1. ORGANIZATION

PRODUCTS, PROCESSES, PROFILE

2.1 Drug Profile

Dithranol IP (anthralin; Dioxyanthranol)

![Chemical structure of Dithranol IP](image)

**Fig. 8 Dithranol IP**

- **Chemical name:** 1, 8-Dihydroxy-9(10H)-anthracenone
- **Molecular formula:** C_{14}H_{10}O_{3}
- **Molecular weight:** 226.23
- **Category:** Topical anti psoriatic
- **Description:** yellow or orange yellow microcrystalline powder
- **Appearance:** A yellow or orange yellow microcrystalline powder
- **Odor:** Odorless or almost Odorless
- **Melting point:** 180°C
- **Solubility:** Dithranol was found to be water insoluble nature, In ethanol slightly soluble, ether, soluble in methylene chloride, benzene
- **Drug category:** a) Keratolytic
b) For treatment of psoriasis (antipsoriatic)

**Bioavailability:** Poorly and erratically absorbed orally.

**Source**
Dithranol/DTH (Anthralin) or (3-methyl dithranol) was acquired from “Vouacopoua araroba” categories in chrysorabin introduced by Portuguese from Brazil to India. DTH is a potent anti-inflammatory as well as anti-proliferative medicine.

**Description of drug and dosage form**
The yellow colour of DTH was due to chrysazin and chrysophanic acid. Present time a several novel preparations are prepare with dithranol e.g. liposomal, Niosomes, Nanoparticles, Nanoemulsion etc. DTH is largely present variety of dosage ointment as well as cream for dealing and management of psoriasis of face, flexures, scalp. Additionally, phototherapy treatment for psoriasis was related to Ultraviolet B and anthralin.

**Mechanism of action of Dithranol:-**
- Inhibition of cell proliferation (Kemeny L., 1990).
- Inhibition of granulocyte function (Ternowitz T., 1987).
- DNA duplication and repairmen (Muller, K., 1995).

More than a century, anthralin has been categories as antipsoriatic drug belongs to the family of hydroxyanthrones. The mechanism of action of DTH has been associated to its capability to produce free radicals It has been shown to collected or accumulated in the power house of cell where it induces morphological as well as functional alterations So that the supply of cellular energy interrupted therefore energy dependent process is inhibited such as replication of DNA which slows mitotic division and its restore, obstruct cyclic nucleotides, down too much cell division resembling seen in plaque psoriasis. Level of cyclic guanosine monophosphate was elevated in psoriatic hyper-proliferative epidermis skin. As DTH has been shown to diminish the high level of cGMP and try to turn back to its normal level.
The regulation of epidermal cell division cyclic nucleosides was play very important role. DTH was barrier with dendritic cells or langerhans cells together with different interleukin receptors such as IL-10, IL-8, IL-6.

The unstable DTH is oxidized to danthron and a dithranol dimer called dianthrone and further insoluble oxidation products. When the drug is direct exposed with sunlight it converted to danthron is which is obtained through the breakdown of DTH. This danthron has been present in the urine of patients taking dithranol treatment.

**Inhibition of cell proliferation**

DTH is a hydroxyanthrone, anthracene derivative drug useful to psoriatic patients revealing both anti-inflammatory and anti-proliferative character.

**DNA duplication and repairment**

DTH is store in mitochondria consequential in a decrease of ATP synthesis which direct to inhibit DNA replication hence losing the excessive cell division which exist in psoriasis disease. According to this concept DNA bases was modified and various enzymes were inhibited. In case of psoriasis disease has been reported that raise epidermal calmodulin and DTH was established to be a powerful competitive antagonist of calmodulin.

**Pharmacokinetics parameter of DTH**

**Absorption**

Penetration of more dithranol into impaired skin was within half an hour than into intact surface of skin over 16 to 20 hours. consequently, weaker dose at concentration of 0.1% to 0.5% formulation are use at overnight, except stronger dose 1% to 2% preparation are used for between half an hour to one hour as short-contact therapy determined on the basis of the preparation. Patients treated for localized action of drug in psoriasis was designed as short-contact therapy. Ranging from ten minutes to an hour dithranol is missing on the concerned skin for a little time period therefore instructed to patients applying of drug may be progressively raise the applying period hence skin turn into adapted to the anthralin.

The absorbed amount of anthralin via the skin has not been entirely known on the other hand, absorption appears to be low with an impaired stratum corneum barrier. Psoriatic lesions and damaged skin penetration of anthralin was faster and greater extent than
normal skin penetrates maybe for reason of better blood flow to the lesions or psoriatic skin where a poor barrier junction present.

**Distribution**
The maximum unchanged dithranol concentration is found in epidemic layer within 24-48 hr still after the skin has been washed. Unoxidised dithranol drug was present in small concentration in deep dermal layers of skin, comparatively of are identified whereas higher concentrations of the dimer of dithranol are found.

**Metabolism**
Dithranol is oxidized to danthron dimer and to additional insoluble polymerization products.

**Elimination**
There are not any determinations completed which designate that unchanged drug is absorbed by the skin. On the other hand, a minute quantity of oxidative products (danthron) has been identifying in sample of urine in applied persons after topical preparation application. Another studies have establish no confirmation of systemic toxicity, still in patients with renal impairments

**Adverse and side effects**
DTH adverse effects include staining of skin, clothing, and furniture as well as may reason of local sensation of burning along with irritation on applying part of body. To diminish that type of adverse outcome, just a short-contact therapy within 5 to 30 minutes treatment and some of chemical use for prevention of staining such as triethanolamine and prepared heat-sensitive drug preparations.

**Dose:** This was present in concentration of about 0.1 to 2% strengths in ointment, creams or pastes.

Marketed products of this drug are tabulated following in table 7.
### Table 7: Marketed products of Dithranol

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>BRAND NAME</th>
<th>MANUFACTURER</th>
<th>DOSAGE FORM</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DRITHOCREME</td>
<td>Summers Laboratories</td>
<td>Cream</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>DITHROCREAM</td>
<td>Dermal Laboratories Limited</td>
<td>Cream</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>ZITHRANOL-RR</td>
<td>Elorac. inc</td>
<td>Cream</td>
<td>1.2%</td>
</tr>
<tr>
<td>4</td>
<td>MICANOL,</td>
<td>Derma UK</td>
<td>Cream</td>
<td>1%</td>
</tr>
<tr>
<td>5</td>
<td>PSORISOME GEL</td>
<td>Life care innovations pvt. Ltd</td>
<td>Gel</td>
<td>0.5%</td>
</tr>
<tr>
<td>6</td>
<td>DEROBIN®</td>
<td>Vardhaman remedies pvt. Ltd, Gsk</td>
<td>Ointment</td>
<td>1.15%</td>
</tr>
<tr>
<td>7</td>
<td>PSORISOME</td>
<td>Lifecare Innovations Pvt. Ltd.</td>
<td>Gel</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

**PRODUCTS**

**2.2 MATERIALS AND EQUIPMENTS**

The drug, chemicals and equipments used for research work are tabulated below. Drug and other compound were of analytical rank with procured as gift samples or purchased.
### Table 8: List of drug and chemicals applying for study work with supply

<table>
<thead>
<tr>
<th>S. No</th>
<th>Chemicals</th>
<th>Grade</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dithranol IP</td>
<td>Pharma</td>
<td>Agon Pharma Pvt.Ltd</td>
</tr>
<tr>
<td>2</td>
<td>Phospholipid (Lecithin)</td>
<td>Pharma</td>
<td>Himedia Laboratories Pvt. Ltd. Mumbai-400086, India</td>
</tr>
<tr>
<td>3</td>
<td>Cholesterol</td>
<td>AR</td>
<td>Loba Chemie Pvt., Mumbai-400002, India</td>
</tr>
<tr>
<td>4</td>
<td>Span 40, Span 60</td>
<td>AR</td>
<td>Ranbaxy Fine Chemical Limited, New Delhi.</td>
</tr>
<tr>
<td>5</td>
<td>Ethanol</td>
<td>AR</td>
<td>S.D. Fine Chem. Ltd., Mumbai</td>
</tr>
<tr>
<td>6</td>
<td>Carbopol 934</td>
<td>AR</td>
<td>Himedia Laboratories Pvt. Ltd. Mumbai</td>
</tr>
<tr>
<td>7</td>
<td>Potassium Dihydrogen Orthophosphate</td>
<td>AR</td>
<td>Ranbaxy Fine Chemical Limited New Delhi.</td>
</tr>
</tbody>
</table>

### EQUIPMENTS

### Table 9: List of Instrument and Manufacturer used for research work

<table>
<thead>
<tr>
<th>S. No</th>
<th>Instrument</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Double Beam UV Visible Spectrometer</td>
<td>Shimadzu Corporation, Japan.</td>
</tr>
<tr>
<td></td>
<td>(UV-1700)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>FT-IR 200 Spectrometer</td>
<td>Perkin Elmer ,USA</td>
</tr>
<tr>
<td>3</td>
<td>Refrigerated Centrifuge</td>
<td>Plasto Craft, USA</td>
</tr>
<tr>
<td>4</td>
<td>Differential Scanning Calorimeter</td>
<td>Shimadzu Corporation, Japan</td>
</tr>
<tr>
<td>5</td>
<td>Electronic Balance</td>
<td>The Bombay Burma Trading Corporation Ltd., Mumbai, India.</td>
</tr>
<tr>
<td>6</td>
<td>Ultra Sonicator</td>
<td>Telsonic,</td>
</tr>
<tr>
<td>7</td>
<td>Particle size analyzer</td>
<td>Malvern</td>
</tr>
<tr>
<td>8</td>
<td>Magnetic Stirrer</td>
<td>Remi Pvt. Ltd., Mumbai</td>
</tr>
<tr>
<td>9</td>
<td>Particle size analyzer</td>
<td>Malvern</td>
</tr>
<tr>
<td>10</td>
<td>Humidity Control Chamber</td>
<td>Lab Control, Mumbai</td>
</tr>
<tr>
<td>11</td>
<td>Jade DSC</td>
<td>Perkin Elmer USA</td>
</tr>
</tbody>
</table>
2.3 CHARACTER OF EXCIPIENTS

Following constituent are contains by proniosomal gel such as

- Nonionic surfactant e.g. Sorbitans and Polysorbitans
- Cholesterol
- Phosphatidyl-Choline e.g. Egg Lechthin and SoyaLechthin
- Alcohol e.g. Butanol, Ethanol, Iso-propanol, Propanol etc.
- Aqueous phase e.g. Water, Glycerol (0.1%), Phosphate buffer pH 7.4
- Miscellaneous Dicetyl Phosphate.

2.3.1 Lechthin

On the basis of their source of origin give the name for example egg lecithin from egg yolk and soya lecithin from soyabeans. A major component of lecithin is phosphatidyl choline which is play variety of function in vesicular system such as (Yadav K et al., 2010) Phosphotidyl choline has little solubility in water (Reddy DN et al., 1993).

a. Permeation enhancers
b. Due to elevated Tc (phase transition temperature) improved drug entrapment percent.
c. Soya lecithin composed vesicle is larger size then egg lecithin composed vesicle which direct to vesicles of lesser size because of augment in hydrophobic nature.
d. Preventions leakage of drug

Moreover, physiological point of view phospholipids is extremely well tolerated. Many drugs monograph listed lecithin as well as FDA inactive ingredients guide approved (Leigh M.2002).

Size of soya lecithin vesicles is larger size compared to size of egg lecithin vesicles whereas compare these penetration ability soya lecithin is a better candidate to select as it contain unsaturated fatty acid, oleic and linoleic acid whereas the egg lecithin contain the saturated fatty acid. Positive charge created by dicetyl phosphate (DCP) amalgamation and negative charge produce by stearylamine (SA) but both are decreased the EE % (encapsulation efficiency) of proniosomal vesicles.
2.3.2 Surfactants [Sorbitan Esters (Sorbitan Fatty Acid Esters)]

HLB value (Hydrophillic Lipophillic Balance)

HLB number play important role for lipophilic and hydrophilic nature of surfactants having between 4 to 8 is good candidate for vesicular and pro-vesicular system formation, as when hydrophilic surfactants are taken into explanation their elevated aqueous solubility on hydration do not allow them to attain a concentrated systems also it inhibits the liberated hydrophilic parts to make aggregates and combine to appearance as lamellar configuration. At whatever time lofty HLB degree consequently diminishes free energy of vesicles which permits forming larger size of vesicles. Higher HLB value of surfactant was decrease the surface free energy which permits larger size vesicles therefore more surface area contact with skin. The Table 10 and 11 are showing a wide range of available surfactant.

**Table 10: Various kinds of Non-Ionic Surfactant**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Example</th>
<th>Kinds of Non ionic Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alcohol of Cetyl, Steryl, Cetosteryl, oleyl type</td>
<td>Fatty alcohol</td>
</tr>
<tr>
<td>2</td>
<td>Decyl glucoside, Brij, Lauryl glucoside, Nonoxynol-9, Triton X-100,</td>
<td>Ethers</td>
</tr>
<tr>
<td>3</td>
<td>Spans, Glyceryl laurate, Tween</td>
<td>Esters</td>
</tr>
<tr>
<td>4</td>
<td>Poloxamers</td>
<td>Block copolymers</td>
</tr>
</tbody>
</table>

**Table 11: Commonly used surfactants with synonyms name for proniosomes preparation**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Surfactant</th>
<th>Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sorbitan monolaurate</td>
<td>Span 20, Sorbitan monododecanoate</td>
</tr>
<tr>
<td>2</td>
<td>Sorbitan monopalmitate</td>
<td>Span 40</td>
</tr>
<tr>
<td>3</td>
<td>Sorbitan monostearate</td>
<td>Span 60, Sorbitan mono octadecanoate</td>
</tr>
</tbody>
</table>
Non-ionic surfactants of low HLB value are suitable candidates. They are classified as:

- Higher fatty acids and low molecular weight (LMW) amino acids.
- Alkyl amides: Galactosides and Glucosides.
- Alkyl esters: sorbitan esters (Spans)
- Alkyl ethers: Mono alkyl glycerol ethers, dialkyl glycerol ether, ester linked chains.

(Surfactant 1) (Surfactant 2) (Surfactant 3), respectively etc.

### 2.3.3 Cholesterol

Cholesterol is a vital component of vesicles, integration of cholesterol affected vesicles stability and permeation capability etc (Nasseri B 2005). According to El-Laithy et al. state that as the content of cholesterol in formulation increase there is a considerable increase in percentage entrapment efficiency but after confident limit further cholesterol level increase consequences in significant decrease in entrapment efficiency. Reason for this type of behavior is cholesterol molecules as “vesicular cement” by accommodate itself in the molecular cavities of surfactant monomers are connected into bilayer to form nio/proniosomal membranes therefore filling of this space results in the increased rigidity along with decreased permeability of membranes which containing cholesterol compared to cholesterol free membranes result the improved entrapment efficiency. On further increase of cholesterol concentration beyond certain level, it competes with the drug for the space within the bilayer, hence excluding the drug molecule and can disturb the normal linear composition of vesicular membranes (El-Laithy HM et al., 2011, Fang JY et al., 2001)

### 2.3.4 Solvent

Choice of solvent is a different important part in formulation of proniosomes as it is having enormous impact on the size of vesicle and permeation rate of drug. Literature

<table>
<thead>
<tr>
<th></th>
<th>Sorbitan monooleate</th>
<th>Span 80, Sorbitan (Z)-mono-9-octadecenoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Polyoxyethylene (20) sorbitan monolaurate</td>
<td>Tween 20</td>
</tr>
<tr>
<td>6</td>
<td>Polyoxyethylene (20) sorbitan monopalmitate</td>
<td>Tween 40</td>
</tr>
</tbody>
</table>
revealed that as the increases solubility of alcohol in water result the size of vesicles increases and they follow the following order (Lopez JM et al., 2005). Ethanol > Propanol > Butanol > Isopropanol

Vesicles prepared by ethanol were large size owing to its more solubility in aqueous media and least size of isopropanolol may be due to branched chain structure (Ishii F et al., 1995).

They were found that niosomes containing propanol and ethanol are less spontaneous formation in niosomes then formulation containing isopropanol and butanol type solvent. Due to their lower solubility isopropanol and butanol in water spontaneously more because to faster phase separation. Ethanol may cause increased the skin permeation because the decrease of lipid polar head interactions within the membrane (Parikh DK et al., 2005, Annakula D et al., 2010).

2.3.5 Aqueous Phase

Aqueous phase in preparation of proniosomal gel are phosphate buffer pH 7.4, glycerol 0.1% and hot water is generally used. Mokhtara et al. found that the entrapment efficiency of formulation dependent on pH of the hydrating medium. The pH scale decreased from 8 to 5.5 of flurbiprofen than encapsulated efficiency was increased to about 1.5 times. The maximum percentage entrapment efficiency of flurbiprofen by lowering the pH may be accredited due to the existence of carboxylic group capable for ionization. Increase in the unionized species of flurbiprofen by decrease in the pH which has more separation to the bilayer lipid phase in contrast to the ionized class. Reason for this phenomena recommended by Ammara et al. for such type of activities is that the type of aqueous medium might affect the tactness of proniosomes as a result affecting their entrapment efficiencies (Ammara HO et al., 2011).

2.4 FACTORS AFFECTING PHYSICOCHEMICAL PROPERTIES OF PRONIOSOMES

Various following factors that affect the physicochemical properties of proniosomes are discussed.

(i) Nature of Surfactants

Preparation of proniosomes requires a surfactant which must have two terminal or head a polar or hydrophilic head and non polar or hydrophobic tail. One sometimes two alkyl or
perfluoralkyl groups or a few conditions a unit steroidal group are made a non polar tail. Single chain alkyl as hydrophobic tail of ether like surfactants was became highly toxicity in nature comparative equivalent chain of dialkyl ether. These kinds of surfactants are more stable in chemically in contrast ester type surfactants. Esterase an enzyme was break down of ester in vivo into triglycerides and fatty acid. Lengths of alkyl chain in surfactants with from C12-C18 are appropriate for formulation of proniosomes. Surfactants for example poly-oxy ethylene cetylether (C<sub>16</sub>EO<sub>5</sub>) as well as polyoxyethylenesteryl ether (C<sub>18</sub>EO<sub>5</sub>) were required for made of polyhedral vesicles. HLB number of between 4 and 8 of different span series surfactants can form niosomes vesicles.

Several forms of energy such as mechanical or heating require for the formation of proniosomes as a self-assembly process due to elevated interfacial tension among aqueous medium and the lipophilic alkyl chain/s resulted in the attachment of non-ionic surfactant monomers into vesicles. At the same time as, the hydrophilic head groups of amphiphilic molecules create water mediated connections counter the earlier created force ultimately results in bilayer formation.

Development of proniosomes requires an amphiphilic molecule containing of two main terminals a polar and a non-polar terminal as hydrophilic head group or hydrophobic tail respectively. This is apparently the usual arrangement of surfactant molecules although in many times the existence CHOL (a wedge-shaped molecule) as is essential for rotating the micellar configuration of surfactant aggregates to bilayer arrangement. Alkyl esters, alkyl amides, Alkyl ethers, amino acids and fatty acids are the main non-ionic surfactant groups used for preparation of niosomes. However, Sorbitan monoesters (Spans) is the most frequently used surfactants in niosomes formulations figure 6. The presence of different and various polar head groups decided the adaptability of compounds capable of forming vesicle is owing to bind to unsaturated or saturated alkyl chain(s) containing of 12 to 18 carbon atoms (C12-C18).

**b) Amount and type of surfactant**

Depending on the temperature, lipid or surfactant type and added components for example cholesterol, the bilayer of the vesicles are either in liquid phase. Alkyl group are present in a regimented structure in case of the gel state and more disordered in the liquid
state. Characterization of surfactants and lipids are based on phase transition temperature (Tc) of the gel-liquid state. Entrapment efficiency was also affected by phase transition temperature (Tc) of surfactant for e.g. Tc of Span 60 having higher shown better entrapment.

Critical packing parameters may be represented by subsequent relation, CPP (Critical Packing Parameters)

\[ \frac{v}{l_c} \times a_o = CPP \] (Critical packaging parameters)

Where

v = volume of hydrophilic group
l_c = length of the hydrophilic group
a = Hydrophobic group area

From the value of critical packing parameter, different type of structure (micelle) produced can be determined as specified below

If value of CPP less than \( \frac{1}{2} \) means spherical micelles formed
If value of CPP greater than \( \frac{1}{2} \) but less than 1 means bilayer micelles formed
c) Nature of Encapsulated Drug

The physicochemical characters of entrapped drug affected charge and stiffness of the proniosomes bilayer. Entrapment efficiency of drug was affected by molecular weight of active drug molecule. Lower the EE when higher the molecular weight. Charge and rigidity of the proniosome bilayer was also affected by the physicochemical properties of entrapped drug. Proniosomes increases vesicle size by entrapment of drug, possibly by interaction of surfactant head groups with solute, rising mutual repulsion and the charge of the surfactant bilayer, thus rising of vesicle size. The degree of entrapment affected by hydrophilic lipophilic balance (HLB) value of surfactant.

d) Concentration of Cholesterol and Charge

Cholesterol molecule was incorporated in vesicular system; give inflexibility in membrane with decrease the escape of API from vesicles and also raises the hydrodynamic thickness and encapsulation competence of niosomes. In general, the attainment of cholesterol is bimodal, first is cholesterol boost the chain order of liquid-
state in bilayer and another is cholesterol reduces the chain order of gel state in bilayer. Higher cholesterol concentration transformed the gel state in to a liquid ordered phase. Cholesterol eliminates the gel to liquid phase transition in vesicular systems, therefore in a smaller amount of leakiness of the vesicles and enhanced niosomes stability. Generally it has been establish that 1:1 is a molar ratio of among Cholesterol and non-ionic surfactants, a most favorable ratio for the preparation of stable proniosomes.

e) Solutes Charged:
Charge on surface of solute was prevent of aggregation of vesicles by develop electrostatic repulsion force. Zeta potential of 30mV is desirable. Charge of niosomes can also alter their in vivo distribution pattern.

a) Positive charge: Stearylamine, Cetyl pyridinium chloride.
b) Negative charge: Dicetyl phosphate, Phosphatidic acid.

f) Composition of Membrane
Adding of different excipients along with surfactants and drugs can be prepared stable niosomes. Constancy and permeability nature of niosomes can be maintained by membrane stabilizer. C16G2 used for preparing polyhedral niosomes and by mixing low concentration of solulan C24 means chemical name is cholesteryl poly-24-oxyethylene ether, the shape of these polyhedral niosomes remains unchanged because due to development of steric hindrance it was prevents aggregation.

PROCESSES

2.5 METHODS FOR PREPARING OF PRONIOSOMES
“Coacervation phase separation method” or technique may be used for preparation of proniosomal but two other methods are also used for preparing proniosomes.

1. Slurry method
2. Coacervation phase separation method
3. Slow spray method

1. Slurry method
Proniosomes can be prepared in a 250- mL round-bottomed flask containing carrier (Maltodextrin powder), surfactants (Span or Tween) and cholesterol with suitable solvent to form slurry. Lower surfactant loading can be made by mixing of little amount of chloroform in the slurry. A rotary flash evaporator to be joined with the flask has to use
for evaporating chloroform at 40 to 60 rpm at 42 ± 20 °C temperatures. The flask was close to the rotary vacuum evaporator until the powder become to be dry and free flowing. As a final point, the prepared proniosomes should stock up in firmly tight bottle at low atmospheric temp (Solanki A B et al., 2007, Hao Y. et al., 2002). The flask was disconnected from the evaporator and kept under vacuum for 12 hour. Powder form of formulation was keeping in seal packed containers at low temperature.

Advantages:
1) Carrier Maltodextrin is soluble in water and it is a polysaccharide. They were without difficulty coat the maltodextrin by just addition of surfactant in organic phase to dry maltodextrin (Yoshioka T et al., 1994).
2) Owing to homogeneous coating on carrier it prevents from hydrolysis and oxidation of the active drug material and surfactants etc.

Disadvantages
1. Time consuming Method and require specific equipment by means of vaccum and nitrogen gas etc.
2. Small quantities or little dose batch can be tiresome one because thin layer approach allows only for a fixed lot sizes so material often wasted.

2. Coacervation phase separation method
All of ingredients are taken such as surfactant, carrier (lecithin), cholesterol weighed accurately with drug in a dirt free and dry broad mouthed glass vial or beaker (5 ml) along with solvent, (alcohol 0.5 ml ) is added to it. All these mixture have to be heated and mixed with help of glass rod. The glass vial open end can be covered through a lid, to avoid the loss of solvent and warmed the mixture on water bath at 60-70 °C for approximate 5 minutes until the surfactant dissolved completely. The dispersion gets converted to a proniosomal gel when the blend should be permitted to become cool at room temperature (Vora B et al., 1998, Tank CJ et al., 2009).
3. Slow spray coating method

Rotary flash evaporator connected with a round bottom flask (100 ml) which hold required amount of carrier. Prepared mixture of surfactants and cholesterol was introduced into round bottom flask with rotary evaporator and spraying of this material as little fraction, onto surface of carrier. Rotating flask can be attached in water bath in vacuum temperature at 65-70°C for 15 to 20 minute. it is necessary this process to be repeated until required surfactant solution loaded has been completed. The coating of surfactant on the surface of carrier is very lean and hydration of this outside layer permit multilamellar provesicles.
2.6 **Excipients Profile** (Rowe R. C.et al., 2006)

2.6.1 **CHOLESTEROL**

**Synonyms:** Cholesterin; cholesterolum.

**BP:** Cholesterol

**USPNF:** Cholesterol

**PhEur:** Cholesterolum

**Chemical Name:** Cholest-5-en-3β-ol

**CAS Registry Number:** [57-88-5]

**Molecular Weight:** 386.67

**Empirical Formula:** $\text{C}_{27}\text{H}_{46}\text{O}$

**Structural Formula:**

![Fig.11 Structure of Cholesterol](image)

**Category:**

- Emulsifying agent
- Emollient
Pharmaceutical applications:-

- This is requiring in cosmeceuticals and dermal p’ceutical preparations in level range of 0.4–6.0% w/w as emulsifier.
- Cholesterol is capacity to holding water in dermal preparation and emollient action.
- Chief ingredient of gallstones is cholesterol.
- Cholesterol is composition of sterol ring structure present in advanced animals, present in whole tissues of body, particularly in the spinal cord and cranium.

Explanation

**Colour:** Faintly yellow or White

**Odor:** Odorless,

**Description:** leaflets pearly structure, Powder, Needles like granules.

**Incompatibility:** Extended contact with light and air, it’s yellow to tan.

**Other Properties**

**Boiling point:** 360° C

**Density:** For anhydrous form 1.052 g/cm³.

**Dielectric constant:** 5.41

**Melting point:** 147–1508 C

**Solubility:** soluble in Acetone

**Specific rotation:** - a) In 2% w/v solution of chloroform is -39.58.

b) In 2% w/v solution of ether value is -31.58.

**Storage and stability:**

- Stored in a tightly closed container
- Protect to light.
- It was shown incompatibilities with digitonin and precipitated out.
**Manufacturing technique**

Cholesterol was commercially manufactured through animal spinal cord with help of petroleum ethers in extraction process. Sometimes wool fat has another source for extraction of cholesterol.

**Safety**

- It has nontoxic as well as nonirritant substance in excipients.
- Cholesterol exhibited experimental shown as teratogenic and reproductive property, and sometimes mutation has been noticed.

**Precautions for handling**

- Risky and toxic in great amount for long time ingestion or inhalation.
- Plastic as well as rubber handbag and gloves are use.
- It was suggested that protected eyes and respiratory system
- Cause some times Atherosclerosis and gallstones.

**Regulatory Status**

- It is an incorporated in the FDA guidelines as inactive elements, Guide as different preparations e.g. injections, ophthalmic, vaginal.
- In United Kingdom it is licensed as non parenteral medicines.

### 2.6.2 LECITHIN

**Synonyms:**
Egg lecithin, Mixed soybean phosphatides, Ovolecithin, Phospholipon 100 H, Soybean lecithin, Soybean phospholipids, Vegetable lecithin etc.

**USPNF:** Lecithin

**Chemical Name:** - Lecithin

**CAS Registry Number:** - [8002-43-5]

**Extract of Soybeans:** - [8030-76-0])

**Egg yolk lecithin:** - (CAS [93685-90-6])
Structure formula

![Structure formula](image)

Fig.12 Structure of lecithin

**Molecular Weight:** - 784.6 g/mol

**Category:**
- Emulsifying agent
- Solubilizing agent
- Emollient

**Pharmaceutical applications:**
- Lecithin is used in a wide variety of pharmaceutical applications as concentration of 0.1 used in Aerosol inhalation, 0.3–2.3 intramuscular (IM) injection, 0.25–10.0 in Oral suspensions.
- Used in cosmetics as well as food products.
- Pharmaceutical products as dispersing, emulsifying, and stabilizing agents.
- In intramuscular and intravenous injections, parenteral nutrition formulations, and topical products such as creams and ointments.
- In suppository bases, to reduce the brittleness of suppositories.
- Investigated for its absorption enhancing properties in an intranasal insulin preparation.
- It is also commonly used as a constituent in enteral and nutritional parenteral formulations.
- It may confirm that phosphatidylcholine (a major component of lecithin) is important as a nutritional supplement to fetal and infant development. Furthermore, according FDA approved, choline is a required component of infant formulas.
Explanation or Description

- It is viscous semi liquids to powders, depending upon the free fatty acid content.
- Depending upon whether they are bleached or unbleached or on the degree of purity from brown to light yellow.
- When they are exposed to air, rapid oxidation occurs, also resulting in a dark yellow or brown color.
- It’s have practically no odor.
- Those derived from vegetable sources have a bland or nutlike taste, similar to that of soybean oil.

Iodine number: 95–100 for liquid lecithin; 82–88 for powdered lecithin.

Density: Liquid lecithin is 0.97 g/cm³, Powdered lecithin was 0.5 g/cm³.

Isoelectric point: Approx 3.5

Saponification value: 196

Solubility: Soluble in aliphatic and aromatic hydrocarbons

Stability and Storage Conditions

- It may decompose at excessive pH. Lecithin is also hygroscopic and microbial degradation.
- When heated, lecithins oxidize, darken, and decompose.
- Degradation will causes at temperatures of 160–180°C within 24 hours.
- Fluid or waxy lecithin grades should be stored at room temperature or above temperatures below 10°C may cause separation.
- All lecithin grades should be stored in tightly closed containers.
- Light protected.
- Purified solid lecithins should be hold in tightly clogged bottle subfreezing temperatures.
**Method of Manufacture**

It is an essential component of cell membranes, achieved from a wide variety of living matter. Vegetable materials also use for their manufacturing such as soybean, peanut, cottonseed, sunflower, rapeseed, corn, or groundnut oils. Soybean lecithin is the most commercially important vegetable lecithin. Vegetable lecithins are obtained as a by-product in the vegetable oil refining process.

**Safety**

- It is a component of cellular membranes and taken in diet.
- Even though excessive consumption may be harmful, it is highly biocompatible and oral doses of up to 80 g daily.
- When taken in topical preparation lecithin was usually nonirritant and non-sensitizing substance.

**Precautions for handling**

- Plastic as well as rubber handbag and gloves are use.
- It was suggested that protected eyes and respiratory tract

**Regulatory Status**

- It was established in food for stabilizer in European countries according to GRAS listed.
- The FDA Inactive Ingredients Guide included for preparation of inhalations, intramuscular (IM) and intravenous (IV) injections, capsules, suspensions and tablets, rectal, topical, and vaginal preparations.

2.6.3 **SORBITAN ESTERS  (SORBITAN FATTY ACID ESTERS)**

2.6.3.1 Sorbitan monopalmitate (Span 40)

**Synonyms:**

Span 40, 1,4-Anhydro-D-glucitol, Ablunol S-40; Arlacel 40; 6-hexadecanoate; Armotan MP; Proto-sorb SMP; Montane 40; Nissan Nonion PP-40R; Nikkol SP-10; Protachem SMP; Sorbester P16; Sorbirol P; sorbitan palmitate;

**USPNF:** Sorbitan monopalmitate

**Chemical Name:** - Sorbitan monohexadecanoate
CAS Registry Number: - [26266-57-9]

Empirical formula C_{22}H_{42}O_{6}

Molecular Weight: - 403

Category:-
  ➢ Nonionic surfactant
  ➢ Emulsifying agent
  ➢ Solubilizing agent
  ➢ Suspending agent
  ➢ Wetting and dispersing

Explanation or Description
  ➢ Sorbitan esters occur as cream- to amber-colored liquids
  ➢ solids with a distinctive odor and taste; Appearance: Cream solid

Density: 1.0

Iodine number: 41

Acid value: \(\leq 8.0\)

Hydroxyl value: 270–305

HLB value: 6.7

Saponification value: 140–155

Melting point: 43–48 °C

Assay for polyols: 32.0–38.0%
2.6.3.2 Sorbitan monostearate (Span 60)

**Synonyms:**
Alkamuls SMS; Ablunol S-60; 1,4-Anhydro-D-glucitol, Arlacel 60; Armotan MS; 6-octadecanoate; anhydrosorbitol monostearate; Atlas 110K; Capmul S; Crill 3; Dehymuls SMS; Drewsorb 60K; Drewmulse SMS; Durtnan 60; Durtnan 60K; E491; Famodan MS Kosher; Glycomul S FG; Glycomul S KFG; Hodag SMS; Lamesorb SMS; Liposorb S; Liposorb SC; Liposorb S-K; Nissan Nonion SP-60R; Montane 60; Norfox Sorbo S-60FG; Polycon S60K; Protachem SMS; Prote-sorb SMS; S-Maz 60K; S-Maz 60KHS; Sorbester P18; sorbitan stearate; Sorbirol S; Sorgen 50; Span 60; Span 60K; Span 60 VS; Tego SMS.

**USPNF:** Sorbitan monostearate

**Chemical Name:** - Sorbitan mono-octadecanoate

**CAS Registry Number:** - [1338-41-6]

**Emperical formula** $\text{C}_{24}\text{H}_{46}\text{O}_6$

**Molecular Weight:** - 431

**HLB value:** 4.7

**Iodine number:** 41

**Acid value:** $\leq 10.0$

**Saponification value:** 147–157

**Melting point:** 53–57

**Hydroxyl value:** 235–260

**Assay for polyols:** 27.0–34.0%
Category:-

- Non-ionic surfactants
- Emulsifier
- Solubilizing properties
- Suspending properties
- Wetting and dispersing

Pharmaceutical applications:-

- These are a sequence of blends of sorbitol along its mono and dianhydrides with fatty acids.
- These are extensively used in foodstuffs and pharmaceutical preparation as lipophilic nonionic surfactants.
- They are used as emulsifier agents in emulsions, creams and other dermal preparation.
- They produce invariable water-in-oil emulsions or microemulsions except in combination with changeable extent of a polysorbate made water-in-oil or oil-in-water emulsions or creams.

Explanation or Description

- Sorbitan esters occur as cream- to amber-colored liquids
- Solids with a distinctive odor and taste;
- Appearance: Cream solid

Solubility:

- These are usually soluble or dispersible in oils
- Insoluble in water
- Soluble in most organic solvents.

Stability and Storage Conditions

- Stored in tight-closed container at cool place.
- Stable in weak acids or bases.
- In strong acids or bases prepare soap in slow rate.
Manufacturing technique

Preparation of Span based on dehydration of Sorbitol to convert a hexitan which subsequently esterified with the preferred fatty acid.

Safety

➢ The sorbitan esters release acrid smoke and irritating gas when heated to decomposition.
➢ These esters are generally nontoxic and nonirritant substance in cosmeceuticals, foodstuffs, and topical p’ceutical formulations.
➢ Sometimes observed as allergic reactions subsequent the dermal products.
➢ Acceptable guideline has been provided by W.H.O for daily intake of these esters.

Precautions for handling

Protect the eyes and suggested wear gloves during handling of chemical

Regulatory Status

➢ It is an incorporated in the FDA guidelines as inactive elements, Guide as different preparations e.g. injections, ophthalmic, vaginal and inhalating drug excipients.
➢ These esters are integrated in acceptable list for non-medicinal ingredients in Canada.
➢ In United Kingdom it is licensed as non parenteral medicines.

2.6.4 Polyoxyethylene Sorbitan Fatty Acid Esters

2.6.4.1 Polysorbate 60 (Tween 60)

Synonyms:-

Tween 60K; Tween 60 VS, Tween 60;Capmul POE-S; Cremophor PS 60; Atlas Armotan PMS 20; Crillet 3; Durfax 60; Durfax 60K; E435; Emrite 6125; Drewpone 60K; Eumulgin SMS; Glycosperse S-20FG; Glycosperse S-20; Hodag PSMS-20; Glycosperse S-20FKG; Hodag SVS-18; Lamsorb SMS-20; Liposorb S-20K; Liposorb S-20; Nikkol TS-10; Polycon T 60 K; Lonzest SMS-20; Norfox SorboT-60 Montanox 60; polyoxyethylene 20 stearate; Ritabate 60; Sorbax PMS-20; Protasorb S-20; sorbitan monoocotadecanoate

Chemical Name: - Polyoxyethylene 20 sorbitan monostearate
**CAS Registry Number:** [9005-67-8] 

**Emperical formula:** $C_{64}H_{126}O_{26}$

**Molecular Weight:** 1312

**HLB value:** 14.9

**Viscosity (mPa s):** 1.1

**Specific gravity at $25^\circ C$:** 600

**Acid value (%):** 2.0

**Hydroxyl value:** 81–96

**Moisture content:** 3.0

**Saponification value:** 45–55

### 2.6.4.2 Polysorbate 80 (Tween 80)

**Synonyms:**
- Armotan PMO 20; Atlas E; Capmul POE-O; Crillet 4; Crillet 50; Cremophor PS 80; Drewmulse POE-SMO; Durfax 80; Durfax 80K; Drewpone 80K;E433; Emrite 6120; Glycosperse O-20; Liposorb O-20; Liposorb O-20K; Hodag PSMO-20; Tween 80.
- polyoxyethylene 20 oleate; Montanox 80; Protasorb O-20; Z-sorbitan mono-9-octadecenoate poly(oxy1,2-ethanediyl) derivatives; Ritabate 80; Tego SMO 80; Tego SMO 80V;

**Chemical Name:** Polyoxyethylene 20 sorbitan monooleate

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

**Emperical formula:** $C_{64}H_{124}O_{26}$

**Molecular Weight:** 1310

**HLB value:** 15.0
Viscosity (mPa s): 1.08

Specific gravity at 25°C: 425

Acid value (%): 2.0

Hydroxyl value: 65–80

Moisture content: 3.0

Saponification value: 45–55

**Emulsifying agent**

- In emulsion of oil-in-water type at 1–15% concentration
- Used to capacity to holding water in 1-10% concentration for ointments
- In oil-in-water emulsions at 1-10% concentration required in blending with hydrophilic emulsifier.
- Solubilizing agent in 1-10% concentration for weakly lipophilic ingredient in lipid base.
- Wetting properties in 0.1–3% concentration -insoluble active constituents in lipophilic bases.

**Category:-**

- Emulsifying agent
- Nonionic surfactant
- Suspending properties
- Solubilizer
- Wetting and Dispersing properties

**Explanation**

**Colour:** Yellow oily liquid and differ from one batch to another batch

**Odor:** Characteristic with warm

**Taste:** Bitter
**Pharmaceutical applications:-**

- Polysorbates are a sequence of sorbitol partial fatty acid esters of anhydrides.
- The final materials have a blend of molecules of different diameter rather a single uniform product.
- Polysorbates are an emulsifier for making of stable oil-in-water emulsion.
- Successful play role as wetting nature in oral and parenteral suspensions of drug.
- Polysorbates may also be employed solubilizer in preparation of oil-soluble vitamins and essential oils.

**Stability and Storage Conditions**

- In electrolytes and weak acids and bases these are stable.
- These are highly sensitive to oxidation.
- It was shown hygroscopic nature so that check water content previous to use if required dry it.
- It was shown slow saponification with presence of strong acids and bases.
- Prolonged storage can lead to the formation of peroxides.
- Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.

**Safety**

- Polysorbates are extensively used in foodstuffs, cosmeceuticals, dermal, oral, parenteral preparation.
- Nontoxic and Nonirritant excipients
- Sometime when applied IV preparation of vita. E with blend of Tween 20 and 80, it causes serious side effects as low-birth weight in infants intravenously
- Occasionally when it was applying dermal and muscular route noticed hypersensitivity allergic reaction.
- Acceptable guideline has been provided by W.H.O for daily intake of polysorbates.
  a) Rat as IV dose polysorbate 60 has LD50 is equal to 1.22 g/kg
  b) Rat as IV dose Polysorbate 80 has LD50 1.8 g/kg but in oral it’s moderately toxic.
Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

Regulatory Status

- Polysorbates 60, 65, as well as 80 are included in list of GRAS.
- These esters are integrated in acceptable list for non-medicinal ingredients in Canada.
- Polysorbates of different grade from 20 to 80 are approved as food excipients.
- It is incorporated in the FDA guidelines as inactive elements, Guide as different preparations e.g. injections, ophthalmic, vaginal and inhalating drug excipients.
- They are incorporate in vesicular and nonvesicular drugs licensed in the United Kingdom.