Introduction

Transdermal route of administration has become more valuable in recent time because it avoids hepatic first pass metabolism and maintains plasma concentration throughout the treatment, thereby decreasing the dosing frequency and reducing gastrointestinal irritation resulting in improved patient compliance. Easy removal of patch at any time from the target site will terminates the treatment preventing the chances of overdose and under dose\textsuperscript{[1-3]}. However, transport of compounds via skin is a considerable challenge due to the complex structure of skin. Therefore, suitable polymer matrix is required through which drug should be release at predetermined rate throughout the treatment. Psyllium husk obtained from the plant of \textit{Plantago ovata} is rich in polysaccharide and uronic acid contents, which renders it the property of making good thin patches. Hence, a polymeric mixture of psyllium husk and HPMC K15M was use as a controlled drug delivery component, but If drug from the transdermal patches neither easily diffuse out nor permeate the different layers of the skin it will not matain the therapeutic level. To improve permeation of drug through the skin permeation enhancers are used they modify the structure of the \textit{stratum corneum} and allow the drug to penetrate into the skin. The natural permeation enhancers available from literature review are essential oils, terpenes, terpenoids, fatty acids, glycols and herbal extracts\textsuperscript{[4-6]}. Essential oils gained more attention from the researchers because they are compatible with a huge range of hydrophilic and lipophilic drugs along with being non-toxic, non-allergic and clinically acceptable\textsuperscript{[7-9]}. Pumpkin seed oil, Linseed oil, and Jojoba oil are the well-known essential oils have higher permeability because it contains unsaturated fatty acids which alleviate the lipid structure of stratum corneum by dekeratinization of corenocytes and increasing the diffusion of drug molecules through the skin\textsuperscript{[10,11]}. Propylene glycol, polyethylene glycol 400 and Dibutyl Phthalate are the commonly used plasticizers. Therefore, all three here optimized and PG was selected based on folding endurance study results. Selective drug candidates, Lercanidipine hydrochloride (LH) and Diltiazem hydrochloride (DH) used in the treatment cardio-vascular disorders like hypertention and angina pectoris, their physicochemical and biological properties makes them
suitable candidates for transdermal drug delivery. A solvent evaporation method used for preparation of transdermal matrix patch due to its ease of manufacturing and the possibility of achieving a higher release and flux of the lipophilic drug loaded matrix as suggested by literature\textsuperscript{[12-15]}. Hence, in this present research work hydrophilic polymeric matrix patches formulated using HPMC K15M and psyllium along with essential oils as permeation enhancers for the controlled drug delivery of antihypertensive agents.

1.1 Transdermal Drug Delivery System

Antihypertensive agents are very potent but due to the extensive hepatic metabolism they lose their potency and required another route of administration. By applying these agents via skin it bypass the hepatic metabolism and also avoid the side effects related to the GI tracts. With the use of suitable polymers and permeation enhancers this route becomes more beneficial for the treatment of several cardio vascular disorders. For the development of transdermal device suitable drug candidate required which having sufficient permeability through the skin\textsuperscript{[16-19]}.

Benefits of TDDS\textsuperscript{[20-23]}

1. It avoids hepatic metabolism and gastrointestinal side effects, such as GI irritation, degradation in GI tract etc.
2. It avoids the risks and inconveniences of parenteral therapy.
3. It minimizes the metabolism of drug and leads to reduces the daily requirement of drug.
4. Its release the drug continuously for longer period, therefore drug have short half life can be used for the development of transdermal device.
5. Its release drug in a controlled manner with predetermined rate and time for a long period, so less chances of over dose and dose dumping.
6. It improved patient compliance by self administration and painless delivery of drug.
7. It offer less friability problems than the other solid unit dosage forms.
8. It is very simple to terminate the treatment by removing the patch from the site of application.
9. Simple formulation required less ingredients so chance of toxicity is less compare to other dosage forms in which complicated formulation required.
10. TDDS systems apply simply by any type of patients as compare to parenteral delivery which needs specialized person and some time hospitalization.

1.1.1 Factors Affecting Transdermal Permeation

Following are the physicochemical and biological parameters which affect on permeation of drug molecules through the different layers of skin.

**Physicochemical Properties of the Penetrate Molecules.**

(1) Log P value

Those drugs have balance of water and lipid solubility can easily penetrate the different layers of skin. If the log P value (partition coefficient) of any drug in between 1 – 4 suggest good permeability through the skin.

(2) pH

pH value of any drug is very much important for the permeation of drug molecules through the skin. If at a skin pH ionization takes place than ionized drug molecules cannot permeate the skin layers. Some drugs with high and low pH values may irritate the skin or damage the outer layer of the skin.

(3) Concentration penetrate molecule

Concentration of penetrate molecule is directly affect the permeation of drug through the skin. According to fix second low of diffusion higher amount of dissolved drug causes increase in flux but if it will not penetrate than act as a reservoir and slowly release the drug for a long period of time. It will help in maintaining plasma concentration and achieve controlled release.

**Physicochemical Properties of the Drug Delivery Systems**

Following physicochemical properties of selective drug candidate directly and indirectly affect on formulation and evaluation of transdermal device.

(1) Release Characteristics
Release of drug from the transdermal device is depending on solubility of drug in to the selected vehicle. If drug having very good solubility than higher amount of drug first dissolved and it is available for diffusion.

(2) Composition of the Drug Delivery Systems

Formulation of transdermal device required suitable composition of polymers and permeation enhancers than only drug will diffuse out from the polymeric matrix and permeate the different layers of the skin. Here it required selection of water soluble and lipid soluble polymers therefore it will maintaining hydrophilic and lipophilic balance and achieve required flux to maintain therapeutic concentration of drug throughout the treatment.

(3) Enhancement of Transdermal Permeation

Normally drug will not easily permeate the different layers of the skin. To achieve requird flux for maintaining therapeutic plasma concentration of the drug up to predetermined period permeation enhancers are added in the transdermal device. Chemical and natural permeation enhancers are used for the improvement of permeation of drug through the different layers of skin.

**Physiological and pathological conditions of the skin**

(1) Outer most horny layer

Thick horny layer will affect the solubility and permeability of drug through the skin. For the fabrication of transdermal device most critical criteria is permeation of drug through the skin, therefore for the development of successful transdermal device thickness of horny layer will also affect.

(2) Hydration of application site

Hydrated skin improves the permeation of drug through the skin. Higher permeation higher will be the skin flux it will leads to achieve controlled release of drug through the skin for long period of time.

(3) Effect of temperature on drug release
Higher temperature improves both solubility and diffusivity of drug through the skin. It will again lead to improve skin flux and improve patient compliance. Due to increase in temperature dilation of vessels occurs it will lead to improve in permeation and absorption of the drug.

(4) Effect of Application Site

Transdermal device can apply on different sites of skin for example near to chest, near to knee joints, arm site etc. But each and every site has different permeation property so it will affect the release pattern of drug through the skin. At the same time some drug like salicylic acid has very good permeation from the forehead and scalp, therefore according to the flexibility of drug and its requirement application site should be selected.

(5) Effect of Some Injury of Skin

Some injury on skin may disturb the structure of stratum corneum and it will either increase or decrease the permeation of drug through the skin. Some well known injury like erythema, edema and some redness on skin may alter the permeation pattern of drug through the skin.

(6) Effect of Capacity Metabolism of Drug By The Skin

Some active molecules have possessed such type of physicochemical properties they will directly metabolized on the skin and loss maximum amount of drug on the site of application. These types of drugs are not suitable drug candidates for the fabrication and evaluation of transdermal devices.

(7) Effect of Blood Circulation

Higher blood circulation at the site of application will improve the permeation of drug through the different layers of the skin. Some tome according to chemical properties of drug it will shows vice-versa.

(8) Effect of Difference Species of Skin

Different skin species have different anatomy of structure, for example same mammalian gland collected from different sources possessed different
anatomical structural properties which show different rate and pattern of drug release through the skin. These properties will also change permeation and absorption of drug through the skin.

**Biological Properties of Drug**

Biological properties of all the active pharmaceutical agents will direct or indirect way affects the permeation of drug. For example drugs’ capacity to binding the plasma protein depends on its physiological and pathological properties.

Uptake of Erythrocyte

Erythrocyte means cell eating process. If maximum amount of drug uptake by the erythrocyte than less amount of drug will available for absorption and it will change the skin flux value as well as controlled release pattern of drug.

Uptake of lipophilic drug occurs on the cell membrane, which is made of lipid. Some drug may be uptake by cells itself when it will enter inside the cell wall.

Absorption property of skin

Some chemical parameters like pH, PKa value, solubility of drug in to the vehicle will change the absorption of drug through the skin. Diffusion pattern like active or passive diffusion also alter the absorption of drug through the skin.

**1.1.2 Criteria for the Selection of Drug Candidate for TDDS**

The proper choice of the drug plays an important role in the successful development of a transdermal product. Various points’ needs to consider during the selection of a drug candidate for TDDS are as follows:

Drug should be very potent (Ideally less than 50 mgs/day) and molecular weight less than 500 Dalton.

Drug must have required solubility in water and lipid (ideally, greater than 1 mg/ml and log p value between 1 to 4.)
Drug saturated solution must have a pH between 5 and 9. Drug should have short half-life. Drug should not metabolize in the skin.

Drug should not irritant and allergic to human skin. Drug should have melting point less than 200°F.

1.1.3 Transdermal Patch

Transdermal patch is the device in which drug will first dissolved into the polymeric matrix and then diffused out and permeate the different layers of the skin. Transdermal route of administration has become more valuable in recent time because it avoids hepatic first pass metabolism and maintains plasma concentration throughout the treatment, thereby decreasing the dosing frequency and reducing gastrointestinal irritation resulting in improved patient compliance. Easy removal of patch at any time from the target site will terminates the treatment preventing the chances of overdose and under dose [31-33]

Figure 1.1: Transdermal Patch

1.1.3.1 Different form of Transdermal Patches

Available different transdermal patches are below explained in detail.

Drug-In-Adhesive type single layer
In this type of patch drug was directly dispersed with the polymers it called adhesive layer. This adhesive layer later attach with release liner and finally attach with backing membrane.

(A) Drug-In-Adhesive type but in multiple layers

As discussed in previous type here instead of one single layer multiple layers were prepared and separate by using simple polymeric membrane. These multiple layers finally attach with release liner at the bottom side and backing layer at the top side.
(C) Drug Reservoir-In-Adhesive

![Diagram of Drug Reservoir-In-Adhesive](image)

**Figure 1.2 (C) Drug Reservoirs – in Adhesive.**

This type of reservoir system mostly prepared for the liquid and semisolid preparation. Here liquid and semisolid mass of the drug entrap into the semi permeable membrane of the skin from which slowly - slowly drug will diffused out and release for a long period of time.

(D) Drug Matrix-In-Adhesive

![Diagram of Drug Matrix-In-Adhesive](image)

**Figure 1.2 (D) Drug Matrix - in-Adhesive.**

In this type of system drug and polymer were dissolved into the common either aqueous vehicle or organic solvent. In to this polymeric solution other ingredients like plasticizers, permeation enhancers added. Then this
polymeric solution casted on a petri plate and after drying this matrix was removed and attach with release liner and backing layer.

1.1.3.2 Components of Transdermal Drug Delivery System

Transdermal patch may include the following components [34 - 36]

![Component of a Transdermal Patch](image)

**Figure 1.3 Component of a Transdermal Patch**

**Backing Material**

Backing material is the outer most layer so It should be flexible and having good tensile strength. Now days as a backing materials polyolefins are widely used, some time biaxial oriented polyethylene film also used as a backing membrane.

**Drug Reservoir**

This layer of transdermal patch containing drug either in a solid or liquid form entrap inside the polymeric matrix. Generally it was composed of organic solvents or silicon fluid. For the preparation of polymeric reservoirs polymers such as ethylene-vinyl acetate copolymer, polyisobutylene, or silicone elastomer or polymer blends such as a polyvinyl alcohol/polyvinyl pyrrolidone blend were used. To improve the permeation of drug from the device chemical enhancers or natural type of permeation enhancers were added. For proper plasticity some time plasticizers are also used.

**Rate-Controlling Membrane**

This rate controlling membrane was used to control the release of drug from the device in a controlled manner for long duration of time. Polymers used in this membrane have micron size pores on the surface from that drug will
diffused out at a predetermined rate and time. To control the release rate of drug through the membrane proper combination of polymers and permeation enhancers were used.

**Pressure-Sensitive Adhesive**

These pressure sensitive adhesive layers give adhesion of patch on the skin. With the help of this layer transdermal device can firmly stick on the skin for long period of time. These adhesive materials should be compatible with the skin because it will adhere on the skin for a multi days also. Long time adhesion may be irritating the skin or some time may alter the structure of stratum corneum. As a adhesive materials in a marketed products polyacrylate, polisobutylene and polysiloxane widely used.

**Release Liners**

Release liner is the last layer which protects the drug adhesive layer from the any type of environmental contamination. Normally polyethylene or polyester coated release liners of silicone were used in the commercial transdermal patches..

**1.1.4 Hypertension** [37-39]

Hypertension is one in which prolonged and persistent elevation of blood pressure occur above the normal range. If it will not control earlier, it can cause severe complication such as stroke, coronary heart disease and kidney failure. Patient who suffers with hypertension must take antihypertensive drug for a long period or until the death. Although these drugs cannot give a radial complete treatment, they can majorly prevent heart failure and acute stroke, which induced by hypertension. Some time a heart specialist can also facing a major problem when the patients on oral antihypertensive do not follow proper drug regimen. In addition, oral antihypertensive therapy has many disadvantages such as extensive first-pass metabolism, unpredictable or low bioavailability, Dose dumping, Sustained toxicity.

Some time it leads to severe cardio vascular diseases and end with patient death. It is dangerous for stroke myocardial infarction patients. If proper
treatment was not avail by the patient slowly it will damage kidney and vascular system. In normal condition our heart behaves as a pump that suction the blood purifies it and finally distributed throughout the body. But in case of hypertension our heart cannot function normally. In case of low blood pressure it become very slow it called diastolic pressure and in case of high blood pressure it works faster than the requirement it called systolic blood pressure. The normal blood pressure reading is below 120 – 80 mm hg, pre hypertension is observed in range of 120 - 80 and 139 - 89 mm Hg and hypertension is observed in a range of 140 - 90 and higher; or some time it may be lied in range of 130 - 80 and higher if patient suffers from diabetes or kidney disease. If readings exceed these limits repeatedly, then doctor diagnosis hypertension. Oral treatment as well as some diet and exercises can treat the hypertension. But oral treatment have several GI side effects, so to overcome those side effects now a day’s transdermal prove as a beneficial route for the treatment of the hypertension.

Figure 1.4 Figure Show Normal Heart Vs Hypertensive Heart
Causes and Symptoms of Hypertension:

For the occurrence of hypertension which are the responsible causes still not found, moreover some common factors such as Smoking, fat, absence of regular exercises, high intake of salt, habit of alcohol, lots of work pressure. It also develop at higher age, genetically transferred from one generation to another generation, some kidney related disease also responsible, adrenal and thyroid disorders may play an important role in the development of hypertension. Suitable diet and regular exercises with some yoga may helpful in the treatment of the hypertension. Healthy working environment as well as stress free life style can also very nicely treat the hypertension[40].
1.2 Introduction of Drugs Used In Present Research Work

1.2.1 Lercanidipine hydrochloride

Description: Lercanidipine hydrochloride is a long acting calcium channel antagonist. Used as a once daily treatment for hypertension. It exerts antihypertensive effect by inhibiting the influx of extracellular calcium across the cell membranes of myocardial and vascular smooth muscle.

Category: Antihypertensive drug,

Therapeutic Classification: Calcium channel blocker,

Kingdom: Organic,

Class: Dihydropyridine

Substructures: Nitro compounds, Enamines, Aliphatic and Aryl Amines, Diphenyl methanes, Heterocyclic compounds, Aromatic compounds, Phenyl propyl amines, Aniline.

Appearance: Light yellow microcrystalline powder

Chemical Name: 2[(3, 3-diphenylpropyl)(methyl)amino]-1,1-dimethylethyl methyl2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

Molecular Weight: 648.1gm/mol

Solubility: Soluble in chloroform and methanol, practically insoluble in water,

Molecular Formula: C36H41N3O6.HCl

CAS Number: 132866-11-6

Trade Name(s): India- Landip-10 Tab, Lerka Tab, Lervasc Tab, Lotensyl Tab, Lotensyl-At Tab,

International- Lercanil, Lercapress, Zanidip, Carbimen, Cardiovasc,

Structural Formula:

![Structural Formula of Lercanidipine hydrochloride](image)

**Figure 1.5: Structural Formula of Lercanidipine hydrochloride**

Dosage and Administration: 10 mg once daily, increase to 20 mg daily after 2 weeks if needed.
Storage conditions: Store it in room temperature.

Pharmacodynamics:
Lercanidipine hydrochloride is used in the treatment of hypertension and angina pectoris. It is used once or twice in a day depends on severity of disease. It may irritate GI mucosa and leads to severe liver disease also.

Mechanism of Action:
Lercanidipine hydrochloride prevents the entry of outer side calcium inside the muscle cell membranes and this decrease in calcium prevent the contraction processes of the myocardial smooth muscle cells which leads to dilation of the coronary and systemic arteries, due to this oxygen delivery to the myocardial tissue was increased and total peripheral resistance decreased. Finally it will decrease the blood pressure.

State: Solid

Indication: Treatment of hypertension and management of angina pectoris.

Experimental properties: Log P - 6.42, pKa-9.36

Pharmacokinetics:
Absorption:
Lercanidipine hydrochloride is absorbed throughout the gastrointestinal tract after oral administration.

Half Life – 2.8 – 4.4 hrs

Protein Binding - 98%

Distribution:
This drug distributed throughout the body and its plasma protein binding capacity is 98%. Those who suffered from hypertension their plasma protein binding capacity may be decrease and the free fraction of drug increase in the body. This free amount leads to several other side effects such as liver and kidney damage.

Metabolism:
It is very potent antihypertensive agent but extensively metabolized in the liver and decrease its potency. Metabolism in the liver occur by the enzyme CYP3A4.

Elimination:
Elimination half life of Lercanidipine hydrochloride was 5.8 ± 2.5 and 7.7 ± 3.8 hours for S and R enantiomers, respectively [41-43].
1.2.2 Diltiazem Hydrochloride

**Generic Name:** Diltiazem hydrochloride

Chemical name: \((2S,3S)-5-\text{[2-(dimethylamino)ethyl]}-2-(4\text{-methoxyphenyl})-4-\text{oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate}\)

**Structure formula**

![Structure formula of Diltiazem Hydrochloride](image)

**Figure 1.6: Structure of Diltiazem Hydrochloride**

**Physicochemical Properties**

- **Molecular formula:** \(C_{22}H_{27}ClN_{2}O_{4}S\)
- **Molecular weight:** 450.98 g/mol
- **Partition Coefficient:** 2.8,
- **Bioavailability:** 40%,
- **Half-life:** 3 - 4.5 hrs,
- **Dose:** 120mg once daily,
- **Toxicity:** LD\(_{50}\)=740mg/kg (orally in mice),

**Physical form:** Solid

**Solubility:** Soluble in water, methanol, and chloroform.

**Category:**

Antihypertensive Agents / Vasodilator Agents / Calcium Channel Blockers / Cardiovascular Agents
Mechanism of Action

It treat the hypertension by controlling the peripheral vascular resistance. To control the resistance diltiazem hydrochloride causes the relaxation of vascular smooth muscle. The effect of this drug is depending on severity of disease condition.

Pharmacokinetics:

Pharmacokinetics of any drug means its absorption, distribution, elimination and metabolism. These four parameters are very important for the development and evaluation of transdermal matrix patch of diltiazem hydrochloride. This drug is absorbed from all over the gastrointestinal tract. After that it will distribute all over the GI tract but there extensive hepatic metabolism occur. Due to this hepatic metabolism bioavailability of drug was decrease up to 40%. After that only 5 to 6 % drug should be available as a unchanged form in the urine.

Pharmacodynamics

This drug is a calcium channel blocker from the group of benzodiazepine. It is used in the treatment of hypertension and angina pectoris. It prevents the entry of calcium channels and causes vasodilatation to reduce the blood pressure. Due to decrease in calcium influx peripheral constriction of smooth muscle decrease and heart can regulate the blood supply with normal pressure and beats. By this vasodilatation oxygen supply was also increase and it will help in controlling the blood pressure.

Marketed Preparation of Diltiazem hydrochloride : 1) Dilacor, 120 mg, Extended release capsule, 2) Cardizem, 120 mg, Extended release tablet, 3) Dilzem, 30 mg, tablet [44,45].
1.3 Introduction to Patch Forming Polymers Used In Present Work

1.3.1 HPMC K 15M (Hydroxy Propyl Methyl Cellulose K 15M)

Chemical Name

Chemical name of HPMC is “Cellulose hydroxyl propyl methyl ether”
Its CAS number is – [9004-65-3]

Molecular Weight

Molecular weight is approximately 10000–1500000 g/mol.

Structural Formula

![Figure 1.7 Structure of HPMC K15M](image)

Functional Category

This polymer is used as a coating agent, film-former, rate-controlling polymer, stabilizing agent, suspending agent and tablet binder for the preparation of conventional and controlled delivery dosage forms.

Applications in Pharmaceutical Formulation or Technology

This polymer used as a binder for the preparation of tablet. It is also used in preparation of liquid and ophthalmic dosage forms. It is used in the formulation of gel, ointment, cream and paste types semisolid and topical dosage forms as a thickening agent. Now a day it is very widely used in the preparation of controlled delivery dosage form as a matrix former polymer.

This polymer also used as a main ingredient in the cosmetic preparations. It is also used in the food products. It is used in the preparation of biphasic liquid dosage forms like suspension and emulsion as a suspending agent and emulsifying agent respectively.

Description

It is white and creamy in color granulator powder. It is odorless and tasteless.

pH

Its pH is found in a 1% w/w water solution in between 6 – 7.5.
Ash value
Its ash value is found in between 2 – 4 %, this value may change with change in viscosity.

Auto ignition Temperature
360°C – 362°C

Density
(bulk) 0.341 g/cm³
(tapped) 0.557 g/cm³
(true): 1.326 g/cm³

Melting point
Browns at 190 – 200°C and chars at 225 – 230°C. Glass transition temperature is 170 – 180°C.

Moisture Content
It’s have capacity to absorb moisture from the surrounding but it is depend on how much initial moisture content and humidity present in the atmosphere.

Solubility
All the grades of HPMC easily soluble in hot water but in cold water it may forms some lumps and thick viscous mass. It is some time not easily soluble in organic solvents but in some combination and mixtures of organic solvents, it is easily soluble. Some well-known optimized mixtures are dichloromethane with ethanol and dichloromethane with methanol.

Incompatibilities
Majorly incompatibilities of HPMC found with oxidizing compounds due to its nonionic nature. Sometime it produces some complex with oxidizing compounds and form precipitates.

Viscosity
This polymer is available in wide range of viscosity. This polymer available in number of grades, according to change in grade viscosity will be change. All grades with their viscosity shown in Table 1.1. Viscous solution of this polymer prepared with organic solvent. Dichloromethane and ethanol in a combination used to prepare viscous HPMC solutions, increasing concentration will increase viscosity of solutions [46].
Table 1.1: Typical viscosity values for 2% (w/v) aqueous solutions of HPMC [All viscosities measured at 208°C]

<table>
<thead>
<tr>
<th>HPMC Grades</th>
<th>Viscosity (mPa s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC K100 Premium LVEP</td>
<td>100</td>
</tr>
<tr>
<td>HPMC K4M Premium</td>
<td>4000</td>
</tr>
<tr>
<td>HPMC K15M Premium</td>
<td>15000</td>
</tr>
<tr>
<td>HPMC K100M Premium</td>
<td>100000</td>
</tr>
<tr>
<td>HPMC E4M Premium</td>
<td>4000</td>
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<tr>
<td>HPMC F50 Premium</td>
<td>50</td>
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<td>HPMC E3 Premium LV</td>
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<td>5</td>
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<td>HPMC E6 Premium LV</td>
<td>6</td>
</tr>
<tr>
<td>HPMC E15 Premium LV</td>
<td>15</td>
</tr>
<tr>
<td>HPMC E50 Premium LV</td>
<td>50</td>
</tr>
</tbody>
</table>

1.3.2: Psyllium Husk Powder [45-47]

Synonyms and Biological Source
Plantagoarenaria, Plantagoispaghula, Plantagoovata, Plantagoovate, psyllium huskpowder. It is obtained from dried husk of plant, plantagoovata

Brand name
Metamucil

Description
It is obtained from seeds of isphagula in a form of husk. It is available also in a powder form. Its main constituents are laxative materials. It has very good swelling property. It also has very good film forming property. It contains high levels of dietary fibers.

Physical Form
Powder and whole Husk

Odour
Slight characteristic odour

Taste: Tasteless

Molecular formula: C22H25 N7O5
Molecular Weight: 467.477
CAS NO: 80576-83-6
Vapor Pressure: 20 °C

Composition
Psyllium fiber fractionated into three components. A highly fermentable component total 15–20% of psyllium weight, an unfermentable (less than 20%) component comprising 10–15% of psyllium weight and poorly fermentable (30%) bulk-forming component constituting 55–60% of psyllium weight. Psyllium fiber is comprised of indigestible carbohydrate chains (fibers).

Effective Agent
There are 2 effective agents in psyllium, beta-Sitosterol and hemicellulose. Beta sitosterol is the more prominent agent in psyllium and can be found in the seed. Hemicellulose is found in multitude of plants and found in the husk of the plant. Hemicellulose is a heteropolymer of pentose and hexosemonomers. It has a large molecular weight of around 70,000. Hemicellulose has a random, amorphous structure with little strength. It is easily hydrolysed by dilute acid or base, but nature provides an arsenal of hemicelluloses enzymes for its hydrolysis. It is an insoluble polysaccharide not absorbed by GIT. Hemicellulose is found in many plants especially the cell walls.

Botanic Characteristics
The epidermis is composed of large cells having transparent walls filled with mucilage, and the cells swell rapidly in aqueous mounts and appear polygonal to slightly rounded in a surface view, when viewed from above (from below they appear elongated to rectangular). The swelling takes place mainly in the radial direction. The mucilage of the epidermal cells stains red with ruthenium red and lead acetate TS. The occasional starch granules that are present in some of the epidermal cells, and that found embedded in the mucilage, are small and simple or compounded with four or more components

Powdered psyllium Seed Husk
It is a pale to medium buff-colored powder, having a slight pinkish tinge and a weak characteristic odor. Entire or broken epidermal cells filled with mucilage. In surface view, the epidermal cells appear polygonal to slightly round. Mucilage stains red with ruthenium red TS and leadacetate TS.
Microbial limits
The total combined molds and yeasts count does not exceed 1000 per g, and it meets the requirements of the test for absence of Salmonella species and Escherichia coli.

Total ash: not more than 4.0%.

Acid-insoluble ash: not more than 1.0%.

1.4 Plasticizers Profile
1.4.1 Glycerin

Nonproprietary Names
BP: Glycerol, JP: Concentrated glycerin, PhEur: Glycerulum, USP: Glycerin,

Chemical Name
Propane-1,2,3-triol

CAS Registry Number
[56-81-5]

Molecular Formula
C₃H₈O₃

Molecular Weight
92.09

Functional Category
It is use as a plasticizer, antimicrobial preservative, emollient, humectant, solvent, sweetening agent, tonicity agent.

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

Typical Properties

Boiling point
290°C (with decomposition)

Density
1.2656 g/cm³ at 15°C; 1.2636 g/cm³ at 20°C; 1.2620 g/cm³ at 25°C.

Flash point
176°C (open cup)

Hygroscopicity
Hygroscopic

Melting point
17.8°C

**Surface tension**

63.4 mn/m (63.4 dynes/cm) at 20°C.

**Applications in Pharmaceutical Formulation**

Glycerin used in a wide variety of pharmaceutical formulations including oral, otic, ophthalmic, topical, and parenteral preparations. Glycerin used primarily for its humectants and emollient properties. In parenteral formulations, it use mainly as a solvent. In oral solutions, it used as a solvent, sweetening agent, antimicrobial preservative and viscosity-increasing agent. It also used as a plasticizer. Glycerin used as a plasticizer of gelatin in the production of soft-gelatin capsules and gelatin suppositories. Glycerin is employed as a therapeutic agent in a variety of clinical applications and is also used as a food additive

**1.4.2 Propylene Glycol**

**Chemical Name** 1,2- propanediol [57-55-6] (-)-1,2- propanediol [4254-14-2] (+)-1,2- propanediol

**CAS Registry Number** [4254-15-3]

**Empirical Formula:** C3 H8 O2

**Molecular Weight:** 76.08

**Functional Category** It is use as a plasticizer, solvent, and stabilizer for vitamins, water-miscible co-solvent and humectants.

**Description** It is a clear, colourless, viscous, practically odourless liquid with a sweet, slightly acrid taste resembling that of glycerin.

**Typical Properties**

**Boiling point:** 188°C

**Density:** 1.038g/cm³ at 20°C

**Melting point:** 57 - 59°C,

**Refractive index:** 1.4324,
Solubility

Propylene glycol is easily miscible with acetone, chloroform, ethanol (95%), glycerin, and water. It is soluble at 1 in 6 parts of ether and not miscible with light mineral oil or fixed oils, but it will dissolve in some essential oils.

Stability and Storage Conditions

It is stable in cool condition but at higher temperature oxidation occurs. It is chemically stable when miscible with some organic solvents. In topical preparation it is used as humectants. It is always stored in a dry as well as cool place. If it is used in injection any other ophthalmic and parenteral preparation then sterilization carried out by autoclaving. Due to its hygroscopic nature it absorbs moisture from the atmosphere so stored it in a well closed container.

Applications

Propylene glycol used as vehicle in number of pharmaceutical products such as liquid and semisolid preparations. It used as a solvent and co-solvent in some preparation where API has poor water solubility. In case of semisolid and topical dosage form, it is use as humectants. In case of transdermal devices, it is use as plasticizer. It is chemically very inert and having good compatibility with other excipients use in the formulation of any type of pharmaceutical dosage form. It used with alcohol as a solvent and stabilizer in number of liquid and semisolid dosage forms. It is very safe chemical so very widely use in food and cosmetic preparation.

1.4.3 Polyethylene glycol 400[48]

Non proprietary Names

BP: Macrogols, JP: Macrogol 400

Functional Category

It is used as humectants in the semisolid dosage form. It is used as solvent and co-solvent in the preparation of liquid, ophthalmic and parenteral dosage forms. It is used as coating agent in topical preparation, in tablet and capsule
it is used as diluents. It is used as plasticizer in Transdermal and topical device.

Applications

Polyethylene glycols are widely used in semisolid and liquid type of pharmaceutical dosage forms as a vehicle. It is also use in parenteral, ophthalmic, oral, and rectal dosage forms as a base. It is also used in the preparation of novel controlled drug delivery dosage forms. It is also use in the preparations of biopharmaceutical products. It is use in the formulation of some topical cosmetic preparation.

Description

It is a low-molecular weight grade of polyethylene glycol. It is a transparent, viscous liquid. polyethylene glycol 400 have very less toxicity compare to other grade of polyethylene glycol 400 so widely used in the food and cosmetic products.

Physico chemical Properties

Density obtained from the reliable source is 1.128 g/cm$^3$

Melting point found in the range of 39 - 41°C

Solubility

It is easily soluble in both hot and cold water. It is also soluble in aromatic hydrocarbons, but it is slightly soluble in aliphatic hydrocarbons.

Stability and Storage Conditions

Polyethylene glycol 400 has very good stability but always stored it in a tightly closed container. If work with polyethylene glycol 400, before start your work removes contaminated clothing and shoes and wash clothing before reuse.

1.4.4 Dibutyl Phthalate [48]

Non proprietary Names

BP: Dibutyl Phthalate, PhEur: Dibutyl Phthalate, USP-NF: Dibutyl Phthalate,
Chemical Name

Dibutyl benzene-1, 2-dicarboxylate

CAS Registry Number

[84-74-2]

Empirical Formula C16 H22 O4

Molecular Weight 278.34

Description

It is slightly yellow in colour viscous liquid. It is odourless, colourless and oily in nature liquid.

Physico chemical Properties:

Boiling point found in the range of, 340°C – 342°C

Density found, 1.0627 g/cm³

Melting point found, -35°C

Refractive index found, 1.490-1.495

Solubility

It is easily soluble and miscible with organic solvents like acetone, benzene, ethanol (95%), and ether. It is also soluble 1 in 2500 part of water at 20°C.

Stability and Storage Conditions

Dibutyl phthalate should be stored in a well-closed container in a cool and dry area. Residues of some hazardous materials are present in empty containers so immediately discard it after use.

Applications

It is used in the preparation of various conventional and controlled dosage forms. In the preparation of film coating device it is used as plasticizer material. It is also used as a solvent and co-solvent in number of liquid and
semisolid dosage forms. It is also used in the preparation of cosmetic products like antiperspirants and hair sprays.

1.5 Permeation Enhancers [49-50]

1.5.1 Pumpkin Seed Oil

Botanical Name: Cucurbitapepo

Description

Pumpkin seed oil obtained by expression from the dried seed of cucurbitapepo. The fruit pulp removed from the ripe pumpkin seeds. The kernels are wased, dried, chopped and mildly roasted. The oil obtained by a gentle mechanical pressing, without filtration. Only by sedimentation for a longer period, solid particles separate from the oil. The oil is of dark green colour and has a characteristic slightly nutty and fresh odour and taste. It has mild flavour with bland taste. Its specific gravity is 0.910-0.920 at 20°C.

Origin India

Solubility

It is Insoluble in water and miscible with some natural oils and organic solvents

pH: Neutral

CAS NO: 8016-49-7/89998-03-8.

Chemical characteristics

Its acid value is 7 mg KOH/g, iodine value is 110,0-130 gI_2/100kg, saponification value is 187-197 and peroxide value is 20mcq O_2/kg.

Chemical constitutes

Its mainly contains saturated fatty acids such as palmitic acid, stearic acid, oleic acid, linoleic acid.

Absorption: It is well absorbed in all over GIT.
Shelf life: 18 months

Uses

It is used as a fragrance and flavour ingredient in the pharmaceutical and cosmetic preparations.

Storage

It is always stored in tightly closed airtight containers, away from sunlight and heat preferably in amber colour bottles.

1.5.2 Jojoba oil

It is the essential oil used as fragrance and permeation enhancers in number of pharmaceutical and cosmetic preparations. It is obtained from the seed of jojoba plant. It is one type of shrub found in Southern Arizona and North western Mexico. Unprocessed jojoba oil has golden colour at room temperature but processed oil is colourless and odourless. It is very much stable at room temperature compare to any other natural oils because it does not contain any triglycerides.

Physical characteristics

Refractive Index: 1.4650 at 25 °C.

Specific Gravity: 0.863 at 25 °C

Melting point: 10 to 12 °C

Solubility

It is slightly soluble in alcohol, insoluble in water and miscible with ether, petroleum ether and chloroform.

pH

Here pH become alkali after filtration. Its pH value mainly depends on the soil and climate in which it was grown. Mainly it contains a high proportion of mono-unsaturated fatty acids namely gondoic acid.
Uses

Jojoba oil use as a pharmaceutical and cosmetic preparation in the place of whale oil. It is widely used in the cosmetic preparation which totally prepared from the natural ingredients. It is generally used in formulations of lotions and moisturizers

1.5.3 Linseed oil

Botanical Name: flaxseed oil

Origin

It is found in India. It is natural essential oil obtained from th dried, ripe seed of flax plant (Linumusitatissimum) by solvent extraction process. It is available in two grade food grade and non food grade, food grade oil used in the preparation of food products and non food grade oil used in the preparation of pharmaceutical and cosmetic dosage forms.

Chemical Constituents

Mainly it contains unsaturated fatty acids namely linamarin, palmitic, stearic, oleic, linoleic and linolenic acids.

Appearance It is Pale yellow in coloured odourless clear liquid.

Specific Gravity: 0.927-0.931

Solubility: Slightly soluble in alcohol, insoluble in water and miscible with ether, petroleum ether and chloroform.

pH: Alkali after filtration

CAS NO: 8001-26-1

Physical characteristics

Refractive Index - 1.4786-1.4815

Chemical characteristics

Acid value - not more than 4
Iodine value: 160-200

Saponification value: 188-195

Chemical Constituents: palmitic acid, Stearic acid, oleic acid, Linoleic acid.

Absorption: It is well absorbed in all over GIT.

Shelf life: 18 months.

Use

It is widely used in the preparation of cosmetic and food products. In pharmaceutical transdermal device it is used as permeation enhancers.

Storage

It is stored in cool and dry place, in a tightly closed container in a very good air ventilated area.
1.6 Tween 80

In the present study, tween 80 was used as a lubricating agent for the lubrication of petriplate.

**Chemical Name** Poly oxyethylene 20 sorbitan mono oleate

**CAS Number** [9005-65-6]

**Empirical Formula** C₆₄ H₁₂₄ O₂₆

**Molecular Weight** 1310

**Description**

It is thick transparent oil which is used in the preparation of number of pharmaceutical products.

**Solubility**

It is soluble in ethanol, mineral oil, vegetable oil and water.

**Stability and Storage Conditions:**

It is stable in the presence of electrolytes and weak acids and bases, but there is a chance of gradual saponification with strong acids and bases. It is hygroscopic and should be examined for water content prior to use and dried if necessary.

**Applications**

Tween 80 widely use as emulsifying agent in the formulation of biphasic liquid dosage form emulsion. It is also use as vehicle, stabilizer in the preparations ENT products, topical, and parenteral preparations. Tween 80 also used as permeation enhancer and lubricating agent in the formulation of transdermal devices.