CHAPTER 1. INTRODUCTION AND LITERATURE REVIEW

Currently, Transdermal patches delivery is capable techniques intended for drug administration. Transdermal patches delivery is dosage form intended to transport a beneficially valuable extent of drug through a skin of patient. To transport beneficial drug through human skin for systemic effects, comparatively morphology, physical and chemical characteristic of the human membrane are to be consider.

Transdermal patches release gives a most important perimeter more than injectable and oral route by improving patient fulfilment and stay away from first pass biotransformation correspondingly. Transdermals patches release is never constrained, steady management of the medicaments; it also permit constant enter of medicaments through small biological half-lives and reduces rhythm entrance into complete movement, which repeatedly reasons adverse results. Thus many novel dosage forms such as Transdermal dosage form, sustain dosage form, through mucosal dosage form and all that come out. Numerous main benefits of Transdermal dosage form are restriction of bypass biotransformation, improvement of beneficial effectiveness and continuation of drug stable plasma intensity.

1. Definition

Transdermal patches delivery is topical administration of medicaments intended for therapeutic effects at sustain and controlled manner. [Jain N.K., 1997].

1.1. Advantages over the Oral dosage forms

- It passes up problems related with GI absorbed due to GI pH, drug-food interactions, enzymatic activity etc.
- It is alternate route for oral administration when the route is not suitable, as in case of vomiting, diarrhea etc.
- It passes up hepatic “first pass” effect.
- It avoids the hazards and difficulty of parenteral route.
• It reduces dose frequency, recovering patient compliance.
• It extend action of drugs have small plasma half-life via the drug reservoir nearby controlled release characteristics.
• It rapidly terminates action of drug by eradicate of dosage form from the skin surface.
• It rapidly recognition of the medication in urgent situation. (e.g. Non-responsive, unconscious, or coma patient)
• It reduces hazards and difficulty of I.M. injections or I.V. infusions.
• It increases therapeutic effect, decreased adverse effect due to enhancement of the blood concentration-time profile and removal of pulse entry of drugs into the systemic flow.
• It supplies conventional action over extended duration of time and ability to approximate zero-order kinetics.
• It developed control of the concentration of drug with short therapeutic index.
• It reduces inter and intrapatient variation.
• It offers suitability for self-administration [Jonathan et al., & Scheindlin S et al., 2004].

1.2. Limitation of transdermal delivery
• It has need of optimal physicochemical properties for the medicament to go through stratum corneum and small dose of medicament need for therapeutic value.
• It is not easy and some time it may not be possible. Normally, drugs with beneficial dose less than 5 mg/day are chosen to be transport through Transdermal route.
• Skin Membrane irritation and contact dermatitis reported sometimes due to some of the adjuvant are penetration enhancers are another limitation for such delivery.
• Investigational is also a region that has to be examined carefully before a decision is made to develop a Transdermal product [Barry B W et al., 2001& Indian Pharmacopoeia, 1996]
1.3. Assortment of drug candidate for transdermal patches delivery

These routes of administration cannot be used for a large number of drugs. Correct option of the drug substance is the most important decision in the successful development of transdermal patches [Chien Y W., 1992]. The drug candidate should have three ideal characteristic features: adequate skin permeability, adequate skin acceptability and adequate clinical need. To be specific, it can be discussed in detail as under:

A. Adequate skin permeability

- Medicaments with small molecular weight
- Medicaments with short melting point
- Medicaments with reserved oil and water solubility
- Potent Medicaments

B. Adequate skin acceptability

- Non-irritating Medicaments
- Non-metabolizing Medicaments

C. Adequate clinical need

- Require to extend administration
- Need to decrease side effects on target tissues
- Necessitate increasing patient fulfillment.
1.4. SKIN

1.4.1. Structure

It is the heaviest sole organ of body which divides the internal body structure from external environment. For an average 70 kg human with skin surface area of 1.8 m², a typical square centimeter 12 nerves, covers 10 hair follicles, 100 sweat glands, 15 sebaceous gland and 3 blood vessel with 92 cm total length [Prausnitz M R et al., 2008]. The skin has numerous functions, which can be summarized as follows.

1.4.2. Functions of skin

- **Safeguard** – It gives protection from attack by microorganisms, chemical agent and physical agent (e.g., UV light, mild shock), drying out.
- **Reaction** – It occurred owing to stimuli from sensory nerves.
- **Control temperature of body** – It maintains temperature of about 98.4°F (36.8°C) with deviation of 0.5°C - 0.75°C.
- **Vitamin D Formation** – It is produced due to oily material contain in human skin, 7-dehydro cholesterol, It converted to vitamin D in occurrence of UV light.
- **Absorption** – It absorbed toxic chemical like mercury and few drugs having low molecular weight.
- **Secretion** – It excreted urea urinary excretion, sodium chloride in sweat. [Vyas S P et al., 2005 & Shankar M S et al., 2010].

Now, it’s important to understand the structure of skin so as to understand the concept related to permeation of drugs.
Figure No. 1.1: Cross section of skin
1.4.3. **Structure and Composition of skin**

The skin consists of distinct three Layers but jointly reliant layers.

A. Epidermis (a vascular and stratified)

B. Dermis (connective tissues)

C. Hypodermis

![Diagram of human skin different cell layers](image)

**Figure No. 1.2:** A diagram of human skin different cell layers
A. Epidermis

The enclose of the epidermis differ into width, depend on amount of cell layers, varying from palms and soles on the eyelids. Outermost layer of Epidermis are stratum corneum and rest of part called viable epidermis comprise four layers covered a major part of skin.

I) Stratum corneum

The outermost skin layer also called as Horney layer. It is approximate 10mm thick. The stratum corneum is the main barrier for diffusion. The nature of barrier depends on its ingredient 75-80% proteins and 5-15% lipids on a dehydrated weight basis. Protein portion mainly include alpha-keratin (70%) with a little beta keratin (10%) and cell packet (5%). Lipid ingredients differ with body spot. Phospholipids are mostly not present, an exceptional characteristic of mammalian film. The structural design of Horney skin may be replicated as a wall-like. Keratinize cell role proteins “bricks” surrounded within fatty material “mortar.” The fatty material is set into numerous bilayers and it is recommended to near be enough amphipilics substance into fatty material portion, for example glacial liberated fatty acid with cholesterols, toward preserve bilayer form.

II) Feasible Epidermis

These are located under the stratum corneum and vary in wideness from 0.06mm on eyelids and 0.8mm lying on palms. Going inwards, it consists of a variety of four layers as stratum lucidum, stratum granulosum, stratum spinosum, germinativum layer and the stratum basale. Within basale coat, mitosis of the cells always renovates the Epidermis and these productions reimburse the loss of dead Horney cells from the skin surface. As the cells formed via the basale layer go on the outside they change morphological as well as histochemical, go through keratinizations shape to remotest cover of stratum corneums. Complete replacement of epidermis takes 40 days [Amnuaikit C. et al., 2005].
B. Dermis

Dermis is 3 to 5mm wide film with compiled of a mold of connectives tissues, which includes nerves, blood vessels as well as lymph vessels. The cutaneous blood provides has vital role into body temperature controlled. In addition supply nutrient with oxygen’s skin with eliminates poisons and squander products. Capillaries arrive at to in 0.2 mm of skin face and give be submerged situation for nearly all molecules go through the skin member. The blood provides therefore remains the dermal concentration of diffuse very small, the resulting concentration variation transversely the epidermis supply the necessary powerful force for transdermal penetration [Verma P R P et al., 2000].

C. Hypodermis

It maintains the epidermis with dermis. It provides storage of fats to space region. These levels assist toward control temperatures, supply support of nutritional in addition to mechanical safety. It transmits standard blood vessel and nerve toward skin and might include sensory force organ. For transdermal patch release drug have toward go through three layer and reached into complete movement even as in case of topical drug release only diffusion throughout stratum corneums is necessary and afterward maintenance of drugs in human skin layer is needed [Biswajit M et al., 2005].

1.5. Permeation pathways through skin

It includes passive transmission of the materials throughout the human skin. The particle might employ two transmission way to go through ordinary whole skin. There are two routes Appendageal route and the epidermal route shown Figure no.1.4 [Rakesh P et al., 2009].

1.5.1 Appendageal route

The usual human skin includes 50-80 hair follicles with 210-260 sweat ducts per square centimeter. Especially hydrophilic substances pass faster through these ducts; still these ducts don’t contribute much for skin permeation.
Therefore, most neutral molecules pass through stratum corneum by passive diffusion. Thus, the stratum corneums act passive, but never inert, transmission mediums. Sequence of step in series:

- Penetrates Sorption particle on exterior layer of stratum corneum.
- Finally, permeate through it with feasible epidermis.
- The molecules are full up into the micro-circulation for complete release.

Appendageal route include move through sweat glands and hair follicles with their related sebaceous glands. These pathways avoid diffusion via the stratum corneum and thus known as “shunt” routes. Otberg illustrate follicular digit, follicular volume with aperture diameter are significant. Remarkable, the similar study also explained the historically seized vision of the follicles provided that approximately 0.1% of the surface area of the stratum corneum comes into views to be valid for forearm skin [Krishna R et al., 1994].

Figure No. 1.3: Routes for drug permeation
1.5.2. Epidermal route

The medicaments, which mainly cross-whole Horney stratum, two probable small way of entrance exists, the transcellular and intercellular pathways shown Fig. 1.4

Figure No.1.4: Pathway for drug diffusion by transcellular and Paracellular route
A. Transcellular

Transcellular path indicates transfer of particles across epithelial cellular membrane. Transcellular way needs not only separating diffusion through the keratin bricks but also across the Paracellular lipids. Therefore the intercellular lipids participate in barrier character of the Subcutaneous. The function of lipids in the barrier has been examined via penetration studies using lipid removed Subcutaneous. Skin porosity to water was importantly raised after eliminating skin lipids. Additional the penetrability of skin from unusual body spots can be associated to entire lipid content. Consequently the intercellular path is extensively considered as major method of penetration of nearly all composites even though the comparatively tiny exterior area accessible for this route [Carmelo P et al., 2008].

B. Paracellular

These pathway mean transfer of molecule just about or involving the cells. Fixed junction or parallel situation is present involving the cell. The main path in use by infuse is determined mostly through the partition coefficient. Hydrophilic medicaments particle screen into the transcellular area, while lipophilic saturate pass through the stratum corneum through the Paracellular way. Mainly infuse the stratum corneum with both paths. On the other hand the twisty Paracellular way is extensively measured to supply the main route and main barrier to the penetration of nearly all drugs [Gye J R et al., 1999].
Figure No. 1.5: Free drug diffusion mechanism
1.5.3. Properties that affecting percutaneous absorption

When we apply a preparation topically, the experimental results occur following sequential procedure:

• liberate the drug from the medium
• diffusion through the skin barrier
• Pharmacological reaction activates.

Effective therapy optimizes these steps as they are affected by three components – the drug, the vehicle and the skin. To discuss this complicated process we review the material under headings of biological factors and physicochemical factors. However, because percutaneous absorption is a dynamic process, if one variable changes, it usually causes several effects on drug flux [Kydonieus A.F et al., 2000].

1.5.4. Physiological factors

I. Age of Skin
II. Condition of Skin
III. Skin situates region
IV. Skin Biotransformation
V. Systemic result
VI. Species variation

I. Age of Skin

Adults’ skin is less permeable than fetus, young and elderly. Most probably Children prone to the lethal effects of medicines and chemicals, moderately as of their large exterior part per unit body mass; strong superficial steroids with Hexachlorophene comprise produced rigorous side effects.

II. Condition of Skin

The undamaged skin is a hard layer but lots of agents harm it. Solvents such as acids and alkalis injures cells membrane and thus help penetration, through cuts, roughs and dermatitis. Solvents such as Dimethyl Sulphoxides (DMSO), Dimethyl Acetamide (DMA), and Dimethyl Formamide (DMF) may
be employed clinically to potentiate drug absorption, Disease also responsible to alter skin condition.

III. Skin situates region

Difference in subcutaneous penetrability bases on the breadth and character of the stratum corneum, the mass of skin appendages, examination produce unusual for the penetrability spots of skin; for easy little molecules, the permeation reduces in the sort: Plantars, palmars, dorsums of hand, scrotals, post auriculars, axillary, scalps, arms, legs, and trunks.

IV. Skin Biotransformation

It metabolites to steroid hormones, chemical carcinogens and drugs such metabolism can decide the remedial effectiveness of the topically apply composite (mainly Prodrug) and the carcinogenic reaction in the skin.

V. Systemic result

Hypothetically, alters in the peripheral movement might influence percutaneous absorption, an enhanced blood flow might decrease the time a penetrant stays in the dermis and also move up the concentration gradient transversely the skin. Usually, the effect is negligible.

VI. Species variation

Skin differs generally in features such as horny cover width, sweat gland with hair follicle mass and skin condition. Such feature influences the directions of diffusion and the struggle to penetration. Relative studies on skin penetration point to monkey and swine skins are mainly similar to that of human, bald mouse skin has little similar features.
1.6. Components of transdermal Patches

Transdermal patches have rapidly emerging nowadays. Before 24 years in US the first patents were issued to these methods; today over 100 patents describing transdermal patches have been subjected.

There are three types of Transdermal patches. Adhesives patches, matrix patches and the Reservoir patches. These patches mainly contain:

- Backing layer
- Drug reservoir
- Release control layer (polymer matrix)
- Adhesive and peel strip
- Enhancers and excipients.

1.6.1. Backing layer

It is elastic and it supplies superior link toward drug reservoir, restrict remedy from exit the dosage form through the peak, allow circulate. It is not porous substances those keep the product during apply on the skin. [Bhaskar P. et al., 2004].

1.6.2. Drug reservoir

It is commonly prepared of adhesive and allowed to transfer of active ingredient at a desired rate. The active ingredient must be chosen based on clinical requirement and their physical and chemical characteristics. The attractive feature of an active ingredient for transdermal patches as followed.

I. Physicochemical Characteristics of drug

- It must have a molecular mass less than approximately 1000 Dalton.
- It must have attraction for both Phases hydrophilic and lipophilic.
- It must have a short M.P.

II. Biological Characteristics of drug

- The drug must be strong with a daily dose of the order of a few mg/day.
- It must short half life.
- The drug must Non allergic and non irritant.
• The medicaments demean in the GIT are proper candidates for transdermal patches.

• The medicaments have to administer for an extended period of time can also be formulated for transdermal patches.

1.6.3. Polymers

It controlled the released of an active ingredient through the patches. It must be accomplished the following criteria employed in a transdermal patches.

• Molecular mass, glass alteration temperature and compound role of It must be such that active ingredient circulates accurately and obtain diffused through it.

• It must be not interacted with the medicament, stable, simply fabricated and produced into the desired form as well as cheap.

• It degradation product should be not toxic or non antagonistic to the host.

• It mechanical characteristics should not decline unnecessary when bulky quantity of drug are included into it [Murthy S.N et al., 1995].

1.6.4. Adhesives

All transdermal patches binds to skin surface depend on force susceptible adhesive. It can be located on the features of the patches or in the reverse of the patches and enlarge peripherally. It must fulfill the subsequent criteria;

• It must non-sensitized the human skin or cause a difference in the usual skin flora throughout it get in touch with the skin.

• It must stay to the human skin insistently throughout the dose time lacking its place being concerned by actions such as bath, work out etc.

• It ought to be simply eliminated.

• It ought to not depart an unwashable deposit on the surface of skin.

• It should have exceptional get in touch with the skin surface at macroscopically and microscopically level.

It must perform the following criteria;
• It should have physicochemical stable among the medicaments, excipient and enhancer of the patches.
• Medicaments Permeation should not be influence.
• The release of combine permeation enhancer should not be influenced [Babwale A. D et al., 1994].

Several commonly employ force susceptible adhesive includes acrylcs, polyisobutylenes, and silicone.

1.6.5. Penetration enhancers

The nature of skin less permeability, pharmacy scientist is search for harmless and efficient skin permeation enhancer. Improvement of permeation enhancers is significant to increase small penetrability of drug transversely the skin. Even though numerous permeation improvers are identified, their mechanism of action is still not wholly unwritten. It is agents increases the permeation of the skin or material that reduce impermeability of the skin, The increase speed reason keratin to enlarge and leached out vital structural substance from the stratums corneums, thus decreasing the diffusion resistance and rising the penetrability of drug throughout skin.

1.6.5.1. Desirable characteristics of penetration enhancers

Penetration enhancer’s possess as following characteristics:

• It should not produce any action itself at skin surface.
• It should non- irritating or non-allergenic, non-toxic.
• The start action should be instant; the length of the effect should be expected and suitable.
• It should be physically and chemically friendly with a wide range of medicaments and excipients.
• It should be an excellently suitable for medicaments.
• It should extend fine on the skin surface and be cosmetically acceptable.
• The substance should be good organoleptic properties, inexpensive.
1.7. Technology in the development of TDDS

1.7.1. Transdermal Membrane moderated system

The compartment of drug reservoir, the drug solids are either scattered in a solid polymer matrix, thick liquid medium e.g. silicon fluid. The rate controlling membrane can be micro porous or nonporous polymer membrane e.g. ethylene vinyl acetate co-polymer on the external surface of the polymeric membrane, a skin layer of drug, compatible adhesive polymer may be applied to achieve an intimate contact of TDD system with skin surface.

The permeability coefficient and the breadth rate controlling polymeric membrane can alter drug release rate.

![Diagram of Membrane moderated TDDS]

Figure No. 1.6: Membrane moderated TDDS

1.7.2. Matrix diffusion system

The drug reservoir is prepared by consistently diffuse the active solids in a polar or nonpolar polymers matrix, and then the drug polymers produced is cast into medicated film along with definite surface area and width. These drug reservoirs enclose polymers film is then rise on occlusive’s base coat in a partition made-up from a drug impermeable
synthetic support. As an alternative of outside layer adhesives polymers straight on the surface of drugs film, it is useful beside the boundary of the film to shape a strip of adhesives rim surrounding the medicated disk.

1.7.3. Drug Reservoir grade Controlled TDDS

To increase over the non-zero-order drug discharge profiles polymeric matrix drug dispersion-type TDDS can be modified to have the drug loading level varied in an increment manner, forming a gradient of drug reservoir along the diffusional path across the multilaminate adhesive layers.

Figure No. 1.8: Drug reservoir grade TDDS
1.7.4. Micro-reservoir system

These systems are considered as mixture of reservoir and matrix dispersion types. In this the drug reservoir is formed by first suspending the drug solids in an aqueous solution of water soluble polymer and then dispersing the drug suspension homogenously in lipophilic polymer, by high shave mechanical force to form unleaseable microscopic spheres of drug reservoir. This dispersion is become constant immediately by cross-linking the polymer chains which produces a medicated disc with constant surface area and thickness [Robert L. et al., 1998].

Figure No.1.9: Drug micro reservoir dissolution controlled TDDS
1.8. General clinical consideration in the application of TDDS

The patients should be recommending of the subsequent common procedure. The patient should be given an opinion of the significance of use the suggested place and revolving position inside. A rotary location is significant to permit the skin to recover its usual penetrability and to avoid skin annoyance.

- It must be apply to germ-free, dried out skin completely hair free and not greasy, swollen, annoyed, busted. Wet or humid skin can increase speed drug penetration further than drug time. Greasy skin can damage the bond of film. it should be carefully slice, If hair is present at the site didn’t wet shaved, nor should a depilatory agent be used, since later can take out stratum corneums and influence permeation.

- Use of lotion must avoid at the use place, for the reason that lotions influence the hydration of skin and it can change partition coefficient of medicine.

- Wounding must not actually change TDDS, because these demolish reliability of the system.

- The defensive support should be detached with care not to contact fingertips. The TDDS must be force down tightly beside skin place with the heel of hand for about 10 seconds [Allen L V et al., 2005].
1.9. INTRODUCTION TO DRUG

1.9.1 Indomethacin [Eugene Braunwald., 2005]

Structural Formula:

![Chemical Structure of Indomethacin](image)

**Chemical Name**: 1-(4-Chlorobenzoyl) -5-methoxy -2–methyl–1H - Indole –3–acetic Acid

**Formula**: C_{19}H_{16}ClNO,

**Molecular Mass**: 357.8

**Functional Categories**: Analgesic agent and anti-inflammatory,

**Volume of distribution**: Ranged between 0.034 - 1.57 L/kg

**Clearance from Plasma**: Ranged between 0.044 – 0.109 L/kg/hr
Pharmacokinetics:

Indomethacin has subject to considerable enterohepatic circulation. The major metabolites being dimethyl Indomethacin (DMI), deschlorobenzoyl Indomethacin (DBI), and desmethyl deschlorobenzoylindometacin (DMBI) and their glucuronides these substances, together with unchanged Indomethacin as well as glucuronides it emitted in both urine (up to 60% of the dose during 48 h) and the faces (up to about 30% of the dose in 96 h) in variable amounts. The average amounts excreted in the urine in 48 h are: unchanged Indomethacin 5 to 20% (dependent on urinary pH), Indomethacin glucuronides 6 to 26%, DMI and its glucuronides 8 to 23%, DBI and its glucuronides 4 to 20%, DMBI and its glucuronides less than 3%; in the feces the major metabolites found are DMBI (up to about 16%) and DMI (up to about 12%), with only small amounts of unchanged Indomethacin and DBI.

Dose:

Orally, 50 – 200 mg daily, in divided doses, with food. As suppositories, 100 mg at night and in the morning if required Maximum combined oral and rectal dose, 150 to 200 mg daily [Li D M, 2005].
1.9.2 PIROXICAM

Structural formula

Proprietary name : - Feldene, Feldora, Roxam
Chemical name : - 4-hydroxy-2-methyl-2-(N-pyridinyl)-2H-1,2-Benzothiazine 3 Carboxamide 1 1-dioxide
Molecular formula : - C_{15}H_{13}N_{3}O_{4}S
CAS No : - 36322-90-4
Molecular weight : - 331-346
Functional Categories : - NSAID
Description : - A white off crystalline powder.
Melting point : - 198-200°C
Solubility : - Scantily soluble in water and alcohol.
Storage : - It is store in cool and tightly packed container
Doses : - 20 mg given orally once per day
Half life : - Plasma half–life, about 30 to 60 h,
Increased in elderly subjects
Protein binding : - In plasma, about 99%.
Volume of distribution : - 0.14 L/kg
1.9.3. Ondansetron hydrochloride

Drug class : Antiemetic Proprietary
name : Zophren, Zofran. Molecular formula
: [C18H19N3O, HCl, 2H2O] Molecular weight
: 365.9

pKa : 7.4
Half life : In healthy volunteers 3 hour.
Volume of distribution : In healthy volunteers 2.5 L/kg.
Renal Clearance : In patients 16.6 L/h 15.9 L/h, in healthy volunteers 28.3 L/h.

Blood Distribution : 70 to 75%.
Dose : orally 8 mg for 12 hr. intravenously 4 mg for 12hrs. [United States Pharmacopoeia, 2005]

Uses and administration

- Ondansetron is a 5-HT3 antagonist
- Ondansetron hydrochloride 4.99 mg is approximately equivalent to 4 mg of ondansetron base [K.D.Tripathi, 2004].
1.10. INTRODUCTION TO POLYMERS

1.10.1. Ethyl Cellulose

Structural Formula:

![Structural Formula for Ethyl Cellulose](image)

**Synonyms**: Ethocel, Surelease, E462

**Chemical Name**: [Cellulose ethyl ether]

**CAS Number**: [9004-57-3]

**Empirical Formula**: $C_{12}H_{23}O_6$

**Non Proprietary Names**:

- BP: Ethyl cellulose
- PhEur: Ethyl cellulosum
- USPNF: Ethyl cellulose

**Moisture Content**: Ethyl cellulose take ups small amount of moisture from moist atmosphere or through concentration and that little quantity disappear easily

**Glass Transition Temp**: 129-133°C

**Melting Point**: 240-255°C

**Viscosity**: Various grades of EC are commercially available which differs in their ethoxy content and degree of polymerization.
Stability: steady a little hygroscopic substance chemically opposing to alkali equally concentrated and dilute.

Safety: Non toxic, non allergic and non-irritating

Application in Pharmaceutical Formulation and Technology

- To form modified release tablet formulation.
- Drug encapsulation by high viscosity grade.
- Ethyl cellulose dissolved in an organic solvent or it is also use as to prepared hydrophobic film.
- An aqueous polymer dispersion of ethyl cellulose can be used to produce ethyl cellulose film without the need of organic solvent.
- With coats of hydrated ethyl cellulose drug release is via diffusion.
- Ethyl cellulose also widely used in microencapsulation in tablet it may also be used as tablet binder [Raymond C. Rowe, 2009 & Washington D.C, 2009].

1.10.2 Hydroxy propyl Methyl Cellulose (HPMC) E5, E15

Structural Formula:

Nonproprietary Names: BP: Hypromellose
JP: Hypromellose
PhEur: Hypromellose

USP: Hypromellose

**Synonyms** : Hydroxy propyl methyl cellulose; HPMC; Hypromellose; Methocel; Methylcellulose propylene glycol ether; Methyl hydroxy propyl cellulose; Metolose.

**Chemical Name** : Cellulose, Hydroxy Propyl Methyl Ether

**Molecular Weight** : Molecular weight is 10000–1500 000.

**Functional Category** : Bio adhesive material; controlled-release agent; extended-release agent; film-forming agent; modified-release agent; mucoadhesive; release-modifying agent;

**PH** : 5.0–8.0

**Melting point** : Browns 190–200°C; chars at 225–230°C Glass transition Temperature is 170–180°C.

**Specific gravity** : 1.26 at 25°C.

**Viscosity (dynamic)** : Methocel E15 Premium LV has Nominal viscosity (mPas) 15 for a 1% w/v aq. Solution at 25°C.

**Incompatibilities** : it is non-ionic and mismatched with several oxidizing agent. It will not composite with ionic organics or metallic salts to produce insoluble precipitates.
Stability & Storage Conditions:

- Hypromellose powder is stable, hygroscopic after drying and Solutions are stable at pH 3–11.
- After heating and cooling it undergoes to produce reversible sol–gel transformation respectively.
- The gelation temperature is 50–90°C, base on substance grade and concentration.

Safety:

- Hypromellose is also used in cosmetic product.
- Hypromellose usually consider as a non-toxic and nonirritating substance while extreme oral use may have a laxative effect. (16) In fact, high dosages of Hypromellose are being investigated for treating various metabolic syndromes. [Raymond C.R.2009].

1.10.3 Poly vinyl pyrrolidone K30

Structural Formula:

\[
\begin{align*}
\text{N} & \quad \text{CH} \quad \text{CH}_2 \\
\end{align*}
\]

Nonproprietary Names : BP: Povidone  
JP: Povidone  
PhEur: Povidone  
USP: Povidone.

Chemical name : 1.-Ethyl-2.-pyrrolidinone homo polymer

Empirical Formula : C6H9NO) n
<table>
<thead>
<tr>
<th><strong>Molecular Weight</strong></th>
<th>2500–3000 Molecular weights</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Descriptions</strong></td>
<td>A fine, white to creamy-white colour, odourless or almost odorless, hygroscopic powder.</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>3 to 7</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>4 to 7.0 for Povipharm K90.</td>
</tr>
<tr>
<td><strong>Tapped Density</strong></td>
<td>0.39–0.54 g/cm³ for Plasdone</td>
</tr>
<tr>
<td><strong>True Density</strong></td>
<td>1.180 g/cm³</td>
</tr>
<tr>
<td><strong>Flow ability</strong></td>
<td>16 g/s for povidone K-29/32.</td>
</tr>
<tr>
<td><strong>Melting point</strong></td>
<td>Softens at 150°C.</td>
</tr>
<tr>
<td><strong>Moisture content</strong></td>
<td>Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidity.</td>
</tr>
<tr>
<td><strong>Particle size distribution</strong></td>
<td>Kollidon 25/30: 90% &gt;50 mm, 50% &gt;100 mm, 5% &gt;200 mm;</td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
<td>acids, ketones, and water;</td>
</tr>
<tr>
<td><strong>Viscosity (dynamic)</strong></td>
<td>povidone K-30 Dynamic viscosity (mPas) in Ethanol (95%)</td>
</tr>
</tbody>
</table>

**Stability & Storage Conditions:**

- Povidone darkens to some extent on heating at 150°C with a reduction in aqueous solubility.
- It is stable around 110–130°C;
- Steam sterilization of an aqueous solution does not alter its properties.
- Aqueous solutions are requiring the addition of suitable preservatives.
- Povidone may be stored under ordinary conditions without undergoing decomposition or degradation.
• Povidone should be stored in a cool and dry place

Safety:

• It is extensively employed as an adjuvant in oral formulation.
• It might be considered as non-toxic because it does not soak up from the GIT or mucous membrane.
• It has not caused any annoyance effect on the human skin and there is no reason for sensitization.
• LD50 (mouse, IP): 12 g/kg.

Applications in Pharmaceutical:

• In tablet formulations, solutions are used as binder’s wet-granulation processes.
• Employed as a solubiliser in oral and parenteral products, [Raymond C.R.2009].

1.10.4 Eudragit L 100 (Polymethacrylate)

Structural Formula:

Synonyms:
- Ammonio methacrylatis copolymerum; copolymerum methacrylatis butylati basicum; Eastacryl; Eudragit; Kollicoat MAE; polyacrylatis dispersion 30 per centum; polymeric methacrylate.

Chemical Names:
- Poly. [methacrylic acid and methyl methacrylate] 1:1
- Eudragit L 100 Evonik Industries
CAS Registry Number : [25806-15-1]

Empirical Formula : For Eudragit L: R1, R3 = CH₃; R2 = H; R4 = CH₃

Molecular Weight : The molecular weight of the polymer is 5100 000.

Functional Categories : Film-forming agent; tablet binder; tablet diluent.

Typical Properties

Acid value : 300–330 for Eudragit L 100,

Alkali value : 162–198 for Eudragit L 100;

Bulk Density : 0.390 g/cm³

Tapped Density : 0.424

True Density : 0.831–0.852 g/cm³ for Eudragit L 100

Refractive index : 1.39–1.395 for Eudragit L 100

Solubility : Eudragit L 100 is soluble in Acetone and alcohols and also in 1N NaOH, insoluble or immiscible in Dichloromethane, Ethyl acetate, Petroleum ether and Water.

Viscosity (dynamic) : 50–200 mPa s for Eudragit L.

Stability and Storage Condition:

- It is stable at temperatures less than 308°C in dry powder polymer forms. If temperature is more, it tends to formed mass even though this does not influence the value of the material and the mass can be readily broken down.
Incompatibilities:

- It occurs with Poly methacrylate dispersions base on the ionic and physical characteristics of the polymers and solvents.
- Interactions between Poly methacrylate and several active substances can occur, even though solid Poly methacrylate and organic solution are usually more compatible than aqueous dispersions.

Applications into Pharmaceutical:

- Poly methacrylate polymer might moreover be employing to form the matrix layers of transdermal patches and have also been use to form new gel formulation for rectal administrations [Raymond C.R.2009].

1.10.5 Eudragit RLPO

Eudragit RLPO is copolymer of methyl methacrylate.

Chemical structure

![Chemical structure of Eudragit RLPO](image)

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Poly (methyl methacrylate, ethyl acrylate, trimethylammonioethyl methacrylate chloride) 1: 2: 0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS .No</td>
<td>33434-24-1</td>
</tr>
<tr>
<td>Category</td>
<td>Film-forming agent; tablet binder; diluents.</td>
</tr>
</tbody>
</table>
Alkali value : 23.9–32.3 for Eudragit RL PO

Density (bulk) : 0.390 g/cm³

Density (tapped) : 0.424 g/cm³

Density (true) : 0.816–0.836 g/cm³

Solubility : Soluble in acetone, alcohol, dichloromethane and ethyl acetate.

Refractive index : 1.38–1.385

Viscosity (dynamic) : 415 mPas

Stability and storage conditions : It is stable at temperatures less than 30⁰C in dry powder polymer forms. If temperature is more, it tends to formed mass even though this does not influence the value of the material and the mass can be readily broken down.

Incompatibilities: It occurs with Poly methacrylate dispersions base on the ionic and physical characteristics of the polymers and solvents

Applications in pharmaceutical:

➢ The Poly methacrylate polymer might moreover be employing to form the matrix layer of transdermal patches and have also been employing to form new gel formulation for rectal administrations [Raymond C.R.2009].
1.11. Introduction to Plasticizer

1.11.1. Di butyl phthalate

Synonyms : butyl phthalate; DBP

Structure:

Chemical name : Dibutyl benzene 1, 2-dicarboxylate

Empirical formulation : C_{16}H_{22}O_{4}

Molecular weight : 278.3

Functional category : film former; plasticizer; solvent.

Description : Dibutyl phthalate is an odorless, colorless, oily and viscous liquid.

Density : 1.045 g/cm³ at 2⁰C

Boiling point : 340 °C

Solubility : in ether acetone, ethanol, benzene, [Raymond C.R.2009].
1.11.2. Polyethylene glycol 400

Structural formula:

CAS registry number : [25322-68-3]
Synonyms : Carbowax; Carbowax Sentry; Lipo; Lipoxol; Lutrol; PEG; Pluriol E; Polyoxyethylene glycol.
Empirical Formula : HOCH₂(CH₂OCH₂)ₘCH₂OH where \( m \) represents the average number of oxyethylene groups.
Molecular Weight : PEG 400 has 8.7 m value & avg Mol.Wt. 380-400
Functional category : Ointment base; plasticizer; solvent; suppository base.
Density : 1.11–1.14 g/cm³ at 25°C for liquid PEGs
Flash point : 238°C for PEG 400
Freezing point : 4–8°C for PEG 400
Refractive index : \( n_{25}^D = 1.465 \) for PEG 400
Surface tension : Approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols
Viscosity (kinematic) : 6.8–8.0 [mm²/s (CST)]
Safety:

- However, the toxicity of glycols is relatively low.

- Polyethylene glycols administered topically may cause stinging especially when applied to mucous membranes.

- Liquid polyethylene glycols absorbed when taken orally but the higher-molecular-weight polyethylene glycols are not significantly absorbed from the gastrointestinal tract. [Raymond C.R.2009].

1.12. INTRODUCTION TO PENETRATION ENHANCERS

1.12.1 Dimethyl sulfoxide

Synonyms : DMSO

Functional category : penetration enhancer

Empirical formula : (CH₃)₂SO

Molecular weight : 78.13

Description : available as colorless liquid

Density : 1.1004 g/cm³

Boiling point : 189 °C

Refractive index : 1.479

Solubility : Totally soluble in water, light alcohols and diethyl ether [Raymond C.R.2009]
1.12.2 Oleic acid

Structural formula

![Structural formula of Oleic acid](image)

Nonproprietary names : BP: Oleic acid  
PhEur: Acidum oleicum  
USPNF: Oleic acid.

Synonyms : Crodolene; Crossential 094;

Chemical name : \((Z)-9\)-Octadecenoic acid

CAS registry number : [112-80-1]

Empirical formula : \(\text{C}_{18}\text{H}_{34}\text{O}_{2}\)

Molecular weight : 282.47

Category : Skin penetrant

Description : A yellowish to pale brown and oily liquid with characteristic lard like odor and taste. Oleic acid consists chiefly of \((Z)-9\)-octadecenoic acid together with varying amounts of saturated and other unsaturated acids.

Acidity/alkalinity : pH = 4.4 (saturated aqueous solution).

Auto ignition temperature: 363 °C

Boiling point : 286 °C

Flash point : 189 °C.

Refractive index : \(n^2_D = 1.4585\).
Solubility: miscible with chloroform, benzene, ethanol (95%), ether, hexane, and fixed and volatile oils; practically insoluble in water.

Vapor pressure: 133 Pa (1 mmHg) at 176.5 °C.

Viscosity (dynamic): 26 mPa s (26 cP) at 25 °C.

Stability and Storage Conditions:
- On exposure to air, oleic acid darkens in color, gradually absorbs oxygen, and develops a more pronounced odor.
- At atmospheric pressure, it decomposes when heated at 80–100 °C.

Incompatibilities:
- Incompatible with aluminium, calcium, heavy metals, iodine solutions, per chloric acid, and oxidizing agents.
- It reacts with alkalis to form soaps.

Safety:
- In vitro tests have shown that oleic acid causes rupture of red blood cells (hemolysis), and intravenous injection or ingestion of a large quantity of oleic acid can therefore be harmful.
- The effects of oleic acid on alveoli and buccal epithelial cells in vitro have also been studied.
- Oleic acid is a moderate skin irritant therefore it should not be used in eye preparations.
- An acceptable daily intake for the sodium, calcium, and potassium salts of oleic acid was not specified by the WHO since the total daily intake of these materials in foods was such that they did not pose a hazard to health.
  \[\text{LD}_{50} \text{ (mouse, IV)}: 0.23 \text{ g/kg} \]
  \[\text{LD}_{50} \text{ (rat, IV)}: 2.4 \text{ mg/kg} \]
  \[\text{LD}_{50} \text{ (rat, oral)}: 74 \text{ g/kg} \text{ [Raymond C.R.2009].}\]
1.13. Statement of the problem

Transdermal patches delivery is novel class systems, which are growing worldwide accolade, as proofed by the numerous scientific documents being distributed. They have been used to administer the drug, which undergo hepatic biotransformation by administrated orally, those which have a small half life, and undergo degradation on passage through gastrointestinal tract, or not well absorbed from gastrointestinal tract.

Transdermal patches delivery for drug administration is restricted by the barrier characteristic of the skin. Simply potent drug with small each day dose and suitable physicochemical features are candidates for drug delivery. The permeation enhancers can be used that increases the permeability of the skin.

Hence present study intended towards the development of transdermal patch using hydrophilic polymers as solubiliser and hydrophobic polymers as release retardants and the permeation enhancers to increase the permeability of drug. Also the attempt is to be made to study combination of polymers through other development approach to generate synergistic effects in the improvement of drug permeability.
The present study was objective at:

- The various hydrophilic polymer and hydrophilic polymer combination in demonstrating the ability to show useful permeability of drug.
- Design, development and characterized of cost effective formulation that does not required the use of costly polymers and permeation enhancers.
- Investigating the influence of pharmacotechnical properties of combination polymers and permeation enhancers that will subsequently employed within formulation of TDDS.
- Evaluate physical parameter of different formulations and study efficiency of combination polymer with permeation enhancers on diffusion studies of active ingredients.
- Evaluate the influence of combination polymers and permeation enhancers on the release profile of drugs and stability at various temperature and relative humidity.
1.14. LITERATURE REVIEW

- Ahad Hindustan Abdul et al., [2010]; had developed *Ficus carica* fruit mucilage matrix type transdermal patches of Indomethacin by the solvent evaporation technique. In this study shown *Ficus carica* proportion increased, it controlled drug diffused.

- Cordero J. A. et al., [1997]; carried out a comprehensive study of transdermal penetration of NSAIDs such as Aceclofenac, Diclofenac sodium, Ketorolac, Ketoprofen, Indomethacin, Piroxicam, and Tenoxicam. They have determined the permeability’s of NSAIDs to calculate their feasibility for transdermal therapeutic system.

- Pandey S et al., [2000]; prepared different transdermal Nimesulide gels using HPMC, sodium CMC, sodium alginate, and methylcellulose. Diffusion studies of formulation were performed by dialysis membrane. The release pattern of drug from the marketed gel was found to be better than from other gels, the reason may be that the 66% alcohol content of the gels that might have enhanced the solubility of the drug.

- Mandal S.C. et al., 1991]; have reported Ethyl cellulose, Eudragit, Polyvinyl alcohol and Polyvinyl Pyrrolidone as polymer to formulate matrix type transdermal devices of Diazepam, which were then subjected to in-vitro evaluation.

- Manvi F V et al., [2003]; formulated transdermal films of ketofen fumarate using combination of eudragit L100: hydroxyl propyl methylcellulose and ethyl cellulose: hydroxyl propyl methyl cellulose as polymers along with permeation enhancers such as propylene glycol and dimethyl sulfoxide. Polyethylene glycol was used as a plasticizer. It was found that there was decrease in drug release rate from EL100:HPMC films in comparison to EC:HPMC was found, due to the hydrophobic nature o the polymer.

- Ubaidulla U et al., [2007]; developed a matrix type transdermal patches containing drug with polymeric combinations by the solvent evaporation technique and reported that increased effectiveness of drug by using different polymer ratio.
- **Gattani S.G et al., [2007]**; investigated transdermal films of chlorpheniramine maleate using different polymer combinations and concluded that hydrophilic polymer showed higher release than the lipophilic and hydrophilic-lipophilic combination.

- **Shankar V et al., [2003]**; investigated ethyl cellulose films for the permeation of the Nifedipine drug through the film by using castor oil and plasticizers as glycerol. It was found that the drug release from the patches containing the glycerol as the plasticizer was more than that from the one containing castor oil.

- **Agrawal S.S et al., [2007]**; developed matrix type transdermal patches of atenolol and metoprolol using polymers like polyvinyl pyrrolidone, hydroxyl propyl methyl cellulose, cellulose acetate phthalate. The results obtained showed drug release from the formulation containing PVP and HPMC was for 48 hour and it caused no irritation on the skin.

- **Panchagnula Ramesh et al., [2001]**; in these studied determine the flux of transdermal patches of naloxone by using combination of permeation enhancers. Increased the concentration of ethyl alcohol with propylene glycol flux was maximum.

- **Panigrahi, L et al., [2002]**; in these studied the pseudo latex transdermal patches incorporation Terbutaline sulphate was prepared as an effective mode of therapy for nocturnal asthma using Eudragit RS 100 and RL100 and eudraflex as a plasticizers.

- **Jain S. et al., [2003]**; studied the effective transdermal patches of Norgestrel. They concluded that the protransfersomes formulation for transdermal drug delivery of Norgestrel provides effective contraception. Higher entrapment efficiency, Better stability, good for transdermal patches as compared to prolipoprotines.

- **Brown Marc. Et al., [2004]**; in these worked, investigated flux by used various penetrant, the maximum amount of penetrant retained on skin surface show the maximum flux.
Murthy S. Narasimha et al., [2004]; in these research to developed transdermal patches by used natural and semi synthetic polymers. Natural polymer shown better results at low pH than high pH.

Parikh Darshan K. et al., [2005]; in these investigation, determined the penetration of fluoxetine, transdermal patches showed maximum penetration of active ingredient. On the bases of result concluded, fluoxetine is suitable for transdermal patches.

Mesih Mounir S. et al., [1995]; in these research worked determined the diffusion and partition characteristics of ethylene vinyl acetate with CPM. Ethanol showed maximum diffusion with CPM.

Obata Yasuko et al., [2010]; in these studied, hydrogel was prepared by using suitable active ingredient and determined all parameters. On bases of result concluded active ingredient is suitable for transdermal patches.

Ammar H.O. et al., [2006]; in these studied included preparation of aspirin in various topical bases. Diffusion results exposed adequate drug release of hydrocarbon gel. Penetration results exposed maximum permeation. Combination of alcohol and propylene glycol explained highest enhancing result.

Olivier J.C. et al., [2003]; in these worked compared diffusion study of Nicorette patches with Nicopatch. Reducing tidy patches surface area guide not only to a decreased of saturated amounts, but also decreased the permeation rates.

Feldstein M.M. et al., [1996]; in the worked compared hydrophilic polymer TDDS with hydrophobic TDDS, both followed zero-order release kinetics from the matrix type transdermal patches.

Lin Senshang, et al., [1993]; in these research worked prepared transdermal of Nicotine, which reduces withdrawal symptoms and provided good support to smokers in smoking termination. This nicotine transdermal patches shown constant permeation rate across human and hairless rat skin which are similar to the steady-state permeation rates achieved.
Thacharodi D. et al., [1996]; in these worked to developed transdermal patches of Nifedipine by collagen, for rate-controlling membrane used as chitosan. Drug reservoir made from alginate to improve stability. Here suggested that drug release is capably restricted by the rate-controlling membranes.

Lee Philip J. et al., [2006]; in these worked to studied the effect of different chemical permeation enhancers on transdermal patches of Lidocaine. The combinations of permeation enhancers improve permeation rate of active ingredient.

Lipp Ralph et al., [2002]; in these studied to investigated polyacrylate-based matrix transdermal patches of antiestrogen. It was shown antiestrogen can be employed as Transdermal patch with combination permeation enhancer PG with lauric acid.

Farinha Ascensao et al., [1997]; in these worked compared nicotine transdermal patches available in markets there was no variation occurred between diffusion studies attained by the different analysis methods for each patch.

Qvist Michael H. et al., [2002]; in these worked investigated, the diffusion rate was depend on enhancers not on polymers. High diffusion coefficient of enhancers are responsible for diffusion rate

Mitragotri Samir et al., [2009]; in these reviewed, mentioned chemical mixtures provided synergistic effect to increased skin permeation. It contains mixture of solvent, micro emulsions, vesicle of complex self-assembled, complex of inclusion and eutectic mixtures.

Jia Zan et al., [2005]; in these studied shown Tween-80 and sodium dodecyl sulphate enhanced solubility as well as release rate of active ingredient in hydrophobic transport areas. Sodium dodecyl sulphate provides stable transdermal Patch than Tween-80. The rate was improved and decreases the entrapment of active ingredient within the skin.
- **Babu R.J. et al., [2005]**; in these studied, prepared reservoir type transdermal patches of bupranolol. The rate of permeation increased due to penetration enhancers of bupranolol patches.

- **Kalai Yogeshvar N. et al., [2001]**; in this reviewed they described the hypothetical ideology employed to explained diffusion of transdermal. It also demonstrates quietly easy barrier transfer model support on suitable result to give details medicament releases kinetic in this composite natural barrier.

- **Lin Shan Yang et al., [1995]**; in these studied, The effect of Piroxicam on the physical properties the results demonstrated that the release rate of Piroxicam from film Cleary increase with the amount of drug loaded but only slightly enhanced by the increasing the plasticizer concentration.

- **Williams Adrian C. et al., [1995]**; in this reviewed many composites had estimated for diffusion improving action, included Sulphoxides (dimethyl sulphoxide), alcohol and alkanols, surfactants, pyrrolidone, terpenes, glycol and Azone.

- **Mukherjee Biswajit et al., [2005]**; in these studied, developed dexamethasone transdermal matrix type patches. The Poly vinyl Pyrrolidone and ethyl cellulose are better suitable than Poly vinyl Pyrrolidone and Eudragit for the preparation of dexamethasone transdermal patches.

- **Rajesh K et al., [2006]**; in this worked, transdermal patches of salicylic-acid prepared combination polymer MC and HPMC with caraway oil demonstrated controlled releases than any other polymer. Relative studies proved that there is twofold increases permeation of drug.

- **Das M K et al., [2006]**; in these studied, prepared pseudo latex Trazodone HCL transdermal patches. The application of triethyl citrate in patches influenced penetration characteristic of Trazodone HCL.

- **Shivaraj A et al., [2010]**; in these worked, transdermal patches of matrix-type includes Ketoprofen fumarate with various ratio polymers combination was prepared and the release mechanism was diffusion mediated. It showed Higuchi kinetics.
Shankar M. S et al., [2010]: in this studied, carrageenan induced edema was reduces 91% on the bases of these results Aceclofenac is suitable candidate for transdermal patches.

Krishna R et al., [1994]: in this study, collective infused crossways hair free skin of rat was maximum in R1, moderate in R2 and low in R3. Enhance the breadth of EVA lead to more retentions of drug in patch and matrix-type release was shown R1 film. it followed zero order kinetics with patches R2 and R3

Rakesh P. et al., [2009]: in these study, the solvent evaporation technique employed to developed matrix type transdermal patches used combination of polymers Aceclofenac as active ingredient. The optimized batch showed maximum diffusion and gave highest permeation of active ingredient.

Garala Kevin C et al., [2009]: in the present worked, UV-visible spectrophotometer was employed to determined the concentration of diffused drug. The sustained release of drug showed transdermal patches contain high concentration of ES.

Puglia Carmelo et al., [2008]: in these worked, the atenolol transdermal patches showed the steady-state plasma concentration of percutaneous absorption within the drug beneficial range. On bases of that recommended atenolol transdermal patches could be possible.

Gye Ju Rhee et al., [1999]: in an attempt showed, Ketoprofen oleo-hydrogel preparation was more valuable than conventional product in improving transdermal penetration of Ketoprofen. The correlation between Invitro and In vivo parameter was good.

Santoyo S. et al., [2000]: in this investigation they worked on various permeation enhancers for transdermal patches of piroxicam. The most effective enhancement shown by Oleic acid

Cheong Hyun-Ah et al. [1995]: in these worked, formulated transdermal patches of Piroxicam and study effects of penetration enhancer on permeability of skin.
- **Gattani S G et al. [2010]**: In these investigations, transdermal films of chlorpheniramine maleate using different polymer combinations and concluded that hydrophilic polymer showed higher release than the lipophilic and hydrophilic-lipophilic combination.

- **Kim Mi-Kyeong et al. [2001]**: In these works, transdermal patches of reservoir-type containing testosterone were prepared with co-solvent. The skin penetration rate of testosterone shows insignificant effect with desirable rheological characteristics.

- **Amos Nussinovitch et al. [2009]**: In this work, determined the effect of plasticizer on mechanical properties patches. The addition of plasticizer reduces tensile strength and reduces in peeling force.

- **Shravani P et al. [2010]**: In this studied, it has been demonstrated that fulvestrant can be administered through transdermal application with predetermined targeted release. Transdermal patches were prepared, using reservoir concept. The data obtained from *Invitro* skin permeability studies is fitted with kinetic models to determine drug release mechanism. These preliminary studies can lead to further studies to evaluate the formulations to achieve therapeutic levels by conducting in vivo also.

- **Thatikonda Saritha et al. [2012]**: In these worked, selegiline contained transdermal patches of reservoir type was formulated with combination of polymers by solvent casting method. The optimized batch shown penetration of drug increases by release mechanism and it followed Higuchi's model kinetics.

- **Prodduturi S et al. [2009]**: In this worked, transdermal patches of fentanyl was prepared with reservoir concept and determined the permeation rates as well as age of patch there was no alteration occurs in these parameters.

- **Chinna reddy palem et al. [2010]**: In these worked, prepared felodipine bilayer patches shows release of felodipine was zero order and controlled by secondary layer of eudragit RLPO.
Madishetti S.K et al. [2010]; in this studied, prepared domperidone bilayered transdermal therapeutic systems which shows required flux and suitable mechanical properties.

Calpena A.C et al., [1994]; in this studied, relative studied of Invitro transdermal permeation of drug that was used in treatment of nauseas and their use in patients receiving oncogenic treatment with chemotherapy. They studied permeation parameters of Antiemetic regulate to calculate their possible beneficial preparation in TDDs.

Elvira et al., [2003]; in this studied, transdermal penetration of diclofenac sodium used different liquid formulations. They have reported that there is no skin irritation with the inclusion of permeation enhancers like oleic acid. They suggested that transdermal patches of diclofenac sodium with permeation enhancers like d-limonene and oleic acid can an efficient for dermas & sub dermal.

Gwak H.S. et al., [2003]; in this worked, developed transdermal patches of Ondansetron using Duro-Tak 87-2196 & Duro-Tak 87-2100 as pressure sensitive adhesives (PSA). Effect of vehicles, PGMC, DGME, propylene glycol (PG) co solvent with 3% oleic acid, was studied & found that increased concentration of its decreased diffusion rate. Also as amount of PSAs increased and the permeation flux was decreased.

Gwak H.S. et al., [2004]; in this studied effects of vehicles and permeation enhancer on transdermal delivery of Ondansetron across dorsal hairless mouse skin. Among medium use, ethyl alcohol & water demonstrated maximum penetration diffusion. The maximum diffusion was attained of D-G-M-E combinations with P-G-M-C & ethanol (80:20) and PGMC & P-G enhanced penetration more correspondingly match up to P-G-M-C alone.

Kale et al., [1996]; in this worked have studied the Preformulation stability and Permeation of Transdermal patches of Salbutamol. The study involves screening a suitable enhancer for the drug. The affects of Lauryl alcohol and Tween 80 was reported to be less but the oleic acid and Sodium lauryl sulphate to be greater extent could enhance the permeation of Salbutamol.
sulphate.

- **Gattani S G et al. [2006]**; in this research formulated transdermal films of anti-emetic drug by using different hydrophilic and lipophilic polymers. In vitro results obtained showed that hydrophilic polymers had higher release than the lipophilic and hydrophilic-lipophilic combination. Permeation enhancers like oleic acid, limonene were found to give favourable permeation enhancement.

- **Suryadevara P.K. et al. [2010]**; in his work prepared matrix type transdermal patches of ondansetron HCl by combination of polymer (PVP:PVA, 5:5) & oleic-acid 10% was use as a penetration enhancers shows 76.69% drug release in 10 hr.

- **Yellela S.R. et al., [2009]**; formulated patches containing EVA1802 membranes as rate controlling membrane which contain chosen concentration of PEG-6000 were formulated & employed for In-vitro penetration study from Nerodilol base reservoir system shows release maximum of PEG-6000.