FORMULATION AND EVALUATION OF TRANSDERMAL DELIVERY SYSTEM COMPRISING CAPTOPRIL AS ANTIHYPERTENSIVE DRUG

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The Tamil Nadu Dr.M.G.R Medical University, Chennai
In partial fulfilment of the degree of

MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by
DHANABAL C
Reg No: 261710753

Under the guidance of
Mr. E. Abraham Theodore Rajaselwin, M.Pharm.,
Assistant Professor,
Department of Pharmaceutics,
RVS College of Pharmaceutical Sciences,
Sulur, Coimbatore.

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DEPARTMENT OF PHARMACEUTICS

RVS COLLEGE OF PHARMACEUTICAL SCIENCES

SULUR, COIMBATORE–641 402.

CERTIFICATE

This is a bonafide dissertation on **"FORMULATION AND EVALUATION OF TRANSDERMAL DELIVERY SYSTEM COMPRISING CAPTOPRIL AS ANTIHYPERTENSIVE DRUG"** by **DHANABAL C (Reg No: 261710753),** the work mentioned in the dissertation was carried out in the Department of Pharmaceutics at R.V.S College of Pharmaceutical Sciences, Sulur , Coimbatore and this work is supervised by me in the academic year 2018-2019.

Station:Coimbatore
Date :

Mr. E. Abraham Theodore Rajaselwin, M.Pharm.,
Assistant Professor
Department of Pharmaceutics
R.V.S. College of Pharmaceutical Sciences
Sulur,Coimbatore -641 402

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Station:Coimbatore
Date :

Dr. Barish, M.Pharm., Ph.D., FAGE., FICS
Head of Department
Department of Pharmaceutics
R.V.S. College of Pharmaceutical Sciences
Sulur,Coimbatore -641 402

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Station:Coimbatore
Date :

Dr. R. Venkatanarayanan, M.Pharm., Ph.D.,
Principal
RVS College of Pharmaceutical Sciences
Sulur,Coimbatore -641 402

DECLARATION

I hereby declare that this dissertation entitled "**FORMULATION AND EVALUATION OF TRANSDERMAL DELIVERY SYSTEM COMPRISING CAPTOPRIL AS ANTIHYPERTENSIVE DRUG"** submitted by me, in partial fulfillment of the requirements for the degree of **MASTER OF PHARMACY IN PHARMACEUTICS** to The Tamil Nadu Dr.M.G.R Medical university, Chennai is the result of my original and independent research work carried out under the guidance **Mr. E. Abraham Theodore Rajaselwin, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, R.V.S College of Pharmaceutical Sciences, Sulur, Coimbatore.

Station:Coimbatore
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DHANABAL C
Reg.No.261710753

EVALUATION CERTIFICATE

Dissertation title	**:**	"**FORMULATION AND EVALUATION OF TRANSDERMAL DELIVERY SYSTEM COMPRISING CAPTOPRIL AS ANTIHYPERTENSIVE DRUG"**
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Institution Name	**:**	RVS College of Pharmaceutical Sciences, Sulur, Coimbatore.

INTERNAL EXAMINER **EXTERNAL EXAMINER**

Place : Coimbatore

Date :

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We express our sincere thanks to our Principal **Dr. R. Venkatanarayanan, M.Pharm, Ph.D.,** R.V.S College of Pharmaceutical Sciences, Sulur, Coimbatore for his hearted cooperation in rendering us all the facilities required to proceed with this study.

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Above all we remain greatly indebted to our Parents who inspired and guided us in this right path and are also the back bone for all our successful endeavors in our life and we humbly submit this work in to the hands of **"The Almighty"**.

DHANABAL C

Reg No: 261710753

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1.0 INTRODUCTION

To provide continuous drug infusion through an intact skin, various transdermal systems have been designed for topical application and it control the delivery of drug and its permeation via the skin tissue. Historically, developments related to TDDS have been incremental, concentrating on overcoming issue related with the skin barrier properties, minimizing skin irritation and improving the outlook related with passive patch systems. TDDS defined as self-contained, discrete dosage form applied to the unharmed skin then it deliver the drug, via skin at controlled manner in the systemic circulation. Transdermal drug delivery via the skin provides a suitable route of administration for a various clinical indications. A pharmaceutical scientist focuses on the development of transdermal drug delivery over the last 25 years. The skin offers a large and easily penetrable surface for drug delivery. Transdermal routes, from that of other routes are quite non-invasive, like simple adhesion of a "Patch" similar as that of application of a Band-Aid. A transdermal drug delivery systems transfer a precise dose of drug through the skin and into systemic circulation.

Percutaneous Absorption

Designing of transdermal delivery systems requires an understanding of the permeation behavior of drug via the skin (stratum corneum), dermis, into the microcirculation area. Percutaneous absorption affected by various factors and complex process. Percutaneous absorption understanding is required for evaluation of quality of a chemical to cause skin disorders or systemic toxicity. Here skin acts as a passive barrier to the diffusing molecule. Most of the areas of the skin are limited by diffusional resistance encountered for molecular penetration. The total diffusional resistance to permeation for skin described by Chien as, RSkin = RSC + RE +RD. The greatest resistance to penetration is offered by stratum corneum.

Hypertension treated with transdermal delivery systems

Transdermal route one of the major potential route for the both systemic and local delivery of drugs as compare to conventional dosage form. Advantageous of TDDS such as

systemic delivery, reduced administration frequency, decrease side effect and bypass first pass metabolism, improved patient compliance. Most of the death and disorder in the world occurs due to heart diseases like hypertension. Report of global disease study there were 5.2 million deaths from cardiovascular diseases in developed countries and 9.1 million deaths from the same diseases in other developing countries, about 7.1 million death yearly occurs due to hypertension. In India 57% stroke deaths and 24% coronary heart disease deaths were observed and for that hypertension are directly responsible. Hypertension present in urban area 25% and 10% rural area from the Indian epidemiological studies[1].

The skin is the largest and most readily accessible organ in the body and its use for topical and systemic effect of drug has been well documented. Many formulations used traditionally include ointments, gels, creams etc. Alza Corporation developed first transdermal patch for motion sickness. Modern commercial drug products accepted the benefits and applicability of this method of administrations. There are several products in last-stage development for various therapeutic areas like parkinson disease, sexual dysfunction, hypertension in angina, motion sickness. TDDS represent a convenient option for drug delivery because of flexibility, dose change facility according to patient demand and self regulation of dosage by patient. TDD can use in a patient with minimal co-operation here other person also involve in the administration process other than the patient. The non-invasive nature of transdermal delivery systems easily accessible to a large patient populations and most acceptable alternative for drug dosing.

To provide continuous drug infusion through an intact skin, various transdermal systems have been designed for topical application and it control the delivery of drug and its permeation via the skin tissue. Historically, developments related to TDDS have been incremental, concentrating on overcoming issue related with the skin barrier properties, minimizing skin irritation and improving the outlook related with passive patch systems. TDDS defined as self-contained, discrete dosage form applied to the unharmed skin then it deliver the drug, via skin at controlled manner in the systemic circulation. Transdermal drug delivery via the skin provides a suitable route of administration for a various clinical indications. A pharmaceutical scientist focuses on the development of transdermal drug

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Table No. 1 Newer TDDS and its employers

Compounds	Delivery System	Stage of Development	Company
Alprostadil	Gel-Alprox-TD	Launched in China	Nex Med
Buprenophine	Patch – Transtec	Launched in Europe	Grunenthal
Dihydrotestosterone	Gel-Andractim	Introduced in France, Netherlands	Unimed/Solvay
Estradiol	MDTS	Phase II	Acrux
Estradiol/ progestogen	Gel	Phase II ,USA	Antares
Ethinylestradiol & norelgestromin	Patch – Ortho Evera	Launched in USA	J & J
Fentanyl	Patch– iontophoresis : E-TRANS	Pre-registration	Alza / J & J
Granisetron	MDTS	Preclinical	Acrux
hGH	Microneedle – Macroflux	Phase I	Alza / J & J
Hydromorphone	Patch – thermal	Phase I ,USA	Alza / J & J
Insulin	Sonophoresis	Preclinical	Altea
Patch – Thermal	Phase I in USA	Imarx	
Lidocaine	Patch – Lidoderm	Launched in USA	Endo
Methylphenidate	Patch –	Pre-registration	Noven

Advantages

- Delivers predictable infusion of a drug and increase span of activity.
- Adverse effects or failures due to intermittent dosing can be avoided.
- TDDS can increase therapeutic value of most of the drugs by improving pharmacological and physiological response.
- Improved patient compliance.
- Inter and intra patient variations.
- Better patient compliance because of elimination of multiple dosing.
- Simple applications.
- The therapy terminated easily.

Disadvantages

The drug required desirable physicochemical properties.

- High dose drug candidates are not suitable for TDDS.
- Some patients develop Skin irritation with drug, excipients, and penetration enhancers.
- Before development of transdermal product, clinical study must be fulfilled.
- The barrier function alters from person to person, one site to another site on same person, and with age[2,3].

Figure No 1. Structure of skin

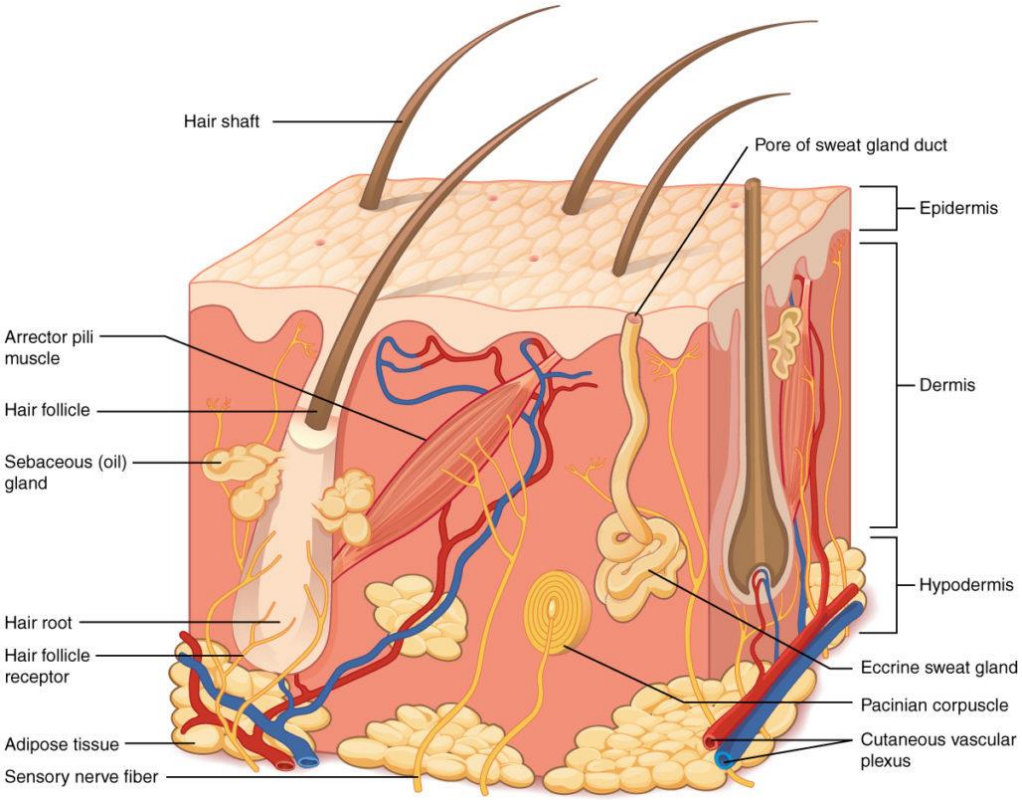
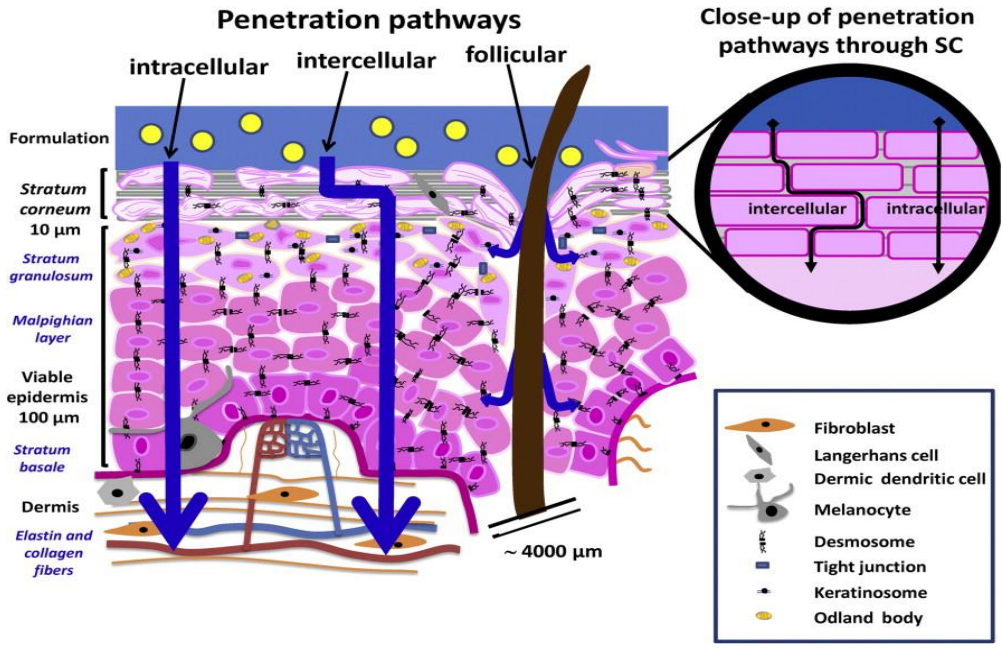


Figure No 2. Drug Skin Penetration pathways



The skin as a delivery target

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Limitations

The drug required desirable physicochemical properties.

High dose drug candidates are not suitable for TDDS.

Some patients develop Skin irritation with drug, excipients, and penetration enhancers.

Before development of transdermal product, clinical study must be fulfilled.

The barrier function alter from person to person, one site to another site on same person, and with age.[5]

1.5 Factors affecting transdermal drug delivery

1.5.1 Biological factors

- Skin condition
- Skin age
- Blood flow
- Regional skin sites
- Skin metabolism
- Species differences

1.5.2 Physicochemical factors

- Skin hydration
- Temperature and pH
- Diffusion coefficient
- Drug concentration
- Partition coefficient
- Molecular size and shape.6

It is the biggest organ of the body in surface area and weight. It covers the upper layer of the body. An average human skin is known to contain, on an average 40-70 hair follicles, 650 sweat glands, 20 blood vessels, 60,000 melanocytes per average inch2 of skin. Skin appendages, however actually occupy grossly only 0.1% of total stratum corneum surface henceforth the trans-appendageal route of percutaneous absorption has less contribution to the overall kinetic profile of transdermal penetration. The skin made up of mainly two major parts. The superficial, thinner portion, which is having epithelial tissue, is the epidermis and the deeper, thicker connective tissue part is the dermis.[8, 9]

Function of skin8, 9

Protection: keratin in the tissue safeguards under tissues from chemicals, heat, and microbes. It also protects from physical agent like dehydration, UV light.

Regulates body temperature: The skin helps for thermoregulation, homeostatic regulation of temperature, in two ways: by liberating sweat and adjusting the flow of blood.

Absorption: Absorption of lipid soluble substances like fat soluble vitamins A,D,E and K some drugs, steroids, organic solvents, O2 and CO2.

Excretion: It has small role in the excretion; daily 400 ml of water evaporates through skin. It also eliminates nitrogen containing wastes.

Cutaneous sensations: These include tactile sensation- thermal sensation and pain.

Synthesis of vitamin D: It performed with UV rays in sunlight.

Blood reservoir: The dermal vascular supply hold large volumes of blood.

1.10 Anatomy and Physiology of skin: [5, 8,9,10]

Human skin consists of three distinct but mutually dependent, tissues.

- Stratified,
- Vascular,
- Cellular epidermis, connective tissues and Hypodermis.

1.10.1 Epidermis

Epidermis consists of various layers with different thickness, due to cell size and cell layers. Eyelids size 0.06 mm and palm 0.8 mm. Skin has three layers:

Horney layer (Stratum corneum)

Upper layer of skin also known as Horney layer having 10 μm thicknesses in dry conditions and in hydration conditions swell the thickness. It has 10 to 30 layers of corneocytes.

Viable epidermis

This is located under the uppermost layer having differences in thickness scale from 0.06 mm on eyelids and up to 0.8 mm for palms. Various layers of epidermis are stratum granulosum, stratum lucidum, stratum spinosum and the stratum basal. The basal layer consist of mitosis divisions of cells constantly regenerate the epidermis and this occurs proliferation towards the loss of dead horney cells from skin layer. These layers are flexible but impenetrable. The stratum corneum is main barrier for permeation of drug.

Dermis

The epidermis contains dermis which has tough connective tissue, sweat glands and hair follicles. Dermis is 3-5 mm thick layer of skin and mainly of a matrix type. Dermis contains connective tissue, which contains blood vessels, nerves and lymph vessels. Capillaries that reach within 0.2 mm of skin and offer sink conditions for molecules penetration through skin barrier. The cutaneous blood supply has essential function in the control of body temperature. The blood supply that retains the skin surface concentration of a permeant very low and the final concentration difference in the epidermis provide the appropriate concentration gradient in transdermal penetration. Dermis provides nutrients, oxygen for skin to remove toxins and waste materials.

1.10.3. Hypodermis

The hypodermis consists of connective tissue and fat. The hypodermis supports the upper layer of skin and inner layer of skin and store the fat. Layer helps to control temperature

and provide nutrition and protect mechanically. For TDDS, drug has to cross three layers and achieve systemic circulation in other case of skin and crossing of stratum corneum is required for the retention of drug in skin surface.

1.10.4 Sebaceous Glands

It secretes sebum, an oily substance which helps skin from dryness. Various glands are situated in the follicles.

1.10.5 Sweat Glands

In case of stress, it secretes sweat and produce cooling sensation. Sweat glands are presents on the body but more on palms, soles, and underarms.

1.10.6 Hair Follicle

Live follicle initiate growth of hair with roots in fatty layer known as subcutaneous tissue.

Collagen

It is the important protein in the skin, 75% part of skin contains collagen.

1.10.8 Elastin

Word elastin is similar to elastic. Elastin is protein situated in the dermis with collagen and gives structure to skin and also organs.

1.10.9 Keratin

Keratin present mostly in hair and nails and keratin is strongest protein present in the skin.

1.11 Drug permeation pathway

Chemicals permeate the skin through either the transepidermal pathway (intact epidermis) or via appendageal or shunt pathway (sweat glands, hair follicles). The available diffusional area of the appendageal route is approximately 0.1% of total skin area; therefore the transepidermal pathway forms the major and potential pathway for permeation. The transepidermal pathway further consists of two potential pathways i.e., transcellular (lipid matrix and corneocytes) and intercellular (via lipid domain between corneocytes). Both routes, the stratum corneum structure prescribe that permeants must cross the intercellular lipid layers and this is the principle pathway for diffusion of most drugs. The conventional insight is that for the most part lipophilic compounds transfer preferentially stratum corneum through the lipoidal intercellular phase while comparatively more hydrophilic compounds pass through stratum corneum through the transcellular domain. The

appendageal pathway may be more significant for ions and polar molecules that slowly permeate through intact skin. 1cm2 of human skin includes 15 sebaceous glands, 10 hair follicles, and 100 sweat glands that bypass the low diffusivity domain for stratum corneum, which may function as a diffusional shunt. Percutaneous absorption means passive diffusion of the substances via the skin. A molecule diffuses through normal skin by using diffusional routes like appendageal route and epidermal route.

Chemicals permeate the skin through either the intact epidermis (transepidermal pathway) or through sweat glands and hair follicles (Appendageal or shunt routes).

Appendageal route (shunt route)

Epidermal

a. Transcellular.

b. Paracellular.

Appendageal route

Available diffusional area of the shunt is approximately 0.1% of total skin area, appendageal route include transfer through sweat glands and hair follicles and associated sebaceous glands. The drug penetration via stratum corneum so called as “shunt” routes.

1.11.2 Epidermal route

1.11.2.1 Transcellular

Transcellular pathway involves transfer of molecules between epithelial cellular membranes. Drugs entering the skin via the transcellular route pass through corneocytes which contains highly hydrate keratin that provides aqueous conditions through which hydrophilic drugs can pass.

1.11.2.2 Paracellular

Intercellular i.e. lipid domain between corneocytes permeants must diffuse across the intercellular lipid layers and this is believed to provide the principle pathway for permeation of most drugs. Paracellular pathway includes diffusion

of molecules across the cells. The partition coefficient (log *k*) is essential factors for permeation. Lipophilic drug penetrate the stratum corneum through intercellular route.11

1.12 Role of Stratum Corneum barrier in Permeation

Per square centimeter of human skin includes 10 hair follicles, 15 sebaceous glands and 100 sweat glands that bypass the low diffusivity area of the stratum corneum. Most of the neutral molecules cross stratum corneum through passive diffusion. Permeation via skin involves the steps.

- Surface assimilation of a penetrant molecule on the surface of stratum corneum.
- Diffusion and finally reaches to dermis.
- The molecule goes to microcirculation for systemic distribution.

The skin contains a dead layer stratum corneum and viable layers, the viable tissue contains catechol-o-methyl transferase which metabolizes the drugs papillary layer of dermis containing capillaries and most molecules enter the micro circulation after leaving the epidermis. Total resistance time of a drug in the dermal aqueous phase may be fraction of minute.12

1.13 Basic Components of TDDS

Various components includes,

Liner - Protections of the patch in storage.

Drug - Drug having direct link up with release liner.

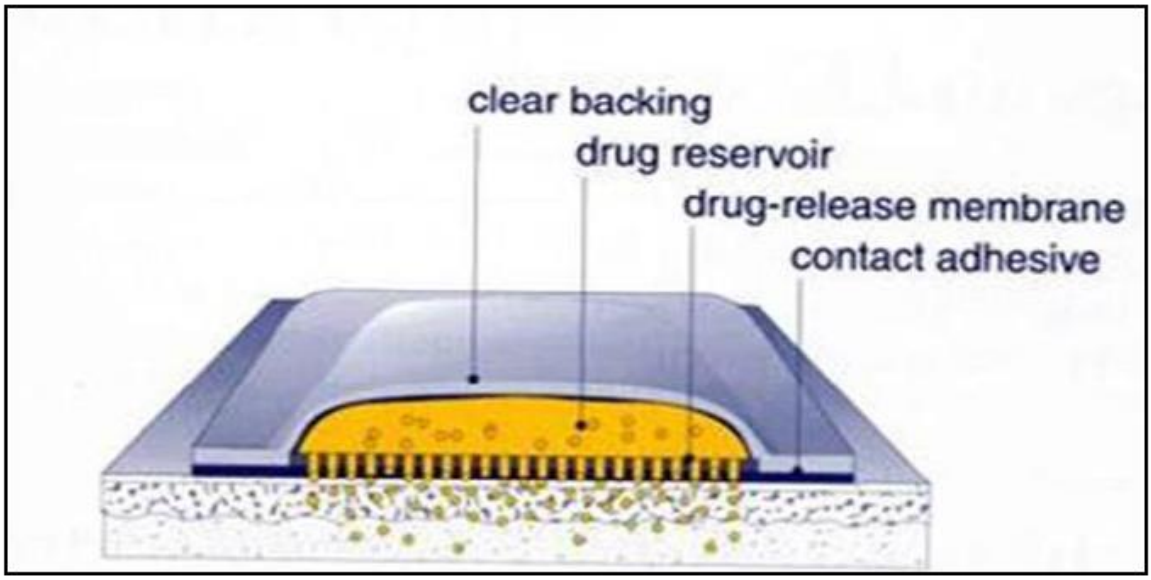
Adhesive – Perform the role of adhesion of the patch with the skin.

Membrane - Controls over the drug release through the reservoir.

Backing – Give protection to the patch from environment.

Other additives - plasticizers, solvents.

Figure No 3. Components of Transdermal Patch



The polymers control the release of the drug from device. Selections of polymer based on various criteria that to be used in transdermal system, various characteristics of polymers such as molecular weight, glass transition temperature and chemical functionality, should be such that the certain drug diffuses in a suitable manner and get released. Transdermal delivery manufactured as multilayer polymeric laminates in that a drug reservoir / a drug–polymer matrix is interpolate between two polymeric layers: an outer impenetrable backing layer and an inner polymeric layer that act as an adhesive and or rate-controlling membrane. Challenge in the development of a polymer matrix, through optimization of the drug matrix, physicochemical properties, compatibility and stability with other components of TDDS as well as with skin. The polymer performs the role of controls over release pattern of the drug from the device.

Criteria for polymer selection in a transdermal system

- Molecular weight, chemical functionality, glass transition temperature.
- The polymer should be chemically non reactive, stable, drug compatibility, easily developed and manufactured into the specific product.

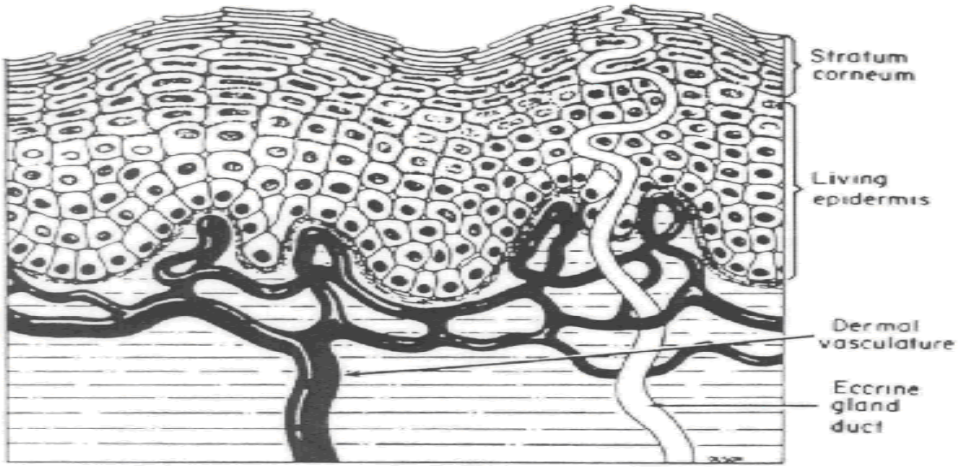
At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks, namely poor bioavailabiltity due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient.

To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (ie site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses.

New drug delivery system are also essential for the delivery of novel , genetically engineered pharmaceuticals (ie peptides , proteins) to their site of action , without incurring significant immunogenecity or biological inactivation. Apart from these advantages the pharmaceutical companies recognize the possibility of repattening successful drugs by Appling the concepts and techniques of controlled drug delivery system coupled with the increased expense in bringing new drug moiety to the market.

One of the methods most often utilized has been transdermal delivery - meaning transport of therapeutic substances through the skin for systemic effect. Closely related is percutaneous delivery, which is transport into target tissues, with an attempt to ***avoid*** systemic effects.

Figure No 4. Skin Structure



- There are two important layers in skin: the dermis and the epidermis.
- The outermost layer, the epidermis, is approximately 100 to 150 micrometers thick, has no blood flow and includes a layer within it known as the stratum corneum.
- This is the layer most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out.
- Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body.
- If the drug is able to penetrate the stratum corneum, it can enter the blood stream. A process known as passive diffusion, which occurs too slowly for practical use, is the only means to transfer normal drugs across this layer.
- The method to circumvent this is to engineer the drugs be both water-soluble and lipid soluble.
- The best mixture is about fifty percent of the drug being each. This is because "Lipid-soluble substances readily pass through the intercellular lipid bi-layers of the cell membranes whereas water-soluble drugs are able to pass through the skin

because of hydrated intracellular proteins". Using drugs engineered in this manner, much more rapid and useful drug delivery is possible.

- The stratum corneum develops a thin, tough, relatively impermeable membrane, which usually provides the rate limiting step in transdermal drug delivery system. Sweat ducts and hair follicles are also paths of entry, but they are considered rather insignificant.

Transdermal Drug Delivery System

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate**.**

A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. In theory, transdermal patches work very simply. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.

This approach to drug delivery offers many advantages over traditional methods. As a substitute for the oral route, transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation. This method also allows for reduced pharmacological dosaging due to the shortened metabolization pathway of the transdermal route versus the gastrointestinal pathway. The patch also permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medications. Multi-day therapy with a single application, rapid notification of medication in the event of emergency, as well as

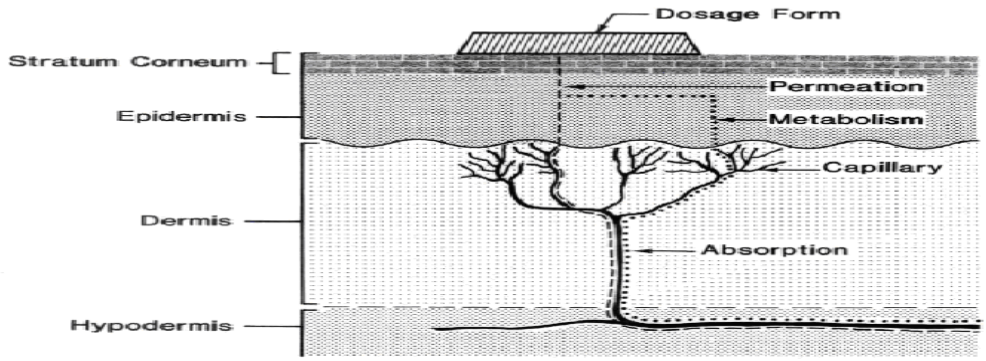
the capacity to terminate drug effects rapidly via patch removal, are all further advantages of this route.

However this system has its own limitations in which the drug that require high blood levels cannot be administered and may even cause irritation or sensitization of the skin. the adhesives may not adhere well to all types of skin and may be uncomfortable to wear. Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product.

Properties that Influence Transdermal Delivery

- Release of the medicament from the vehicle.
- Penetration through the skin barrier.
- Activation of the pharmacological response.

Figure No. 5. Kinetics of Transdermal Permeation



Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems. Transdermal permeation of a drug involves the following steps:

1. Sorption by stratum corneum.

2. Penetration of drug through viable epidermis.

3. Uptake of the drug by the capillary network in the dermal papillary layer.

Thus permeation can be possible only if the drug possesses certain physiochemical properties.

The rate of permeation across the skin is given by:

$$\mathbf{dQ/dt} = P_s (C_d - C_r) \quad .$$

where $\mathbf{C_d}$ and $\mathbf{C_r}$ 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:

$$P_s = \frac{K_s D_{ss}}{h_s}$$

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 h_s is the overall thickness of skin tissues. As K_s ,D_{ss} and h_s are constant under given conditions the permeability coefficient Ps 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:

$$\mathbf{dQ/dt} = P_s C_d$$

And 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:

$$(\mathbf{dQ/dt})_m = P_s C_s$$

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.

Basic Components of Transdermal Drug Delivery Systems

The components of transdermal devices include:

1. Polymer matrix or matrices.

2. The drug

3. Permeation enhancers

4. Other excipients

1. Polymer Matrix

The Polymer controls the release of the drug from the device.

Possible useful polymers for transdermal devices are:

a) Natural Polymers:

e.g. Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b) Synthetic Elastomers:

e.g. Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

c) Synthetic Polymers:

e.g. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy etc.

2. Drug

For successfully developing a 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[11-16]

Physicochemical properties

- The drug should have a molecular weight less than approximately 1000 daltons.
- The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
- The drug should have low melting point.

Along with these properties the drug should be potent, having short half life and

be non irritating.

3. Permeation Enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant.

These may conveniently be classified under the following main headings:

a) Solvents

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide ; pyrrolidones – 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone), miscellaneous solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

b) Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

Anionic Surfactants:

e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.

Nonionic Surfactants:

e.g. Pluronic F127, Pluronic F68, etc.

Bile Salts:

e.g. Sodium ms taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Binary system:

These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways.

e.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.

c) Miscellaneous chemicals

These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents.

Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein.

4.Other Excipients

a) Adhesives:

The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive systems should fulfill the following criteria

(i) Should adhere to the skin aggressively, should be easily removed.

(ii) Should not leave an unwashable residue on the skin.

(iii) Should not irritate or sensitize the skin.

The face adhesive system should also fulfill the following criteria.

(i)Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.

(ii) Permeation of drug should not be affected.

(iii) The delivery of simple or blended permeation enhancers should not be affected.

b) 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. 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.

Desirable features for transdermal patches

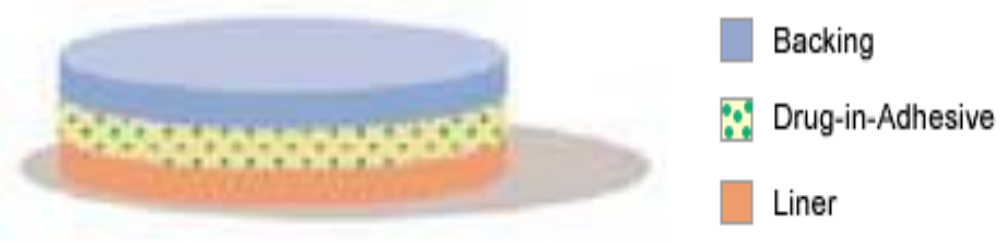
- Composition relatively invariant in use.
- System size reasonable.
- Defined site for application.
- Application technique highly reproducible.
- Delivery is (typically) zero order.
- Delivery to be efficient.

Types of Transdermal Patches

Four Major Transdermal Systems

1. **Single-layer Drug-in-Adhesive**

Figure No 6. 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:

$$dQ/dT = \frac{Cr}{1/Pm + 1/Pa}$$

where Cr is the drug concentration in the reservoir compartment and Pa and P m are the permeability coefficients of the adhesive layer and the rate controlling membrane , Pm is the sum of permeability coefficients simultaneous penetrations across the pores and the polymeric material. Pm and Pa , respectively, are defined as follows.

$$Pm = \frac{K_{m/r}.Dm}{}$$

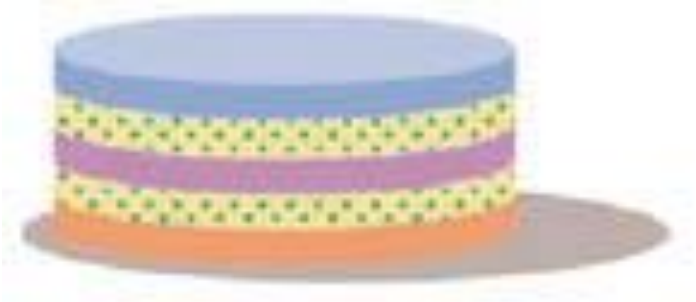
$$Pa = \frac{K_{a/m} \cdot Da}{\frac{hm}{ha}}$$

where $K_{m/r}$ and $K_{a/m}$ are the partition coefficients for the interfacial partitioning of drug from the reservoir to the membrane and from the membrane to adhesive respectively; Dm and Da are the diffusion coefficients in the rate controlling membrane and adhesive layer, respectively; and hm and ha are the thickness of the rate controlling membrane and adhesive layer, respectively.

2. 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.

Figure No 7. Multi-layer Drug-in-Adhesive



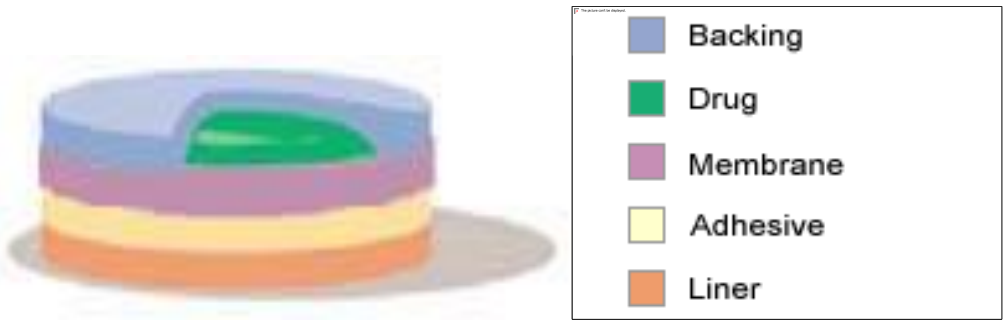
Backing
Drug-in-Adhesive
Membrane
Drug-in-Adhesive
Liner

The rate of drug release in this system is defined by:

$$\mathbf{dQ/dt} = \frac{K_{a/r} \cdot D_a}{ha} \mathbf{x} C_r$$

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

Figure No 8. 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.

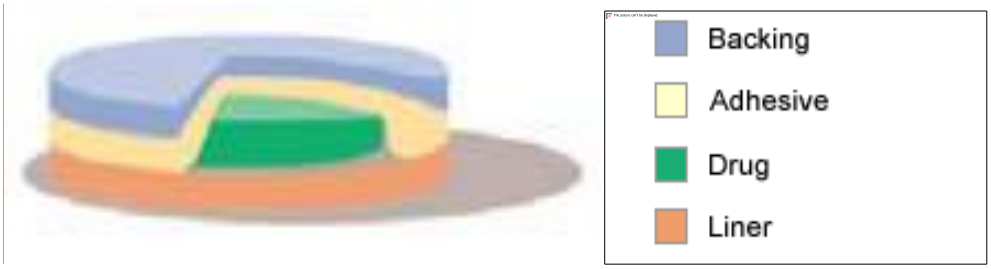
The rate of drug release from this drug reservoir gradient controlled system is given by:

$$\mathbf{dQ/dt} = \frac{K_{a/r} \cdot Da \ \mathbf{x} \ A\ (ha)}{ha\ (t)}$$

In the above equation, the thickness of the adhesive layer for drug molecules to diffuse through increases with time ha (t). To compensate for this time dependent increase in the diffusional path due to the depletion of drug dose by release, the drug loading level is also increased with the thickness of diffusional path A (ha).

4. **Drug Matrix-in-Adhesive**

Figure No 9. Drug Reservoir-in-Adhesive



The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.

The rate of drug release from this type of system is defined as :

$$\mathbf{dQ/dt} = \frac{AC_p D_p^{\frac{1}{2}}}{2t}$$

where A is the initial drug loading dose dispersed in the polymer matrix and C_p and D_p are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release, C_p is essentially equal to C_R , where C_R is the drug concentration in the reservoir compartment..

Matrix diffusion –controlled transdermal drug delivery system [2]

(Monolithic device)

The matrix dispersion type of transdermal system are formed by homogeneously dispersing the drug in a mixture of hydrophilic, lipophilic polymer (matrix) and the medicated polymer is molded on the medicated disc of definite surface area and thickness[17-19]. This drug reservoir containing the polymer disc is then glued over an occlusive plate consisting of a compartment fabricated using an impermeable backing.

The rate of drug release from this type of matrix diffusion system controlled TDD system is defined as follows.

$$dQ/dt = (A C_p . D_p/2t)^{1/2}$$

Where A is the initial drug loading dose dispersed in the polymer matrix, and Cp and Dp are the solubility and diffusibility of the drug in the polymer respectively. Since only the drug species dissolved in the polymer can be released , Cp essentially equals to C_R .At steady state , a Q verses $t^{\frac{1}{2}}$ drug release profile is obtained as:

$$Q/ t^{\frac{1}{2}} = [(2A-C_p) C_p D_p]^{\frac{1}{2}}$$

Transdermal Market

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 than35 TDD products have now been approved for sale in the US.

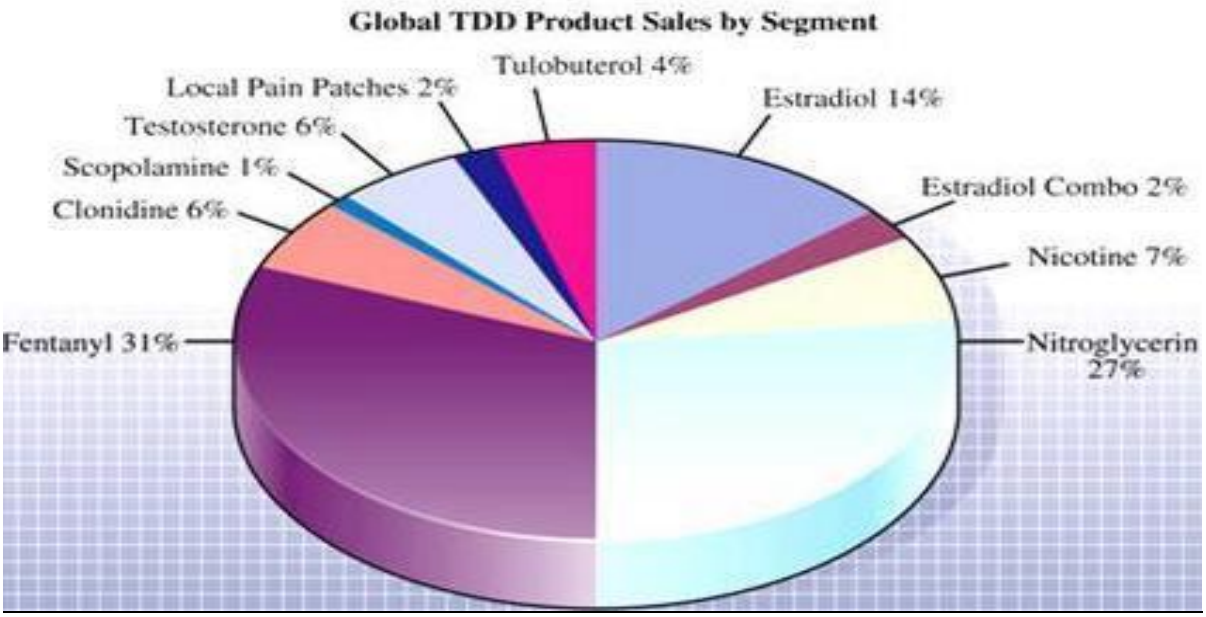
Table No. 2 Marketed Products

Product name	**Drug**	**Manufacturer**	**Indication**
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
CombiPatch	Estradiol/Norethindrone	Noven , Inc./Aventis	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Duragesic	Fentanyl	Alza/Janssen Pharmaceutica	Moderate/severe pain
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome

Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Habitraol	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Nicotrol	Nicotine	Cygnus Inc./McNeil Consumer Products, Ltd.	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Nuvelle TS	Estrogen/Progesterone	Ethical Holdings/Schering	Hormone replacement therapy
Ortho-Evra	Norelgestromin/estradiol	Ortho-McNeil Pharmaceuticals	Birth control
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Testoderm TTS	Testosterone	Alza	Hypogonadism in males
Transderm Scop	Scopolamine	Alza/Norvatis	Motion sickness

The pie diagram given below shows that Fentanyl and nitroglycerine are the drugs most popularly marketed using transdermal patches.

Figure No. 10 Market value of TTDS



Drug in adhesive technology has become the preferred system for passive transdermal delivery, two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch.

Innovation in Transdermal Technology[3]

The conventional passive means of applying drugs to skin include the use of vehicles such as ointments, creams, gels and patch technology. More recently, such 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 approaches include the use of penetration enhancers, supersaturated systems, hyaluronic acid, prodrugs, liposomes and other vesicle. However, the amount of drug that can be delivered using these methods is still limited since the barrier properties of the skin are not fundamentally changed and as such, with the exception of patches, the majority are used

to treat localized skin diseases where systemic absorption is not required. Thus, while new passive technologies typically offer an improvement in dose control, patient acceptance and compliance compared to more traditional semisolid formulations, they do not have the potential to widen the applicability of transdermal drug delivery unlike active transdermal drug delivery technologies.

Active Methods

A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. Recent progress in active transdermal drug delivery technologies has occurred as a result of advances in precision engineering (bioengineering), computing, chemical engineering and material sciences, which have all helped to achieve the creation of miniature, powerful devices that can facilitate the generation of a required clinical response.

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 .

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. Products have already reached the US market using iontophoresis e.g., recently , FDA approved a pre-filled, pre-programmed iontophoric device for sale in the United States. This product, called Lidosite^{TM} , delivers lidocaine and epinephrine to intact skin to provide local anesthesia for superficial dermatological procedures.

Electroporation

This method involves the application of high voltage pulses to the skin which has been suggested to induce the formation of transient pores. High voltages (Ž100 V) and short treatment durations (milliseconds) are most frequently employed. Other electrical parameters that affect delivery include pulse properties such as waveform, rate and number. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater that 7kDA.

As electroporation improves the diffusion of such a wide range of compounds, it is thought that the pores created in the superficial layers of the skin are directly responsible for the increase in skin permeability. Genetronics, Inc. has developed a prototype electroporation transdermal device, which has been tested with various compounds with a view to achieving gene delivery, improving drug delivery and aiding the application of cosmetics. 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 topmost layer of the skin that serves as the greatest barrier to drug diffusion. Such devices include microstructured arrays , sometimes called microneedles, that, 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. The very first microneedle systems, described in 1976, consisted of a drug reservoir and a plurality of projections (microneedles 50 to 100 mm long) extending from the reservoir, which penetrated the stratum corneum and epidermis to deliver the drug. More recently, as a result of the rapid advancement in microfabrication technology in the last 10 years, numerous cost-effective methods of producing microneedle devices have been developed . The ALZA Corp. has recently commercialized a microneedle technology named Macroflux which can either be used in combination with a drug reservoir or by dry coating the drug on the microprojection array; the latter being better for intracutaneous immunization.

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. microdermabrasion) which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes.

Microscissuining is a process which creates microchannels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules. Carlisle Scientific is currently in the process of developing a pen-like handheld device called the microscissioner.

In addition, MedPharm Ltd. has recently developed a novel dermal abrasion device (D3S) for the delivery of difficult to formulate therapeutics ranging from hydrophilic low molecular weight compounds to biopharmaceuticals. In vitro data has shown that the application of the device can increase the penetration of angiotensin into the skin 100-fold compared to untreated human skin. This device is non-invasive and histological studies on human skin show that the effects on the stratum corneum are reversible and non-irritating.

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.

This method of administering drugs circumvents issues of safety, fear and pain associated with the use of hypodermic needles. Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. The PMED device consists of a helium gas cylinder, drug powder sealed in a cassette made of plastic membrane, a specially designed convergent-divergent supersonic

nozzle and a silencer to reduce the noise associated with the rupturing of the membrane when particles are fired.

The mechanism involves forcing compressed gas (helium) through the nozzle, with the resultant drug particles entrained within the jet flow reportedly traveling at sufficient velocity for skin penetration. An essential difference between administration of a DNA vaccine by needle injection or by PMED is the efficiency with which the administered DNA generates the encoded protein for presentation on the surface of antigen-presenting cells (APCs). Using PMED, it is possible to deliver the DNA directly to the intracellular compartment of cells within the epidermis, and because the epidermis is rich in APCs, significant numbers can potentially be targeted with each administration. This is supported by non-clinical studies in pigs that have included histological examination of PMED administration sites.

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, handheld device consists of a control unit, ultrasonic horn with control panel, a disposable coupling medium cartridge, and a return electrode.

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 drugs. A handheld 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. The Norwood

Abbey system has been approved by the U.S. and Australian regulatory bodies for the administration of a topically-applied anaesthetic. Laser systems are also being developed to ablate the stratum corneum from the epidermal layer. As with microneedles, the ablated regions offer lower resistance to drug diffusion than non-ablated skin. One company has recently received FDA approval to market this device with a lidocaine cream Dispenser for Transdermal Patches

Magnetophoresis**,** which is still in the research phase, enhances skin permeability by applying a magnetic field.

The Future of TDDS - New Systems

Several exciting 'active' transdermal drug delivery systems are also on the horizon. Systems using external stimuli to drive the drug into the skin will offer rate-controlled, on-demand delivery of those drugs with a larger molecular weight which until now were not deliverable by passive transdermal patches. For example, iontophoresis uses a miniature battery to establish an electrical potential between the adhesive and the skin in a TDD patch, which uses a conductive adhesive.

A mild electrical current delivers an ionically charged drug into the skin. Currently, reverse iontophoresis has been developed for use as a diagnostic tool in the medical diagnostics industry for blood glucose monitoring, attracting fluid out of the skin that can be analysed. Sonophoresis, which uses ultrasound waves, is also being tested. A portable device emits sound waves through a patch attached to the device for painless delivery of a drug through the skin. The adhesive used must be able to withstand the effects of the sound waves.

Yet another method is electroporation, which uses electric currents to change the surface properties of the skin, creating channels of low transmission-resistance and thereby accelerating drug delivery.

Further, buccal or transmucosal patches have been designed to be placed in the mouth to deliver a drug through the mucous membranes. This technique will allow much higher drug

flux and enable large, higher molecular weight drugs to be administered transdermally[15,17,18,20]. The challenge for adhesive manufacturers is to develop an adhesive that adheres to wet surfaces on the interior of the mouth and will not dissolve in the presence of an aqueous environment.

In the future, we can expect advances in passive transdermal patches to include:

- Extended' wear patches with stronger cohesion properties to remain at a fixed point on the skin without movement
- Bi-phasic drug delivery profiles such as time-delayed or time moderated delivery
- Smaller, more aesthetically acceptable patches with increased solubility of the drug in the adhesive for a higher diffusion rate
- Generic drug patches

2.0 LITERATURE REVIEW

***Lewis Shaila, et al* (2004)[21]** studied, different transdermal patches of nicotine, which are cost effective and conducive to the Indian market. Two types of patches, monolayered and bilayered, were prepared. The monolayered patch bore a rate-controlling membrane, whereas the bilayered, served as matrix type. The physical charecteristics of the patches were evaluated by standard techniques. *In vitro* release studies of transdermal patches showed a biphasic release pattern, with diffusion as the dominating mechanism of drug release for the matrix type, while the membrane-controlled released nicotine, gradually over the 24 h study.

Vagyalakshmi et al(2004)[22] permeation of ampicillin sodium patch from ethanol/pH4.7 buffer solution containing antinucleant polymers across mouse skin, was investigated. The in vitro release of ampicillin sodium was determined under open condition at 25o and 65 percent relative humidity. Therefore the influence of evaporation of vehicle components on the permeation of ampicillin sodium was examined. Evaporation of the vehicle led to drastic compositional changes leading to supersaturation. However, supersaturation solutions started to crystallize reducing the thermodynamic activity of ampicillin sodium. Carboxymethylcellulose and ***hydroxypropylmethylcellulose*** were efficient antinucleant polymers to increase the permeation of ampicillin sodium.

Saraf Swarnlata* et al.,(2005)[23] formulated transdermal patch of timolol meliate as both reservoir as well as matrix system. The physically stable patches regarding drug contents, tensile strength, toughness and WVT were found for PVA10 and HE2 (hydroxy ethylcellulose: ethylcellulose) formulation . Both patches follows diffusion controlled drug permeation and high permeation with PVA10 while reservoir system follows zero order permeation kinetics.

Srinivas Mutalik et al.,(2002)[24]prepared ,membrane moderated transdermal systems were prepared using drug containing carbopol gel as reservoir and ethyl cellulose, Eudragit RS-100, Eudragit RL-100 and Ethylene vinyl acetate (EVA) (2%, 9% and 19% vinyl acetate content) rate controlling membranes. *In vitro* drug release studies and permeation studies

through mouse skin was studied . The blood glucose reducing hypoglycemic activity of the systems was studied in both normal and diabetic mice. Various biochemical parameters and histopathological studies were carried out after treating the diabetic mice for 6 weeks. Skin irritation tests, oral glucose tolerance test and pharmacokinetic evaluations were carried out in mice.

Manvi FV et al,.(2003)[25] prepared transdermal patches incorporating terbutaline sulphate .The pseudolatex patches were formulated using combinations of Eudragit RS 100 and R L 100 and Eudraflex as plasticizer. The physicochemical characterization of the films were evaluated for suitability and drug release profile from the films as well as skin permeation aspects were evaluated for therapeutic efficacy. The resulted medicated patches were of average thickness (95-155 mium), and content uniformity of the drug varied from 94.5 to 99.1 percent. The formulation F3 showed least and F7 showed highest percentage of elongation. The percentage of moisture absorption varied from 2.91 to 3.65 at 63 percent relative humidity. The release profiles from the patches followed apparent zero order pattern up to a period 12 h, after which it leaves off.

Jain S, et al.,(2003)[26] formulated transdermal films of ketotifen fumarate using combination of (eudragit L 100: hydroxypropylmethylcellulose)and (Ethyl cellulose: hydroxy propyl methylcellulose)polymeric combinations plasticized with polyethylene glycol 400. Effect of permeation enhancers like dimethyl suffoxide and propylene glycol at different concentrations were studied on skin permeation kinetics by keshary-Chein diffusion cell. In vitro diffusion studies showed that there was increase in permeation rate with increase in permeation enhancer concentration. Both water vapour transmission rate and skin permeation rate followed zero order kinetics.

Sankar V, Jain S et al.(2003)[28] prepared protransfersomes of norgestrel were prepared and the effects of various parameters such as, type of surfactant and amount of drug of formulation on transdermal permeability profile were assessed. In vitro flux, permeability coefficient and release rate pattern of norgestrel was calculated for transdermal delivery of norgestrel. In the release rate study, no lag phase could be detected and the release of

norgestrel from proposed formulation through rat skin was found to be constant but slow (sustained release). Entrapment efficiency was found to be nearly 95 percent and it depends on the type of surfactant and concentration of surfactant..

Shyam S, et al., (2006)[28] explore their suitability ethylcellulose for transdermal patch as the rate controlling membrane. Castor oil, glycerol was incorporated at a concentration of 30 percent w/w, 40 percent w/w of dry polymer, as plasticizer. The dry free films were evaluated for various physicochemical characters. The permeability characteristics of free films were studied using nifedipine as model drug. Drug was incorporated in 4 percent *hydroxy propyl methylcellulose* gel. The backing membrane was a non permeable aluminium foil laminated with polyethylene.

Masuda khatun, P et al.,(2004)[29] fabricated transdermal patch using different concentrations (1:7 to 1:10) of Captopril and chitosan, a natural cationic polymer, by solvent casting method (4 % lactic acid v/v solution). Permeation characteristics of the drug were evaluated across neatly excised rat and human cadaver skin fixed between donor and receptor compartments of a modified Franz diffusion cell. Drug content was measured at absorbance at 332 nm in UV spectrometer (Shimadzu 1601). The optimized formulation was subjected to primary skin irritation studies in rabbits. (control/optimized). In-vivo pharmacokinetic studies in rats (Intraperitoneal/Patch) were carried out .Among the prepared formulations, the optimized formulation of release across the rat and human cadaver skin respectively. Primary skin irritation studies showed no skin reaction and erythema. The average Css was 7.300 ± 0.004 µg/mL with patch as compared to 11.420±0.007 µg/mL with intraperitoneal (ip) administration.

Narasimha Murthy *et al.,(2001)*[30] explore the possibilities of using polymer eudragit RS 100 in transdermal therapeutic system (TTS). Naproxen was used as a model drug and incorporated in two different percent loading (8.3 % w/w and 20.8 % w/w of films). Effects of two plasticizers (PEG 1500 and PEG 4000) and two release modifiers (PVA and HPMC 15cps) on in vitro drug release from naproxen loaded eudragit RS films were assessed. Drug release was found to be a function of drug load, PEG molecular weight and physico-

chemical property of the release modifiers incorporated. At low drug load, highest amount of drug was released from flims containing PEG 1500 (more than 95%). However, a burst release was evident in case of all the experimental batches except that loaded with HPMC 15 cps. With this formulation, more than 75 % of active principle was released after 8 hours while only 12 % of naproxen was liberated in the first hour of dissolution.

Sunil A et al., (2005)[31] designed controlled release matrix type transdermal delivery systems of terbutaline sulphate with half life 5.5 hours using hydroxypropyl methylcellulose as polymer. Because of the low permeability of the drug, enhancers had to be used in the formulations. Preliminary studies on mgnetophoresis and the factors that influence the magnetophoretic permeation of TS are reported elsewhere . This study analyzed the practical application of magnetophoresis for TS transdermaldelivery.

Deepak Gondaily, A et al.,(2003)[32] formulated novel interpenetrating polymeric network microspheres of gellan gum and poly(vinyl alcohol) by the emulsion cross-linking method. ***Captopril***, an antihypertensive drug, was successfully loaded into these microspheres prepared by changing the experimental variables such as ratio of gellan bumpily(vinyl alcohol) and extent of cross-linking in order to optimize the process variables on drug encapsulation efficiency, release rates, size, and morphology of the microspheres. In vitro release studies were performed in the simulated gastric fluid or simulated intestinal fluid. The release of Captopril was continued up to 12 h.

Kanikkannan N, *et al.,(2004)[33]* evaluate unilaminate transdermal adhesive matrix systems capable of diffusing bupropion base at a constant rate over an extended period of time as an alternative route of administration. Unilaminate transdermal ad-hesive matrices have been fabricated with different concentrations of Eudragit E as the adhesive and rate-controlling polymer. The in vitro release and epider-mal flux through human cadaver skin were studied. The release of drug from the matrices obeyed zero order release kinetics (r

^{2}= 0.9810 to 0.9960). The de-livery rate of bupropion ranged from 10.5 mg to 31.4 mg per day from a ***3.14 cm^2*** area of matrix.

Cho YA, et al.,(2004)[34] prepare and evaluate monolithic drug-inadhesive type transdermal patches of melatonin containing penetration enhancers such as fatty alcohols, fatty acids, and terpenes. The patches were prepared using Eudragit E 100 as the adhesive polymer. The release profile of melatonin from control as well as enhancer-containing patches showed an initial burst of melatonin release for up to 4 hours and then a plateau after 8 hours. The release profiles of melatonin from patches containing various enhancers were similar to the control patch. The flux of melatonin observed in the present study is 5-10 times higher than the required delivery rate in humans.

Aboofazeli R,***et al.,(2012)[35]***studied the effects of vehicles and penetration enhancers on the in vitro permeation of ketorolac tromethamine (KT) across excised hairless mouse skins were investigated. Among pure vehicles examined, propylene glycol monolaurate (PGML) showed the highest permeation flux, which was 94.3 +/- 17.3 microg/cm2/h. Even though propylene glycol monocaprylate (PGMC) alone did not show high permeation rate, the skin permeability of KT was markedly increased by the addition of diethylene glycol monoethyl ether (DGME); the enhancement factors were 19.0 and 17.1 at 20% and 40% of DGME, respectively.

Park ES et al.,(2011)[36] evaluated flux and elucidated mechanistic effects of formulation components on transdermal permeation of the drug through the skin. Solubility of NC-HCl in different solvent systems was determined using a validated HPLC method. The solubility of drug in various solvent systems was found to be in decreasing order as propylene glycol (PG)/oleic acid (OA)/dimethyl isosorbide (DMI) (80:10:10 v/v) > PG > PG/OA (90:10 v/v) > polyethylene glycol 300 > ethanol/PG (70:30 w/w) > transcutol > dimethyl isosorbide (DMI) > ethanol > water and buffer 4.7 > 2-propanol. Propylene glycol was then selected as the main vehicle in the development of a transdermal product. In vitro permeation data were collected at 37 degrees C, using Franz diffusion cells. The skin permeation was then evaluated by measuring the steady state permeation rate (flux) of NC-HCl, lag time, and

the permeability constant. The results showed that no individual solvent was capable of promoting NC-HCl penetration.

Thomas N S et al.,(2003)[37] evaluated the effect of simultaneous application of two penetration enhancers of different chemical classes or a chemical penetration enhancer and current application on permeation of zidovudine (AZT) across rat skin. Ex vivo permeation of AZT using combinations of cineole or menthol in vehicle with either oleic acid/linolenic acid or 0.5 mA/cm2 anodal current application for 6 h was studied. Penetration enhancers were significantly different in enhancing the permeability of AZT across rat skin and are in the decreasing order of activity: linolenic acid > menthol > oleic acid > cineole > vehicle. The combination of cineole and oleic acid synergistically enhanced transdermal flux of AZT in addition to reducing lag time..

Narasimha S et al.,(2013)[38] prepared formulations containing theophylline and salbutamol sulphate using hydroxy propyl methyl cellulose. Theophylline was loaded by adsorption with the aid of co-adsorbate, sodium chloride. The formulations were subjected to in vitro release studies and the dose of salbutamol and theophylline were optimized to yield the desired flux. The films were uniform and of 200±40 micron thickness. The in vitro flux of theophylline and salbutamol sulphate from the formulation was 1.22±0.4 mg/hr/sq.cm and 13.36±1.02 mcg/hr/sq.cm respectively. Pharmacokinetic studies were carried out in healthy human volunteers. Theophylline was analyzed in saliva and salbutamol in the blood plasma. The Tmax of the drugs was 3 hours and appreciable concentrations of the drugs above their MEC could be analysed even after 12 hours.

Dnyanesh Tipre et al.,(2003)[39] fabricate an Eudragit E100® pressure sensitive adhesive (PSA)-based stable transdermal therapeutic system (TTS) of nitrendipine, which could deliver drug at a maximum input rate through a transdermal route. Monolithic TTS of nitrendipine was fabricated in Eudragit E100® PSA-based pressure sensitive adhesive. To enhance flux, d-limonene was investigated as a permeation enhancer, and effect of concentration of d-limonene on permeation kinetics of nitrendipine through guinea pig skin was examined.The stability study encourages conducting a clinical study to determine if

an Eudragit E100®-based nitrendipine transdermal patch could become a new product in treatment of hypertension

Ubaidulla U et al.,(2004)[40]evaluated permeability of ***Captopril*** from transdermal films, which is made by using ***hydroxy propyl methyl cellulose*** (HPMC) as polymeric matrix and propylene glycol as plasticizer. Sodium lauryl sulphate (SLS), Tween 20, Dimethyl sulfoxide (DMSO) and Polyethylene glycol (PEG 400) were used as permeation enhancers. permeation of Captopril was studied by Franz diffusion cell using excised rat abdominal skin and comparison of various permeation enhancers on permeation rates of Captopril were determined. permeation enhancers increased the permeation of the drug, Captopril, and arranged in the following increasing order according to their permeation rate: Tween 20 > SLS > PEG 400 > DMSO. The effect of iontophoresis on permeation of Captopril transdermal films were studied alone and mixed with enhancers. The data clearly showed that permeation enhancers and iontophoresis synergistically enhanced permeability of Captopril from its films.

Raymond C et al., (1991)[41] designed transdermal system of verapamil HCl with sodium CMC as a polymeric matrix. Studies on effect of varying proportions of plasticizer propylene glycol as 2.5%, 5.0% and 7.5% of the polymer in transdermal patches showed an increased amount of cumulative release with increase in plasticizer concentration. In-vitro release studies using modified polycarbonate feeding bottle through mouse skin has shown that with decrease in concentration of polymer, there was increase in drug release.

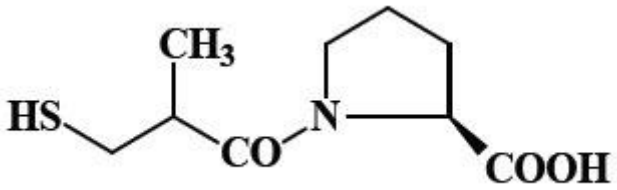
V Nguyen et al.,(2014)[42] formulated patches of Ketoprofen using blend of two polymeric combinations, Ethyl cellulose and Polyvinyl-pyrrolidone K-30 to increase drug bioavailability and decrease toxicity. Here DMSO used to enhance permeation and dibutyl phthalate used to give strength for patches and solvent system chloroform. The formulation (EC: PVP) F4, give optimum release 85.92% after 10hrs., formulation F1 (EC) gives less release 68.32% in 10 hrs. All the formulaions showed non fickian type diffusion.

Kusum Devi V, et al. (2005)[43] developed new spectroscopic techniques in Ultraviolet region for determining Captopril in pharmaceutical formulations. Captopril shows Abs. at 285 nm with approximate absorptivity of 15.4 x 103 l/mol.cm in methanol. Beers law obeyed in the conc. Range 4-36 μg/ml.

2.1 Drug

Captopril, 1 – [(2S)- 3 – mercapto -2 –methylpropionyl]-L-proline (Figure 1), (CPT) is an angiotensin-converting enzyme inhibitor, which reduces peripheral resistance end lowers blood pressure. It is extensively used for the treatment of hypertension [1] and congestive failure.

Figure No 11. Chemical Structure of Captopril



In order to assure the quality of CPT containing pharmaceutical formulations, several methods have been developed for its determination, including batch fluorimetry [3], chemiluminescence [4 – 7], AAS [8, 9], high-performance liquid chromatography (HPLC) [10 – 17], GC [18], differential pulse polarography [19], amperometry [20 – 22], volumetric titration [23], potentiometric titration [24 – 28], capillary electrophoresis [29], conductometry [30], coulometry [31], voltammetry [32] and potentiometry [33]

2.2 Ethyl Cellulose

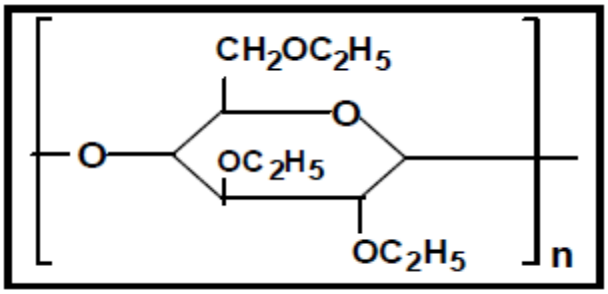
An ethyl ether of cellulose is, of long chain of β-anhydroglucose unit's link with acetyl linkages.

Synonym: Ethocel, Aqualon, Ethylcellulosum, Surelease.

Chemical name: Cellulose ethyl ether.

Structural formula:

Figure No 12. Chemical Structure of Ethyl Cellulose



Functional category:

Coating agent, tablet binder, viscosity increasing agent, film former, tablet filler etc.

Description: Free flowing, white to tan colored powder.

Density (Bulk): 0.4 g. /cm3

Solubility: Insoluble in Glycerin, PG and water. It is freely soluble in Chloroform, tetrahydro furan and in ethanol (95%).

Specific gravity: 1.12-1.15 g/cm3

Viscosity: Ranging from 7-100 cp.

Stability and storage: Stable, resistant to alkalis (dilute and concentrated), salt solutions, sensitive to acidic media.

Incompatibilities: Incompatibility with both waxes paraffin and microcrystalline.

Safety: Employed in oral and topical dosage form**.** Ethyl cellulose is not metabolized due to this it is not used for parenteral products; parenteral use may be harmful to the kidney.

Applications: In tablet coating as a coating material and as a matrix former to enhance the release of formulations.

2.3 Hydroxy Propyl Methyl Cellulose

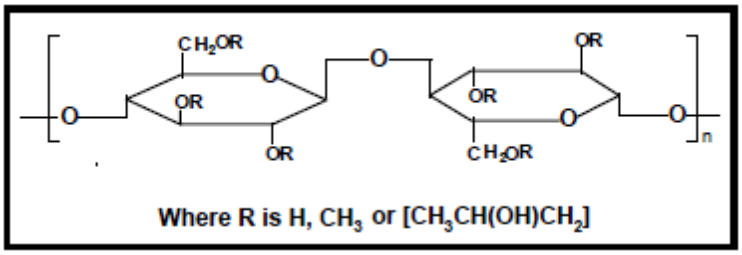
HPMC is O-methylated

cellulose available in various grades with varying viscosity.

Synonym Hydroxy Propyl Methyl Ether, Methocel

Structural formula:

Figure No 13. Chemical structure of Hydroxy Propyl Methyl Cellulose



Molecular weight: 10,000-15, 00,000

Functional category:

Bioadhesive material, coating agent, emulsifying agent, dispersing agent, controlled release agent etc.

Description: Odourless and without taste, white or creamy white powder.

Density (Bulk): 0.341 g. /cm3

Solubility:

It is soluble in cold water, insoluble in chloroform, ethanol (95%), ether, but soluble in mixture of ethanol and dichloromethane.

Specific gravity: 1.26

Viscosity (dynamic): A various types of HPMC available depend on viscosity.

Stability & storage: It is a stable material, although it hygroscopic after drying. It is stored in closed container in cool, dry place.

Incompatibility: Shows incompatibility with 47xidizing agent.

Safety: Non-toxic and not shows irritation.

Applications: Binder in film coating and extended release tablet matrix as a thickness increasing agent in ophthalmic preparation.

2.4 Dimethyl Sulfoxide

Nonproprietary Names:

Synonyms: Deltan; Dimexide; Dimethyl Sulphoxide; DMSO; Kemsol; Methyl sulfoxide; Procipient; Rimso-50; Sulphinylbismethane

Chemical Name and CAS Registry Number: Sulfinyl bismethane [67-68-5]

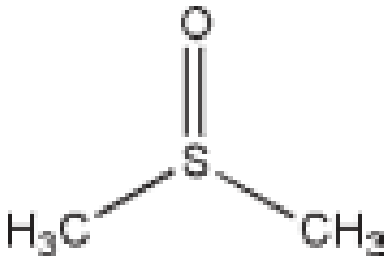
Empirical Formula: C2H6OS

Molecular Weight: 78.13

Functional Category: Penetration agent; solvent.

Structural Formula:

Figure No 14. Chemical structure of Dimethyl Sulfoxide



Description:

Dimethyl sulfoxide occurs as a colourless, viscous liquid, or as colourless crystals that are miscible with water, alcohol, and ether. Has a bitter taste with a sweet after taste, and is odourless, or has a slight odour characteristic of dimethyl sulphoxide,

Acidity/alkalinity pH: 8.5 (for a 50: 50 mixture with water)

Density: 1.0955 g/cm3 at 25.80C.

Dielectric constant: 48.9 at 208C

Dissociation constant Pka: 31.3(24)

Partition coefficient: log (octanol/water) = -2.03

Solubility: Soluble in water by applying heat; also soluble with ethanol (95%), ether and most organic solvents; immiscible with paraffins, hydrocarbons. It is practically insoluble in ethanol (95%), acetone, chloroform, and ether.

Viscosity (dynamic):1.1 mPa s (1.1 cP) at 278C;

Specific gravity: 1.100–1.104 1.095–1.101

Refractive index: 1.478–1.479 1.4755–1.4775

Stability and Storage Conditions:

Dimethyl sulfoxide is reasonably stable to heat, but upon prolonged reflux it decomposes slightly to methyl mercaptan. This decomposition is aided by acids, and is retarded by many bases. Dimethyl sulphoxide packed in air tight, light-resistant containers.

Incompatibilities: - Incompatible with oxidizing agents.

Safety: -

Dimethyl sulfoxide has low systemic toxicity but causes local toxic effect. It absorbed with injection or after oral or percutaneous administration and is distributed in the body. Diethyl sulphoxide produce irritation on skin, showing redness, burning, itching, and scaling; it also causes urticaria. Systemic symptoms include nausea, vomiting, chills, cramps, and lethargy; dimethyl sulphoxide can also cause increases in intra-occular pressure.

Applications in Pharmaceutical Technology: -

Dimethyl sulfoxide polar substance that is aprotic, therefore not have acidic and basic nature. It has exceptional solvent properties for both organic and inorganic components, which are derived from its capacity to associate with both ionic species and neutral molecules that are either polar or polarizable. Dimethyl sulfoxide increases the topical drugs permeation owing to its ability to displace bound water from the stratum corneum; this is accompanied by the extraction of lipids and configurational changes of proteins. The molecular interactions between dimethyl sulfoxide and the stratum corneum have been described. Much of the enhancement ability diminishes with solvent dilution. Increases drug permeation with DMSO concentration low as 15%, but to increase permeability generally used concentrations more than 60–80%. Furthermore, while low molecular weight substances can penetrate quickly[44-47].

2.5 Dibutyl Phthalate

Nonproprietary Names:

BP- Dibutyl phthalate

Synonyms;- Aruldite, benzenedicarboxylic acid, dibutyl-o-phthalate

Chemical Name: Dibutyl benzene-1, 2-dicarboxylate

Empirical Formula: C16H22O4

Molecular Weight : 278.34

Functional Category: Film former, plasticizer, solvent.

Description:

Dibutyl phthalate occurs as an odourless, oily, colourless, or very slightly yellow-coloured, viscous liquid.

Typical Properties:

Density: 1.043 g/cm3

Refractive index: 1.490

Assay: 99.0-101.0

Partition coefficient: log (octanol/water) = 4.50

Solubility: Very soluble in acetone, benzene, ethanol and ether.

Stability and Storage Conditions:

Dibutyl phthalate packed in a closed container at dry location, containers may be hazardous when empty since they can contain product residue such as vapors' and liquid.

Incompatibilities:- Dibutyl phthalate incompatible with oxidizing agents.

2.6 Tween- 80

Nonproprietary Names:

BP-Polysorbate 80

JP: Polysorbate 80

Synonyms: Polysorbate 80

Molecular Formula: C64H124O26

Molecular Weight: 1310

Functional Category: Emulsifying agent; nonionic surfactants; solubilizing agent, wetting, dispersing, suspending agent.

Description:

Refractive index: 1.478–1.479 1.4755–1.4775

Stability and Storage Conditions:

Tween 80 is reasonably show stability with electrolytes, weak acids and bases. Saponifications occur with strong acids.

Incompatibilities:

Discoloration, precipitation occurs with various substances especially phenols, tannins, tars. It reduces action of paraben[48,49].

Safety:

Polysorbates used in cosmetics, food and oral, parenteral and topical preparations. Non toxic and non-irritant materials.

3.0 AIM AND OBJECTIVE

The goal of the present research work is to formulate, development and characterization of transdermal systems with antihypertensive drug.

4.0 PLAN OF WORK

- To develop captopril transdermal patches by using suitable techniques.
- To Study the effect of polymers concentration on drug release.
- To study release mechanism of drug
- To perform preformulation study of drug.
- To study the effect of different permeation enhancers on the drug Penetration.
- To evaluate the transdermal films for different physicochemical properties.
- To study the *In-vitro* drug release/permeation through excised rat abdominal skin.

5.0 MATERIALS & METHODS

Table No. 3 Materials

S.No	Material	Source
1.	Captopril	Sigma aldrich
2.	HPMCK15M	S.D. Fine Chemicals
3.	Polyvinyl pyrrolidone K30	S.D. Fine Chemicals
4.	Ethyl Cellulose	S.D. Fine Chemicals
5.	Polyethylene glycol- 400	Loba Chemie, Pvt Ltd, Mumbai.
6.	Dibutyl phthalate	Loba Chemie, Pvt Ltd, Mumbai.
7.	Tween 80	S.D. Fine Chemicals
8.	DMSO	S.D. Fine Chemicals
9.	Chloroform	S.D. Fine Chemicals
10.	Methanol	S.D. Fine Chemicals
11.	Dichloromethane	S.D. Fine Chemicals
12.	Aluminium foil	Super Wrap India.

Table No. 4 Equipments used

S.No	Machine	Make
1.	UV-Spectrophotometer	UV 1601 Shimadzu, Japan
2.	Magnetic Stirrer	Remi Instuments, India.
3.	Digital pH Meter	Cyberlab pH14L, India.

5.1 Identification test

The identification of Captopril was done by FTIR spectroscopy and UV spectroscopy range 200-400 nm used to record UV spectrum.

5.2 Melting point – It was determined by melting point apparatus.

5.4 Solubility study

The solubility of Captopril was determined in PBS pH 7.4.

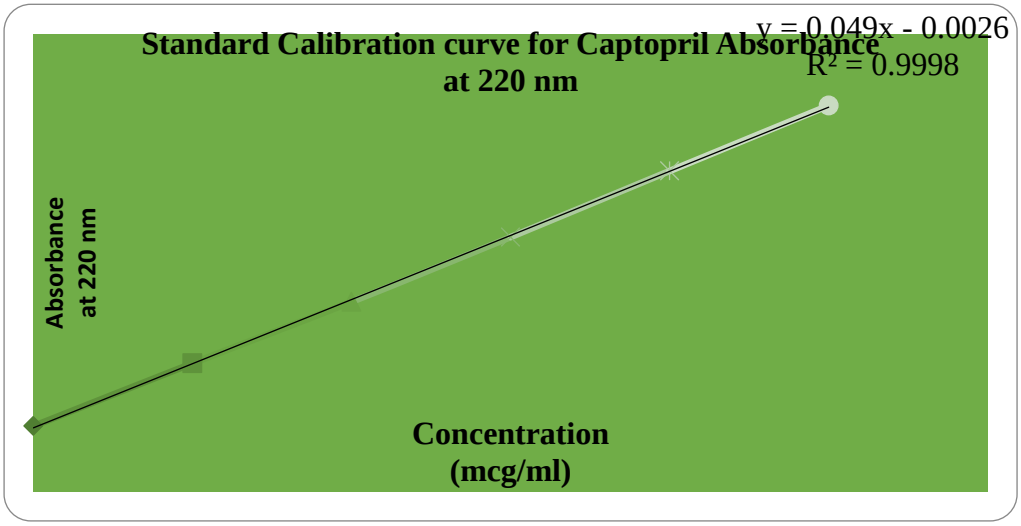
5.5 Estimation of partition coefficient:

The partition coefficient was determined with n-octanol and PBS pH 7.4 as oil and aquous phase respectively. The n-octanol: phosphate buffer saline partition coefficient used to study lipophilicity. 100mg of drug was dissolved in 10 ml n-octanol and was shaken at 370C for 24 h in a sealed container. The two phases were separated and then they were analyzed spectrophotometerically (ShimadzuUV-1800, Japan) for respective drug contents. The Ko/w was calculated using following expression;

5.6 Preparation of calibration curve for Captopril.

Captopril was dissolved in 10 ml methanol and volume is made up to 100 ml in volumetric flask with PBS pH 7.4. From stock solution 1 ml was pipette out (100 µg/ml) then further diluted to get solutions having concentrations 2µg/ml to 24 µg/ml. Absorbance of these solutions were measured using UV Spectrophotometer at 220 nm with PBS pH 7.4 as a blank. The calibration curve was produced for entire range from 2 to 10 µg/ml.

Figure No 15. Standard curve for Captopril



5.7 Compatibility study

FTIR absorption spectra of Captopril, polymers (HPMCK15M, PVPK30, and EC) and dry sample of drug was directly placed after mixing and triturating. Also combined mixture of Captopril and polymer was recorded by using FTIR spectrophotometer (Bruker FTIR).

5.8 Preparations of transdermal patches

The transdermal patches of composition listed in table no.5.3 were prepared by solution casting technique employing a glass substrate (Bangles wrapped with aluminium foil). Membrane type transdermal systems with Captopril prepared using HPMC alone and by employing various proportions of HPMCK15M, PVPK30, and Ethyl Cellulose. The polymers was accurately weigh and dissolved in a suitable solvent mixed until clear solution formed with magnetic stirrer then added Captopril to the uniform polymeric solution and mixed completely to form uniform solution. PEG400 and dibutyl phthalate added as a plasticizer. DMSO and tween-80 were used as a penetration enhancer. The polymer solution was poured into bangles placed in a suitable level, hard rigid surface and patches were dried at a room temperature in a dust free environment for 24 hrs. an inverted funnel was covered over the bangles to avoid fast evaporation of the solvent[50-57]. Patches of 3.14 cm2 were prepared by cutting and packed in an aluminum foil and kept in a desiccator.

Table No. 5 Composition of Captopril transdermal patches

Formulation	F1	F2	F3	F4	F5	F6	F7
Drug (mg)	65	65	65	65	65	65	65
HPMCK15M (mg)	500	450	400	300	-	-	-
PVPK30 (mg)	-	50	100	200	400	300	200
EC (mg)	-	-	-	-	100	200	300
PEG-400*(ml)	0.18	0.18	0.18	0.18	-	-	-
Dibutyl phthalate *(ml)	-	-	-	-	0.2	0.2	0.2
Tween 80*(ml)	0.14	0.14	0.14	0.14	-	-	-
DMSO* (ml)	-	-	-	-	0.11	0.11	0.11
DCM/Methanol (ml)	12	12	12	12	-	-	-
Chloroform (ml)	-	-	-	-	5	5	5

6.0 RESEARCH ENVISAGED

6.1 Thickness of patches 82

The thickness of Patches was measured by digital vernier calipers with least count 0.001mm at three different sites average of three reading was taken with standard deviation.

6.2 Weight variation

The three disks of 3.14 cm2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

6.3 Drug content

Accurately weighed patches were individually dissolved in minimum quantity of methanol and made volume up to 100 ml with PBS pH 7.4 solutions; 10 ml was transferred to flask and made volume 100 ml. The absorbance was recorded at 243 nm. The blank solution was made in the same manner except the patches without drug were used.

6.4 Percentage Moisture content

The films were weighed & placed in desiccators containing calcium chloride at 400c in a dryer for at least 24 hrs or more until it gives a constant weight. The % of moisture content was the difference between constant weight taken and the initial weight and as reported with percentage by weight moisture content.

6.5 Swelling index

The patches of 3.14 cm2 were weighed and added into petri dish which contains 10 ml double distilled water and were permeated to absorb moisture at a fix time interval check the increase weight of the patches. Continue this process till same weight observed until weight remaining the same over a period of time. Swelling index (% S) was determined by applying the formula.

S (percentage) = Wt – Wo / Wo x 100

Where, S percent swelling, Wt patch weight at time t.

Wo patch weight at time zero.

6.6 Folding endurance85

This was obtained by constantly folding one patch at the same place without breaking gave the value of folding endurance. This test performed to check folding ability of transdermal patches also indicate brittleness of patches, more brittle patch when folding endurance value less.

6.7 Percentage Elongation

A film strip (4 x 1cm) was cut on a glass plate with a sharp blade. The %
elongation break is to be determined by observing the length just before the breaking point with formula by pointer on the graph paper.

Percent elongation = IB – Io / Io × 100

Where-

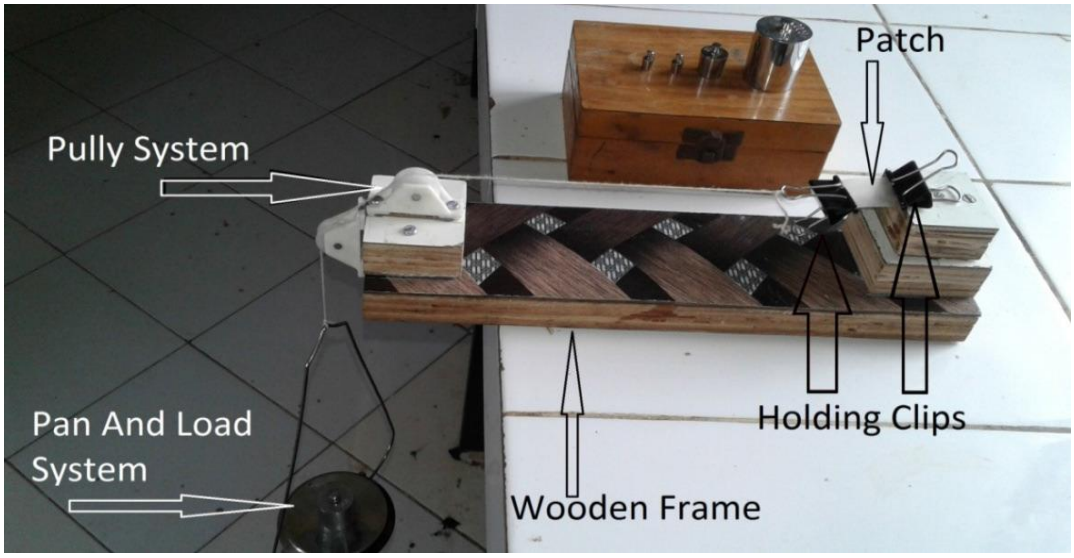
Io = Original film length.

IB = Length of film at break when stress is applied.

6.8 Tensile Strength

The tensile strength of the patches was found by the apparatus designed as shown in fig 5.1. The design of instrument such that, it had one wooden frame that horizontally placed having fixed scale. On the top of frame two clips were attached to hold patches that under study. From two clips one clips fixed and other moved. Instrument also has pulley to hold weight a patch, weight applied to one end of pulley and other end attached to the fixed clip[58-61]. During the test wooden platform not dislocate from the original place so platform was fixed carefully to avoid dislocation. Three patches were cut for study having 3.14 cm2 sizes. Thickness and breadth of patches were noted at three sizes and calculated average value. Rate of stress changes was maintained constant with the addition of 0.5gm per 2 minutes. The elongation was observed and the total weights taken were used for calculation. Formula for tensile strength.

Figure No 16. Assembly for tensile strength.



6.9 In-vitro permeation studies

The permeation studies were done according to the approved protocol by the animal ethics committee IAEC (IAEC NO: NIPS/05/29/2016) at the pharmacology department, NIPS, Bhopal. For in-vitro evaluation of TDDS, albino rat was selected because of its easy availability and suitability. In this work franz diffusion cell was used. The Franz diffusion cell was designed from borosilicate glass generally comprise two compartments, one containing the active compartment (donor compartment) and the other containing receptor solution (receptor compartment) separated with barrier i.e. skin membrane .The cell consist of sampling port and temperature regulating jacket. The outlet and inlet was connected with latex tube so the jacket has stagnant water inside at 370ºC. The volume of receptor cell was 25 ml and effective surface area available for permeation was 3.14cm^2. The two compartment of the cell fixed with strong clips[62-69]. A Teflon bead of 12mm was used to stir the receptor solution using magnetic stirrer.

Figure No 17. Franz diffusion cell

6.10 Stability studies

Stability studies were performed at the different storage condition 25ºC• }20 ºC temp., 60%• }5% RH and 40ºC• }20 ºC temperature, 75%• }5% RH, for 90 days on optimized formulation batches (F4&F5). The parameters studied for stability studies are thickness, drug content, assay, moisture content and uptake and in vitro drug permeation.

7.0 RESULTS AND DISCUSSION

7.1 Appearance and colour of drug

The captopril sample shows white colour in powder form.

7.2 Melting Point

The Captopril M.P. was observed 106 ^{0}C.

7.3 Solubility

The drug solubility in a given vehicle determines the active concentration at which the drug could be presented on the skin surface. Hence, a good solubility in a chosen vehicle ensures the transfer of the drug via delivery systems.

Freely soluble- DMSO, Methylene chloride, Methanol

Sparingly soluble- 95% Ethanol, Isopropanol

Slightly soluble- Ethyl ether;

7.4 Partition Coefficient

The drug without sufficient lipophilicity encounters difficulty in crossing the lipid bilayer. However, when the lipophilicity becomes too prominent, the drug may form a reservoir within these layers. Hence, a balance of hydrophilicity and lipophilicity is desirable in the structure of drug and octanol-phosphate buffer saline partition coefficient is thought be good indicator. We found a partition coefficient value of 3.859±0.02

7.5 Spectroscopic studies

7.6 Characterization of Captopril

Table No. 6 Standard calibration curve of Captopril in PBS pH 7.4

S.No	**Concentration (mcg/ml)**	**Absorbance at 220 nm**
1.	**0**	**0**
2.	2	0.096
3.	4	0.19
4.	6	0.289
5.	8	0.39
6.	10	0.49

Figure No 18. FTIR spectra of Captopril

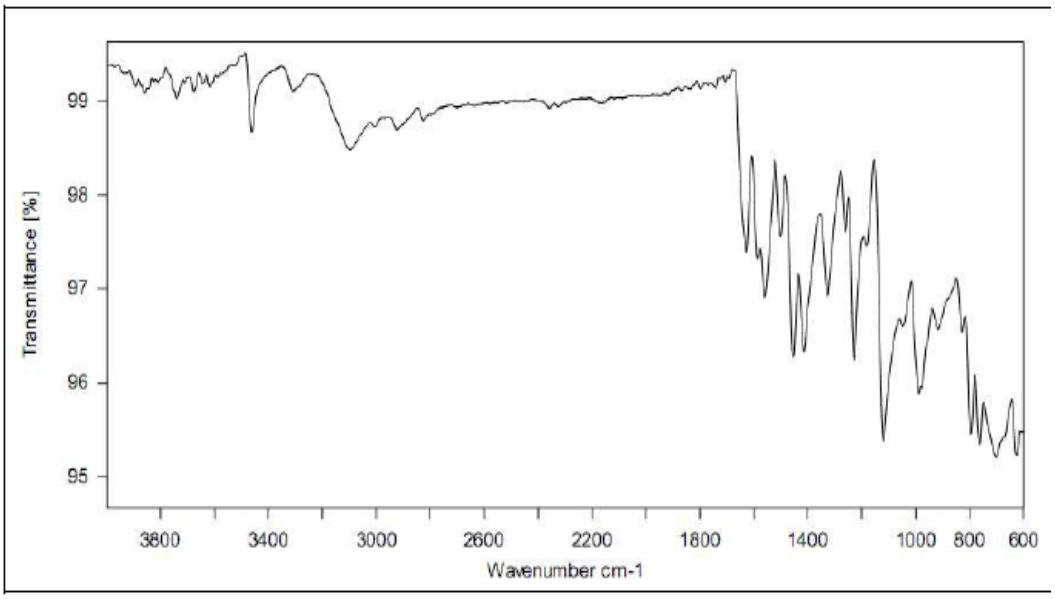


Figure No 19. FTIR Spectra of Ethyl Cellulose.

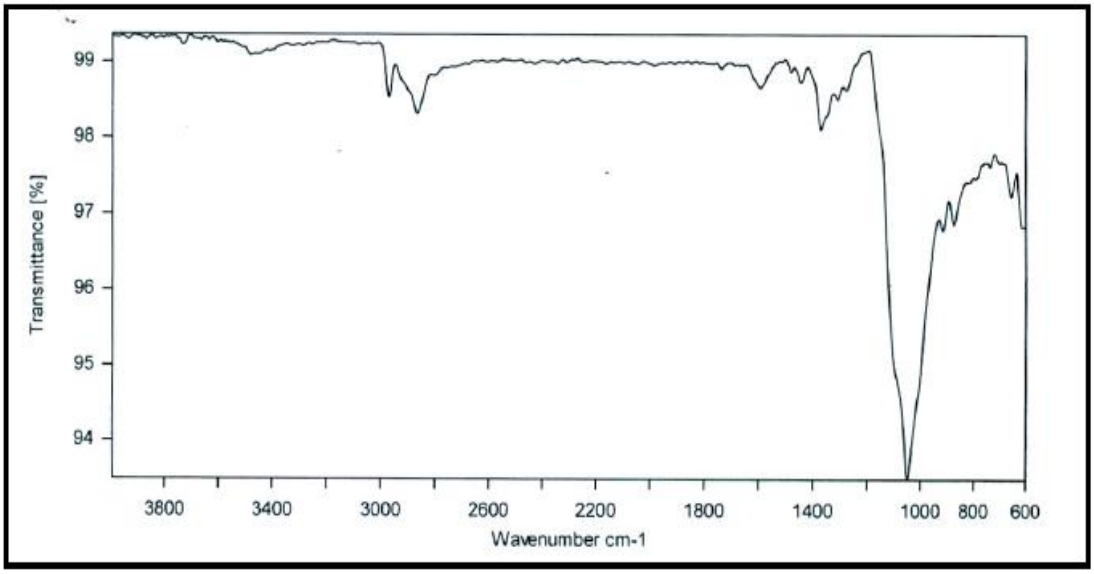


Figure No 20. FTIR Spectra of HPMC $K_{15}M$

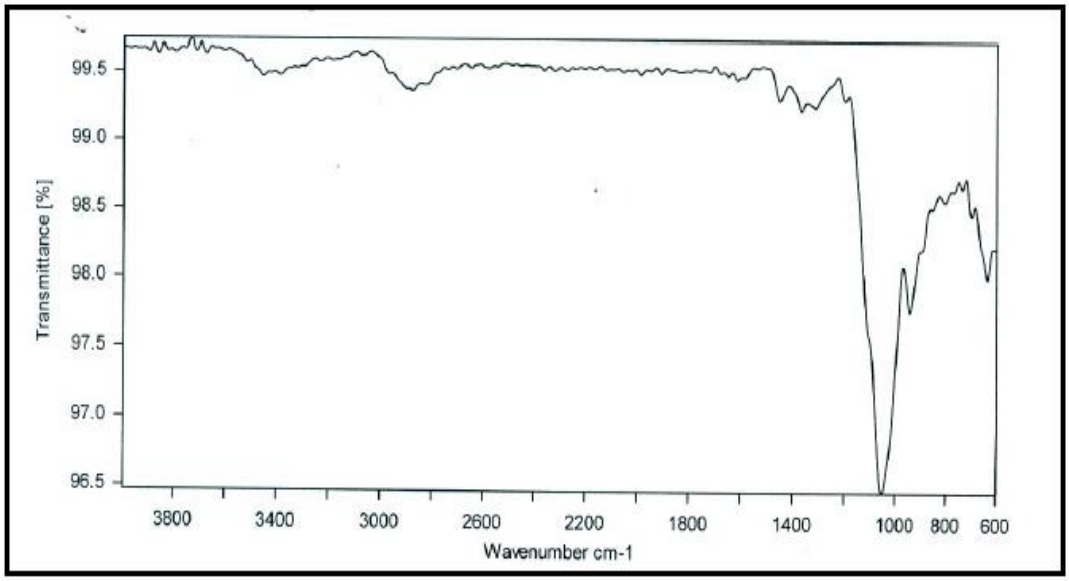


Figure No 21. FTIR Spectra of Polyvinyl Pyrrolidone K30

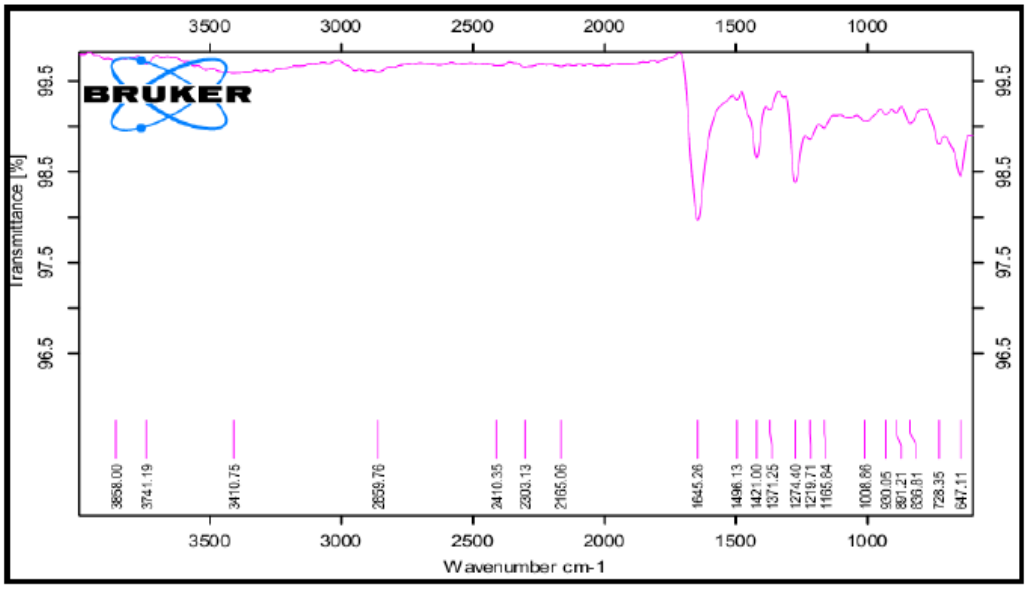


Figure No 22. FTIR Spectra of Captopril +Ethyl cellulose + PVPK$_{30}$

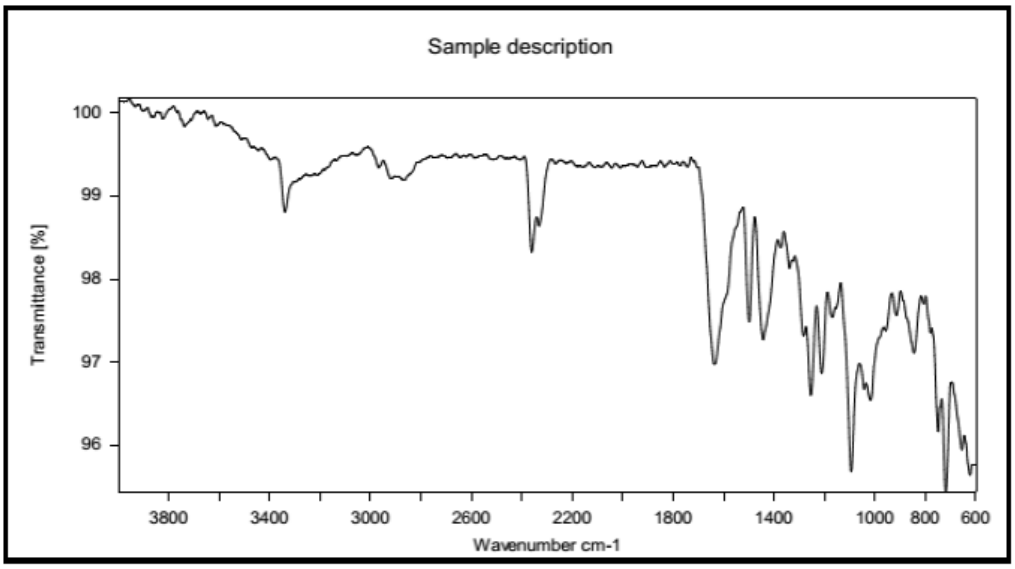


Figure No 23. FTIR Spectra of Captopril + HPMCK$_{15}$ + PVPK$_{30}$

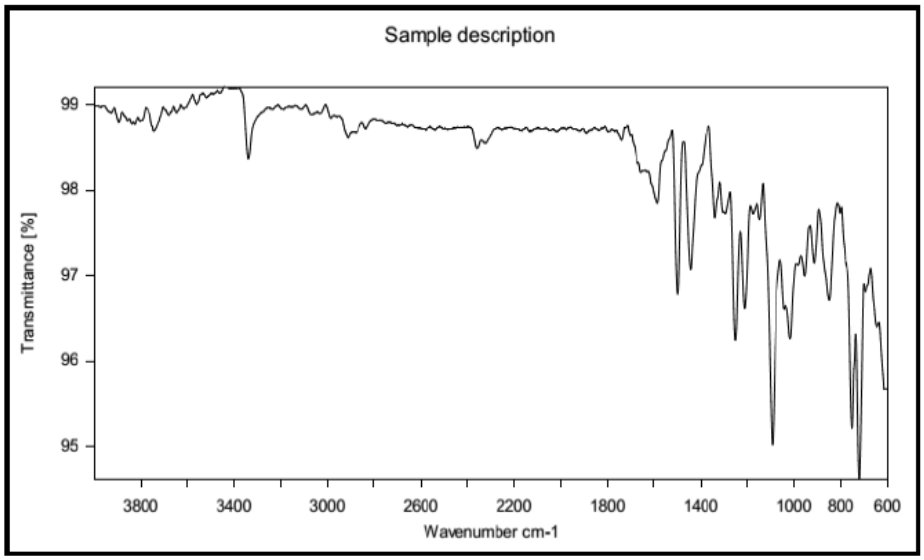
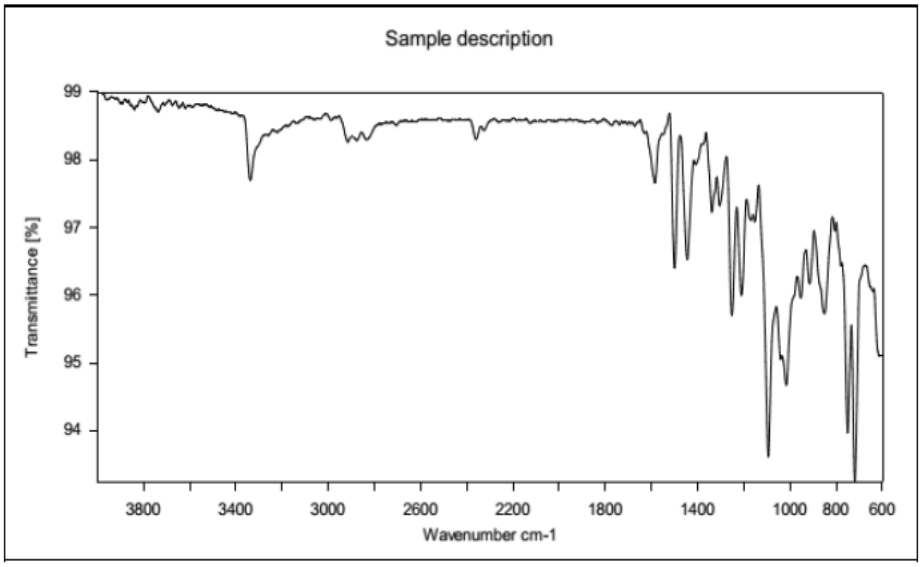


Figure No 24. FTIR Spectra of Captopril + HPMCK$_{15}$



The compatibility studies were performed to find out interaction of drug with the polymer that is used in the formulation of TDDS. The FT-IR spectrum of the drug and polymer did

not show presence of any additional peaks for new functional groups. These results suggest compatibility between drug and polymer.

7.7 Drug-Polymers Interaction Study

The interaction studies were carried out to find out interaction of drug with the polymer used in the preparation of TDDS. The FT-IR spectrum of the drug and polymer did not show presence of any additional peaks for new functional groups. These results suggest compatibility between drug and polymer.

Table No. 7 Comparative FTIR Study of drug and polymer

Name of Compound	N-H	C-H	C=C	NO_2	C-N
Captopril	3330 cm^{-1}	2920 cm^{-1}	1622 cm^{-1}	1585 cm^{-1}	1227 cm^{-1}
Captopril and $HPMCK_{15}M$	3337 cm^{-1}	2914 cm^{-1}	1585 cm^{-1}	1499 cm^{-1}	1210 cm^{-1}
Captopril +$PVPK_{30}$+ $HPMCK_{15}M$	3338 cm^{-1}	2913 cm^{-1}	1586 cm^{-1}	1500 cm^{-1}	1212 cm^{-1}
Captopril + $PVPK_{30}$ + EC	3339 cm^{-1}	2913 cm^{-1}	1637 cm^{-1}	1586 cm^{-1}	1212 cm^{-1}

7.8 Formulations of Transdermal Patches

Seven formulations of Captopril Patches compose with different polymers HPMCK15M, PVP K30, Ethyl cellulose, Chloroform, Methanol, Dichloro methane were used as a casting solvent. PEG400 and dibutyl phthalate used to give plasticity to patches and DMSO, Tween 80 are used to enhance penetration of drug through transdermal systems. The polymeric solution was poured into bangles placed in a suitable level, hard rigid surface and patches were dried at a room temperature in a dust free environment for 24 hrs. an inverted funnel was covered over the bangles to avoid fast evaporation of the solvent. Patches of 3.14 cm2 were prepared by cutting and packed in an aluminum foil and kept in a desiccator. The prepared transdermal therapeutic

Figure No 25. Formulated Transdermal patches of Captopril

Table No. 8 Physicochemical Evaluation data of Transdermal Patches of Captopril

Formulation Code	Thickness (mm)	Weight variation (mg)	% Drug Content	Folding endurance	Tensile strength Kg/mm^2
F_1	0.12±0.01	0.150±0.01	95.92±3.32	57±12.04	2.45±0.81
F_2	0.19±0.02	0.148±0.005	96.59±3.14	36.6±21.0	2.80±0.80
F_3	0.14±0.004	0.155±0.021	97.51±2.17	38±18.20	2.40±0.70
F_4	0.17±0.008	0.160±0.011	99.65±2.42	60±24.33	3.85±1.80
F_5	0.35±0.09	0.149±0.017	98.36±2.02	58±22.03	3.92 ±1.84
F_6	0.37±0.003	0.156±0.014	97.71±1.42	57±10.41	2.81±1.84
F7	0.35±0.003	0.153±0.015	98.71±1.42	59±10.41	2.93 ±1.78

Table No. 9 Physicochemical Evaluation data of Transdermal Patches of Captopril

Formulation Code	% Elongation	% Moisture Content	% Moisture uptake	Swelling index
F_1	24.43±2.51	1.85±0.35	4.87±3.13	24.17±1.38
F_2	23.80±2.12	2.6±0.77	3.6±3.7	25.75±0.72
F_3	25.75±2.61	3.1±1.29	5.3±1.22	25.50±2.12
F_4	26.25±4.12	3.2±1.82	4.7±0.85	23.41±0.74
F_5	28.04±4.71	3.23±2.78	5.7±1.45	22.82±1.25
F_6	25.26±4.19	2.7±0.98	4.76±1.06	24.18±1.37
F7	24.25±4.18	2.8±0.97	4.77±1.05	25.19±1.36

The patches thickness ranges from 0.12±0.01 to 0.37±0.003 mm. The values of thickness for all the batches are given in the table no.6.5. The low SD values of the Patches thickness make sure thickness uniformity in each formulation (Table-6.5). The weight variation was found to be in between 0.148±0.005 to 0.160±0.011mg. The uniform weights were found for all formulations with low SD values. The results of this study revealed that, the drug content uniformity in all systems with relatively low SD values i.e 95.92±3.32 to 99.65±2.42. The folding endurance of patch is frequently used to find out the capacity of patch unaffected with repeated bending, folding and creasing and may encountered as a measure of the patch quality. The folding endurance values were found in the range of 36.6±21.0 to 60±24.33 number of folds. All formulation values showed in the table 6.5. This data showed that the patches had good mechanical strength and flexibility. Tensile strength was determined to check the capacity of patch to withstand rupture. The tensile strength of patches was found in between 2.40±0.70 to 3.92 ±1.84 Kg/mm2. The formulation F4 and F5 showed the best tensile strength. The values for the entire patch are tabulated in the table. The % elongation of the formulation was in the range of 24.25±4.18 to 28.04±4.71%. The results obtained for all the formulations are tabulated. The % moisture content study was performed to check the structural integrity of the patches at dry condition. The moisture content was found in between 1.85±0.35 to 3.23±2.78. The values for all the patches are tabulated in the respective table. The % moisture uptake study was performed to determine physical stability at humid condition.

Table No. 10 *In-vitro* Drug Permeation of Captopril from F1 through skin membrane

Time in (hrs)	*T* (hrs)	Log time (hrs)	F1		
			% Drug Permeated	Log % Drug Permeated	Log % Drug Retained
2	1.41	0.30	35.18	1.54	1.81
4	2.00	0.60	58.75	1.76	1.61
6	2.45	0.78	73.02	1.86	1.43
8	2.83	0.90	80.00	1.90	1.30

Table No. 11 *In-vitro* Drug Permeation of Captopril from F2 through skin membrane

Time in (hrs)	*T* (hrs)	Log time (hrs)	F2		
			% Drug Permeated	Log % Drug Permeated	Log % Drug Retained
2	1.41	0.30	7.53	0.87	1.96
4	2.00	0.60	14.03	1.14	1.93
6	2.45	0.78	27.26	1.43	1.86
8	2.83	0.90	36.47	1.56	1.80
10	3.16	1.00	48.85	1.68	1.70
12	3.46	1.08	60.39	1.78	1.59
16	4.00	1.20	72.38	1.85	1.44
20	4.47	1.30	76.92	1.88	1.36
24	4.90	1.38	83.23	1.92	1.22

Table No. 12 *In-vitro* Drug Permeation of Captopril from F3 through skin membrane

Time in (hrs)	*T* (hrs)	Log time (hrs)	F3		
			% Drug Permeated	Log % Drug Permeated	Log % Drug Retained
2	1.41	0.30	8.58	0.93	1.96
4	2.00	0.60	14.47	1.16	1.93
6	2.45	0.78	27.31	1.43	1.86
8	2.83	0.90	32.65	1.51	1.82
10	3.16	1.00	46.19	1.66	1.73
12	3.46	1.08	57.40	1.75	1.62
16	4.00	1.20	67.03	1.82	1.51
20	4.47	1.30	76.92	1.88	1.36
24	4.90	1.38	88.29	1.94	1.06

Table No. 13 *In-vitro* Drug Permeation of Captopril from F4 through skin membrane

Time in (hrs)	$\sqrt{T}$ (hrs)	Log time (hrs)	F4		
			% Drug Permeated	Log % Drug Permeated	Log % Drug Retained
2	1.41	0.30	8.43	0.92	1.96
4	2.00	0.60	14.42	1.15	1.93
6	2.45	0.78	27.02	1.43	1.86
8	2.83	0.90	33.99	1.53	1.81
10	3.16	1.00	47.46	1.67	1.72
12	3.46	1.08	58.69	1.76	1.61
16	4.00	1.20	68.46	1.83	1.49
20	4.47	1.30	79.27	1.89	1.31
24	4.90	1.38	93.00	1.96	0.84

Table No. 14 *In-vitro* Drug Permeation of Captopril from F5 through skin membrane

Time in (hrs)	T (hrs)	$\sqrt{}$ Log time (hrs)	F5		
			% Drug Permeated	Log % Drug Permeated	Log % Drug Retained
2	1.41	0.30	5.87	0.76	1.97
4	2.00	0.60	11.70	1.06	1.94
6	2.45	0.78	33.95	1.53	1.81
8	2.83	0.90	35.26	1.54	1.81
10	3.16	1.00	46.45	1.66	1.72
12	3.46	1.08	60.05	1.77	1.60
16	4.00	1.20	69.64	1.84	1.48
20	4.47	1.30	80.58	1.90	1.28
24	4.90	1.38	92.05	1.96	0.90

Table No. 15 *In-vitro* Drug Permeation of Captopril from F6 through skin membrane

Time in (hrs)	*T* (hrs)	Log time (hrs)	F6		
			% Drug Permeated	Log % Drug Permeated	Log % Drug Retained
2	1.41	0.30	8.84	0.92	1.96
4	2.00	0.60	15.55	1.19	1.92
6	2.45	0.78	28.78	1.45	1.85
8	2.83	0.90	39.72	1.59	1.78
10	3.16	1.00	49.07	1.69	1.70
12	3.46	1.08	62.60	1.79	1.57
16	4.00	1.20	72.25	1.85	1.44
20	4.47	1.30	79.27	1.89	1.31
24	4.90	1.38	84.15	1.92	1.20

Table No. 16 *In-vitro* Drug Permeation of Captopril from F7 through skin membrane

Time in (hrs)	*T* (hrs)	Log time (hrs)	F7		
			% Drug Permeated	Log % Drug Permeated	Log % Drug Retained
2	1.41	0.30	8.43	0.92	1.96
4	2.00	0.60	15.55	1.19	1.92
6	2.45	0.78	28.78	1.45	1.85
8	2.83	0.90	39.72	1.59	1.78
10	3.16	1.00	49.07	1.69	1.70
12	3.46	1.08	58.69	1.76	1.61
16	4.00	1.20	62.60	1.79	1.57
20	4.47	1.30	69.64	1.84	1.48
24	4.90	1.38	77.15	1.92	1.20

Table No. 17 *In-vitro* Drug Permeation Kinetics

Time (hrs)	F1	F2	F3	F4	F5	F6	F7
2	35.18	7.53	8.58	8.43	5.87	8.84	8.43
4	58.75	14.03	14.47	14.42	11.70	15.55	15.55
6	73.02	27.26	27.31	27.02	33.95	28.78	28.78
8	80.00	36.47	32.65	33.99	35.26	39.72	39.72
10		48.85	46.19	47.46	46.45	49.07	49.07
12		60.39	57.40	58.69	60.05	62.60	58.69
16		72.38	67.03	68.46	69.64	72.25	62.60
20		76.92	76.92	79.27	80.58	79.27	69.64
24		83.23	88.29	93.00	92.05	84.15	77.15

Table No. 18 *In-vitro* Drug Permeation of Captopril Data Batches F1-F7

Cumulative drug permeated in (µg/cm^2)						
F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
728	155	177	174	122	182	174
1216	290	299	298	242	321	321
1511	564	565	559	702	595	595
1656	754	675	703	729	822	821
_	1011	956	982	961	1015	1015
_	1250	1188	1214	1243	1295	1214
_	1498	1387	1417	1441	1495	1295
_	1592	1592	1640	1668	1640	1441
_	1722	1827	1925	1905	1741	1597

Invitro drug release was studied for all patches of Captopril transdermal patches.The studies were performed upto 24 hours for all the patches.The cumulative percentage release of formulation (F1,F2,F3,F4,F5,F6,F7) were found to be (80%,83.23%,88.29%,93%,92.05%,84.15%,77.15%) out of these, F4 has maximum released.

The optimized formulation F4 has high amount drug release due to good compatibility between the drug and polymers.

Figure No 26. In vitro Drug permeation of Captopril

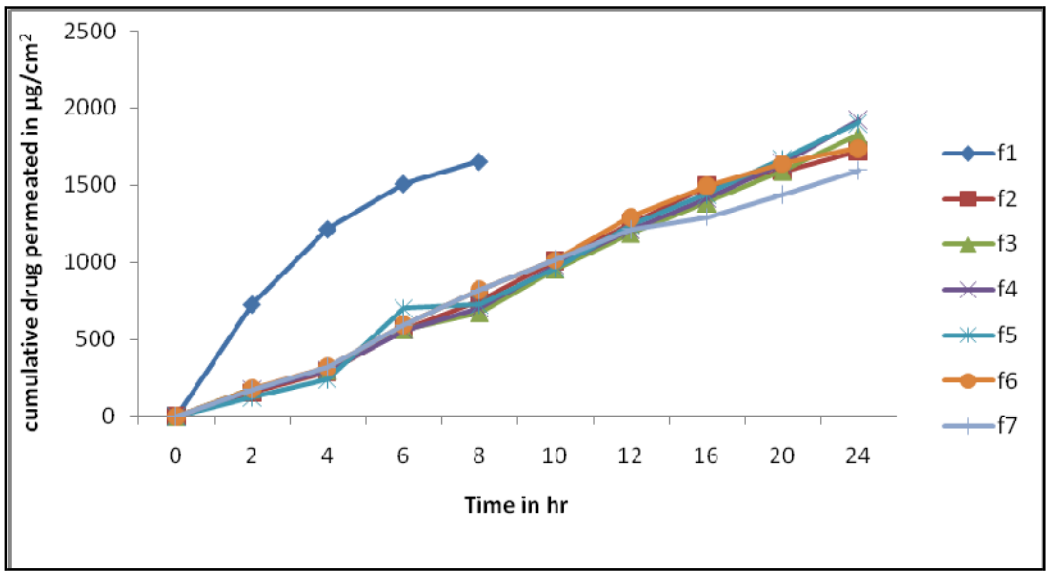


Table No. 19 Kinetic values for drug release from transdermal therapeutic system

Sr. No	Zero Order	First Order	Higuchi plot	Korsmeyer-Peppas		Best Fit Model
	(r^2)	(r^2)	(r^2)	(r^2)	(n)	_
F1	0.926	0.991	0.941	0.893	0.11	Zero order
F2	0.985	0.973	0.989	0.890	0.12	Higuchi matrix
F3	0.995	0.909	0.995	0.927	0.12	Zero order
F4	0.994	0.852	0.995	0.926	0.12	Higuchi matrix
F5	0.916	0.882	0.988	0.906	0.28	Higuchi matrix
F6	0.992	0.974	0.990	0.981	0.22	Zero order
F7	0.988	0.933	0.983	0.870	0.11	Zero order

Figure No 27. Comparative *In-vitro* Permeation Profile of Captopril According to Zero Order model Formulations F_1-F7

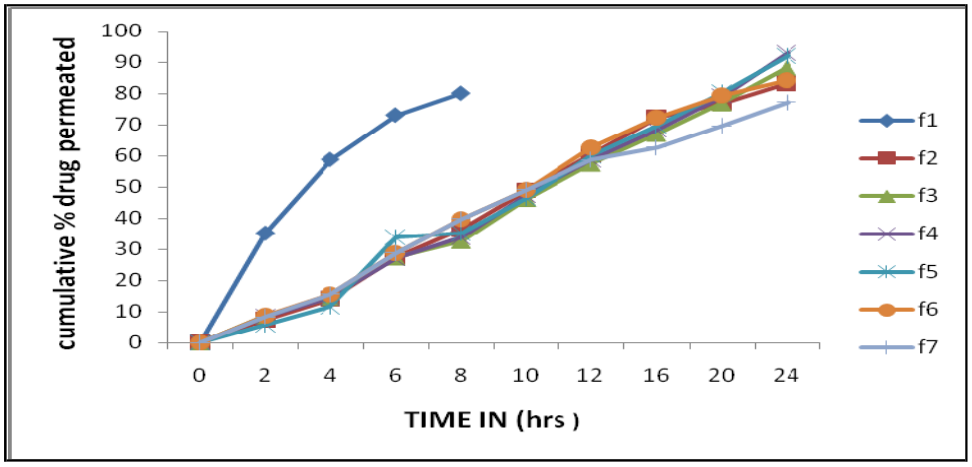


Figure No 28. Comparative *In-vitro* Permeation Profile of Captopril according to First Order release model Formulations F_1-F_7

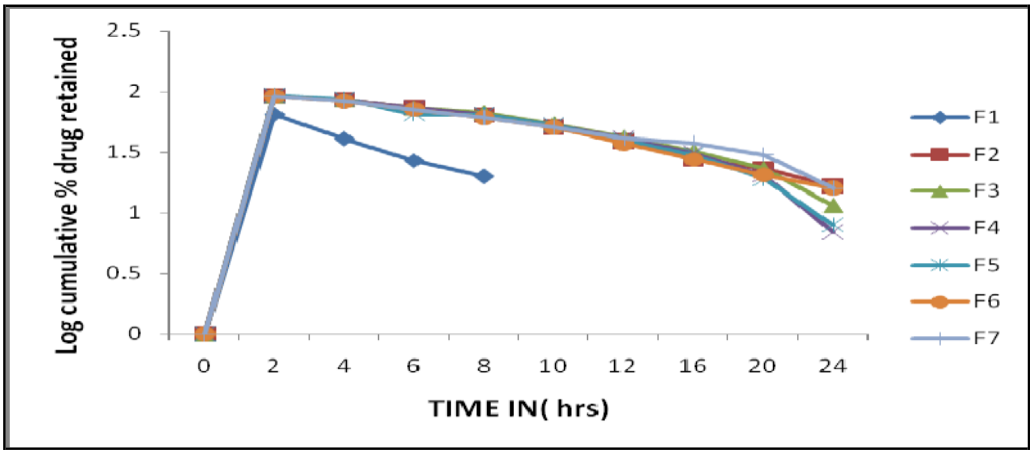


Figure No 29. Comparative *In-vitro* Permeation Profile of Captopril According to Higuchi Matrix Kinetics for Formulations F_1- F_7

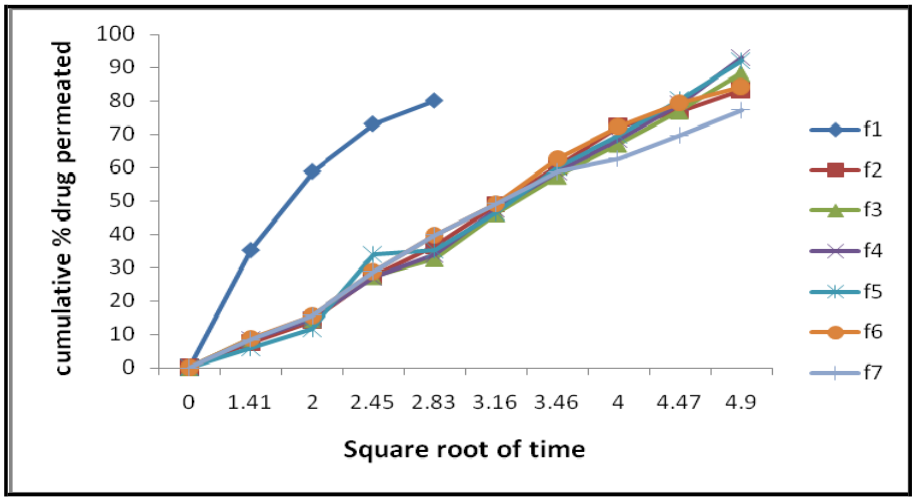
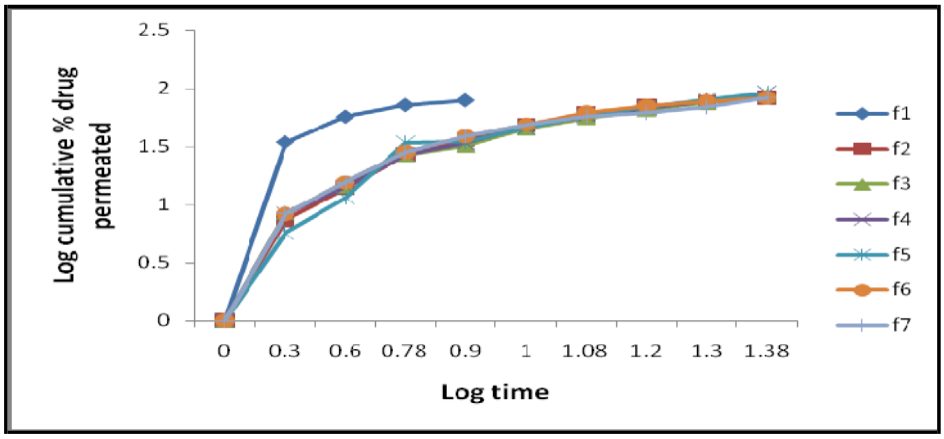


Figure No 30. Comparative *In-vitro* Permeation Profile of Captopril According to Korsmeyer-Peppas Kinetics for Formulations F_1- F_7



- Optimized formula follow zero order release

7.9 Stability Study

Present studies were performed to check the formulation stability of optimized batches F4 and F5 at accelerated conditions of temperature and humidity at an interval of three month.

Table No. 20 Stability Study of batch F4

Sr. no	Evaluation Parameter	At o day	After 90 days
1	Thickness (mm)	0.17±0.008	0.16 ± 0.06
2	Weight variation	0.328±0.011	0.326 ± 0.010
3	% Drug Content	99.65±2.42	98.63 ± 1.25
4	Folding endurance	39±24.33	38 ± 23.32
5	Tensile Strength Kg/mm^2	2.45±2.18	1.43 ± 1.64
6	% Elongation	26.25±4.12	24.41 ± 4.3
7	% Moisture content	3.2±1.82	3.1 ± 0.94
8	% Moisture uptake	4.7±0.85	4.5 ± 3.03
9	Swelling index	23.41±0.74	22.40 ± 0.71

Table No. 21 Drug permeation study: F4

Time in (hrs)	% Cumulative permeated (At 0 day)	%Cumulative Permeated(After 90 days)
2	8.43	7.53
4	14.42	13.40
6	27.02	26.31
8	33.99	32.18
10	47.46	46.85
12	58.69	57.39
16	68.46	67.58
20	79.27	78.18
24	93.00	92.38

Figure No 31. Drug Permeation study of F4

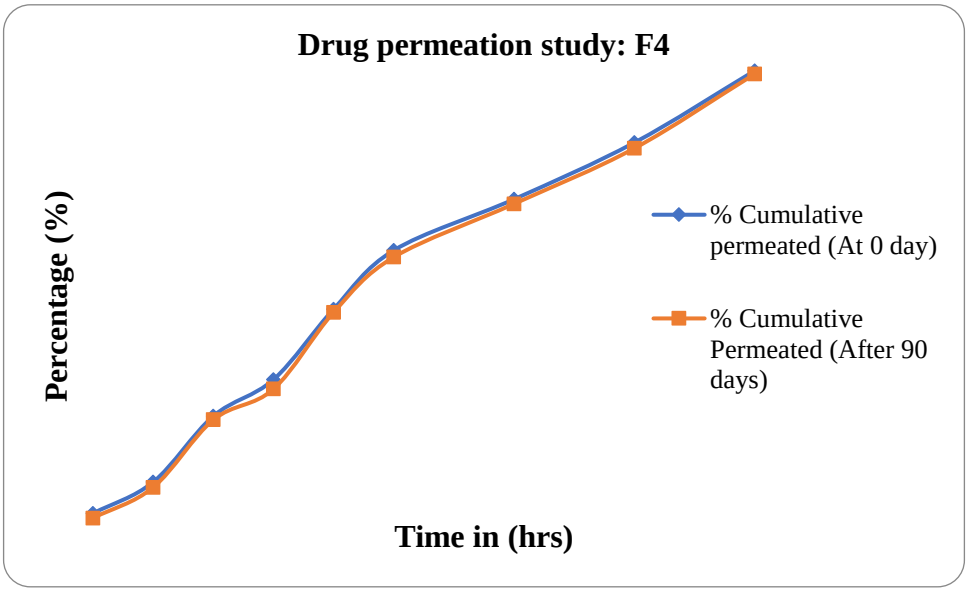


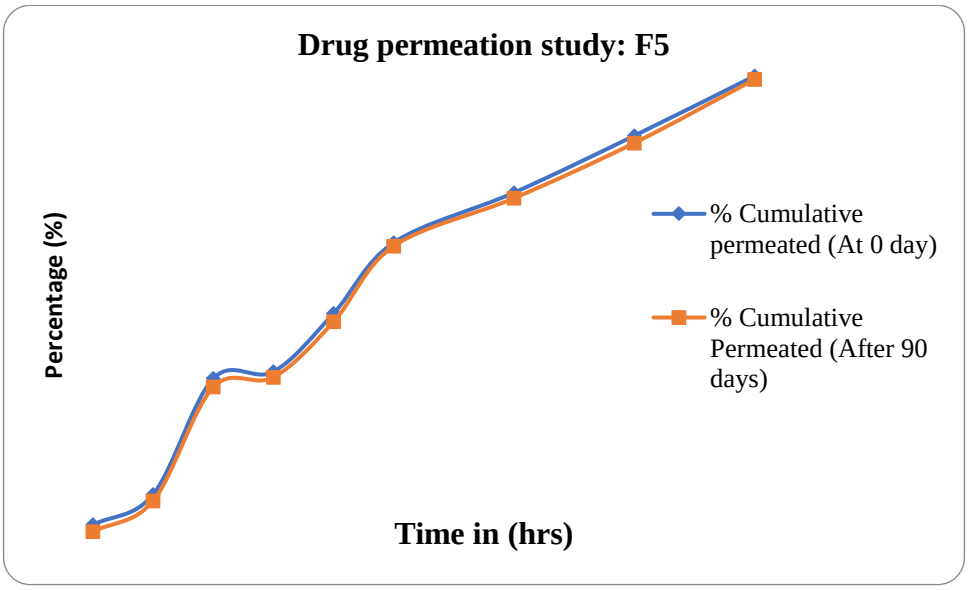
Table No. 22 Stability Study of batch F5

Sr. no	Evaluation Parameter	At o day	After 90 days
1	Thickness (mm)	0.35±0.09	0.34 ± 0.06
2	Weight variation	0.225±0.017	0.224± 0.011
3	% Drug Content	96.36±2.02	95.68 ± 1.25
4	Folding endurance	58±22.03	57 ± 12.14
5	Tensile Strength Kg/mm^2	2.41±0.86	2.40 ± 1.64
6	% Elongation	28.04±4.71	26.41 ± 4.3
7	% Moisture content	3.23±2.78	2.5 ± 0.94
8	% Moisture uptake	5.7±1.45	4.89 ± 3.03
9	Swelling index	22.82±1.25	21.46 ± 0.97

Table No. 23 Drug permeation study: F5

Time in (hrs)	% Cumulative permeated (At 0 day)	% Cumulative Permeated (After 90 days)
2	5.87	4.53
4	11.70	10.47
6	33.95	32.31
8	35.26	34.18
10	46.45	44.85
12	60.05	59.39
16	69.64	68.58
20	80.58	79.18
24	92.05	91.38

Figure No 32. Drug Permeation study of F5



8.0 SUMMARY & CONCLUSION

Eventually, based on results of various evaluation parameters like thickness, strength, elongation, better compatibility and stability the transdermal matrix patches was successfully designed and developed by trial and error method. Formulations were prepared by employing combination of HPMCK15M, PVPK30, and EC in various ratios. From the research, various conclusions were drawn. The patches showed good thickness, tensile strength and content uniformity of drug. The used polymers (HPMCK15M, PVPK30, and EC in various ratios) employed to design transdermal patches in different proportion.

Invitro release from transdermal patches showed extended release of drug for 24 hours.

From the result of present experimental investigation, the formulation F4 showed good results on evaluation studies. Hence F4 formulation were the Optimized formulation.

The Captopril penetration from formulated transdermal patches was found to follow diffusion mechanism and obeys zero order release.

So we can conclude that transdermal delivery system would be used as drug carrier for Captopril.

9.0 REFERENCES

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