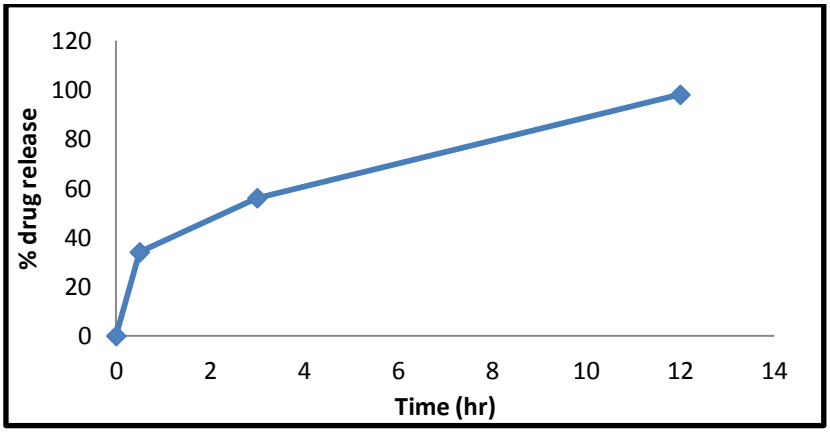


Figure 4.23: Drug Release from Final Patch

Results and Discussion

Performed dissolution of patch in medium where it was highly soluble. From the results of dissolution study, it was observed that formulation was not shown problem of dose dumping in initial 30 min as well as core release in 3 hr time period. Thus patches were stable.

4.5.4 *Ex-vivo* permeation study

The objective of this study was to compare the cumulative permeation from innovator patch and final prepared patch.

4.5.4.1 Procedure

Ex-vivo permeation study of prepared final patches was performed by using procedure given in section 4.3.2.4**.**

Results and discussion

After 12 hrs, the cumulative permeation of Lidocaine from Final Patch and Innovator was found to be 57.39 µg/cm² and 55.72 µg/cm² respectively.

After 12 hrs, skin flux of Lidocaine from Final Patch and Innovator was found to be 5.58 µg/cm²/hr and 5.42 µg/cm²/hr respectively.

From the results, it was concluded that Final Patch showed comparative cumulative permeation and skin flux with Innovator.

4.6 STABILITY STUDY

Stability testing of drug products begins as a part of drug discovery and ends with demise of compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for registration of pharmaceuticals for human use (ICH Guidelines).

The samples of Final Patches were kept at 40^{o}C/75% RH for one month in Barex pouch. Then samples were withdrawn and analyzed for physical evaluation, assay, drug release, and degradation products.

Table 4.51: Stability Data

<table>
<tr><td colspan="5">Stability Study Data</td></tr>
<tr><td colspan="5">Product: Lidocaine Topical Patch</td></tr>
<tr><td colspan="5">Stability Condition: 40˚C/75% RH</td></tr>
<tr><td></td><td colspan="4">Batch no. F16</td></tr>
<tr><td>Test Detail</td><td colspan="2">Initial</td><td>1 Month</td><td>Remarks</td></tr>
<tr><td>Physical Appearance</td><td colspan="2">White to off white colored adhesive matrix layer</td><td>White to off white colored adhesive matrix layer</td><td>Results were satisfactory</td></tr>
<tr><td>% Assay Mean
(90-110% of label claim)</td><td colspan="2">102.6</td><td>101.8</td><td>Results were within limit</td></tr>
<tr><td rowspan="3">% Drug Release
USP Apparatus: V
Medium:1.4pH SGF buffer
RPM: 100
Temperature:32.0±0.5˚C
Patch Size: 12.56cm²
Volume: 900 ml</td><td>30 min</td><td>33.2</td><td>32.9</td><td rowspan="3">Results were satisfactory</td></tr>
<tr><td>3 hrs</td><td>58.0</td><td>61.1</td></tr>
<tr><td>12 hrs</td><td>99.4</td><td>101.2</td></tr>
</table>

Lidocaine, a local anaesthetic drug has half-life of 1.5-2 hrs, undergoes first pass metabolism and low oral bioavailability (35%). In the present work, an attempt has been made to provide topical drug delivery of lidocaine using appropriate pressure sensitive adhesive, permeation enhancer, release liner and backing film. Drug-excipient compatibility studies confirmed that no incompatibility between drug and excipients existed. Absorption study of lidocaine with various release liners and backing films was performed and from this study release liner Saint Gobain 8310 and Backing film EW 9100 was selected due to their less absorption of lidocaine compared to other release liners and backing films. The topical patches were prepared by solvent casting method using Aqueous Gelva as pressure sensitive adhesive, Oleyl Alcohol as a permeation enhancer, talc as a matrix stiffener, Glycerine as a smoothing agent, and Tween 80 as a surfactant.

The skin flux of lidocaine across the skin was increased with increasing in Oleyl Alcohol concentration. Thickness, weight and drug content of the prepared final patches remained uniform with low standard deviation values. Topical patch containing 7.5% of Oleyl Alcohol showed comparable permeation of lidocaine through human cadaver skin as given by innovator. The selected formulation was found to be stable at 45˚C/75% RH. It may be concluded that lidocaine topical drug in adhesive patch containing aqueous Gelva, 7.5% Oleyl Alcohol, 1.5% Tween, 5% Glycerine and 26% Talc have shown promising results. Studies have shown promising results; hence, there is a scope for further pharmacodynamic and pharmacokinetic evaluation.

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