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REVIEW OF TOPICAL LIPOSOMAL GEL FOR TREATMENT OF ACNE

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Abstract:

Acne has been often been nightmare to the majority of the population especially teen aged girls. The same has also impacts on the social life of a person once he/she is affected by Acne. There are varieties of the dosage forms that have been or are being utilized to cure the same. However still drug delivery aspects are being deployed to make the therapy more efficient. In the clinical management of acne, topical formulations are the preferred because of the ease associated with their application. In addition, combination therapy often proves more efficacious and better tolerated than mono therapy with a single drugFarnesol is a compound similar to vitamin A. It helps the skin to renew itself more quickly and may improve the appearance and texture of skin. The brand of Farnesol cream is used to reduce the appearance of fine wrinkles on the face, mottled light and dark skin patches on the face, and benign facial lenities (non-cancerous freckles) in adults and adolescents who are at least 17 years old.

Keywords: Liposomal Gel, Acne vulgaris, Salicylic acid, Hyperkeratinization

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1. INTRODUCTION:

1.1 Liposomal Gel

Most favourable therapeutic outcomes necessitate not only appropriate drug selection but also successful drug delivery. In human body, the skin is a best available space for drug delivery. Developing suitable drug delivery has become increasingly important in the pharmaceutical industry over the past three decades. The pharmacological response including the needed therapeutic effect and undesired adverse effect of a drug is dependent relatively, on the concentration of the drug at the site of action which depends upon the dosage form and the amount of absorption of the drug at the site of action (Kumar et al., 2007).In human body skin covers an area of about 2m2 and this multilayered organ receives approximately one-third of all blood circulating throughout the body. Skin contains an uppermost layer, epidermis which has morphologically distinct regions basal layer, spiny layer, stratum granulosum and stratum corneum. It consists of highly cornified (dead) cells a constant medium of lipid membranous area. These extracellular membranes are unique in their compositions and are poised of ceramides, cholesterol and free fatty acids (Jain et al., 1997).

In total skin surface consist of 1/1000 of hair follicles and 200-250 worry ducts on every tetragon centimetres of the skin area. It is one of the most gladly reachable organs of the human body. The possible area of the whole skin as the harbour of drug administration to the human body has been recognized for some decades, but skin is an extremely difficult barrier to the access of materials allowing only small quantities of a drug to go through over a period of time. Transdermal drug delivery the delivery of drugs crosswise the skin at a controlled rate to the systemic circulation is distinct from topical drug penetration which intention narrow areas. Transdermal drug delivery takes benefit of the relative accessibility of the skin (Kumar et al., 2004).

1.2 Components of Transdermal drug delivery system

1. Polymer matrix/ Drug reservoir- Polymers are core part of TDDS.It is prepared by dispersing the drug in liquid state or solid state and synthetic polymer base. Polymers used in TDDS should be biocompatibile and chemically compatibile with drug and other components of the system eg.- penetration enhancers. Also they should provide uniform and effective delivery of a drug all through the product‟s intended shelf life and should be in safe condition. Polymers used in TDDS are classified as-

- **Natural polymers**:
  E.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.

- **Synthetic elastomers:**
  E.g. polybutadiene, hydrin rubber, silicon rubber, polyisobutylene, acrylonitrile, neoprene, butyl rubber etc.

- **Synthetic polymers:**
  E.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, Polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc. (Pandey et al., 2012).

2. Drug- Some of ideal properties of drug & some factors to be consider during preparation of TDDS are as follows -

Table 1: Ideal properties of drug & some factors to be consider during preparation of TDDS

Parameters	Properties
Dose	Should be low (less than 20mg/day)
Half life	10/less(hrs)
Molecular weight	<400da
Skin permeability coefficient	>0.5*10-3cm/h
Skin reaction	Non irritating non sensitizing
Oral bioavailability	low

Table 2: Factors to be considered for Transdermal dose calculation

Physicochemical	Pharmacokinetic	Biological
Solubility	Half life	Skin toxicity
Crystalinity	Volume of distribution	Site of application
Molecular weight	Total body clearance	Allergic reaction
Polarity	Therapeutic plasma concentration	Skin metabolism
Meting point	Bioavailable factor	--

3. Permeation enhancers- Chemical compounds that expand permeability of stratum corneum so as to attain higher therapeutic levels of the drug molecule. They improve the permeability by interacting with structural components of the uppermost layer of skin.

- **Ideal properties of permeation enhancers-**

1. They should be non-irritatant and non-toxic and non-allergic.
2. They should not bind to receptor site that it should not show any pharmacological activity.
3. They should be cosmetically acceptable with facial skin.
4. **Pressure sensitive adhesive (PSA) –** Adhesive which are pressure sensitive helps to adhere transdermal patches to skin. It easily removed from the smooth surface without leaving any marks on it.
   Ex-Polyacrylate, polyisobutylene and silicon based adhesives are widely used in TDDS.
5. **Backing laminate-** Backing laminates are supports the patch which is impermeable to drugs and also to permeation enhancers. They must be chemically compatible with the drug and other excipients.
   Ex-vinyl, polyethylene and polyester films (Ezhumalai et al., 2011).
6. **Release liner-** Release liner is the primary packing that protects the patch and is removed before application of patch. Release liner is made up of base layer which may be either non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) & a release coating layer which is made up of silicon or Teflon. Release liner should be chemically inert & also permeable to drug, P. E & aqua.
7. **Other excipients like plasticizers and solvents-** Solvents used are chloroform, methanol, acetone, isopropanol and dichloromethane. Plasticizers used dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol (Patel et al., 2011).

- **Advantages**

The advantages of transdermal drug delivery more over other drug delivery systems are as follows:

1. Avoiding decomposition due to hepatic "first-pass" metabolism effect.
2. Reduced plasma conc. levels of drugs, which decreases side effects.
3. Reduction in variations in plasma levels of drugs.
4. Exploitation of drug entity having small half-life and lower therapeutic index.
5. Easy termination of drug delivery in case of toxicity.
6. Reduction in dosing frequency which enhances patient compliance (Kumar et al., 2004).

- **Limitations**

1. Heavy drugs entities (>500 Da) frequently complex to penetrate the uppermost layer of skin.
2. Drugs with extreme partitioning constant are not conducive and so it fails to reach blood circulation.
3. Drug should have a less M.P. can be given by this route due to their low solubility both in water and fat.

Many move towards have been made to deliver medicament crosswise skin barrier and increase the effectiveness. The most important consideration for attractive transdermal delivery are physical enhancers (ultrasound, iontophoresis, electroporation, magnetophoresis, microneedle), vesicles, particulate scheme (liposome, noisome,

transfersome, microemulsion, solid lipid nanoparticle) and chemical enhancers (sulphoxides, azones, glycols, alkanols,terpenes etc.

1.3 Transdermal Applications:
Examples of transdermal application of membrane-controlled transdermal system, adhesive diffusion-controlled system, matrix dispersion-type system and microreservior system are:

1.3.1 Membrane-controlled transdermal system:
Membrane-controlled transdermal system Reservoir encapsulated in shallow compartment molded from drug impermeable metallic plastic laminate & rate controlling polymeric membrane. Drug solid or disperse in solid polymer matrix or suspended in an viscous liquid medium (silicon fluid) Rate controlling membrane-EVAC Adhesive polymer-silicon or polyacrylate.

1.3.2 Adhesive Diffusion-Controlled System:
Adhesive Diffusion-Controlled System Version of membrane moderate system. Reservoirs directly disperse in adhesive polymer. Solvent costing on to impermeable metallic plastic backing. At the end rate controlling adhesive layer.

1.4 Routes of Penetration
At the skin, molecules contact cellular debris, microorganisms, sebum and other equipment, which negligibly change permeation. The penetrant has three potential pathways to the viable tissue - throughout hair follicles with connected sebaceous glands, via sweat ducts, or across continuous stratum corneum between these appendages (Figure 1.1).

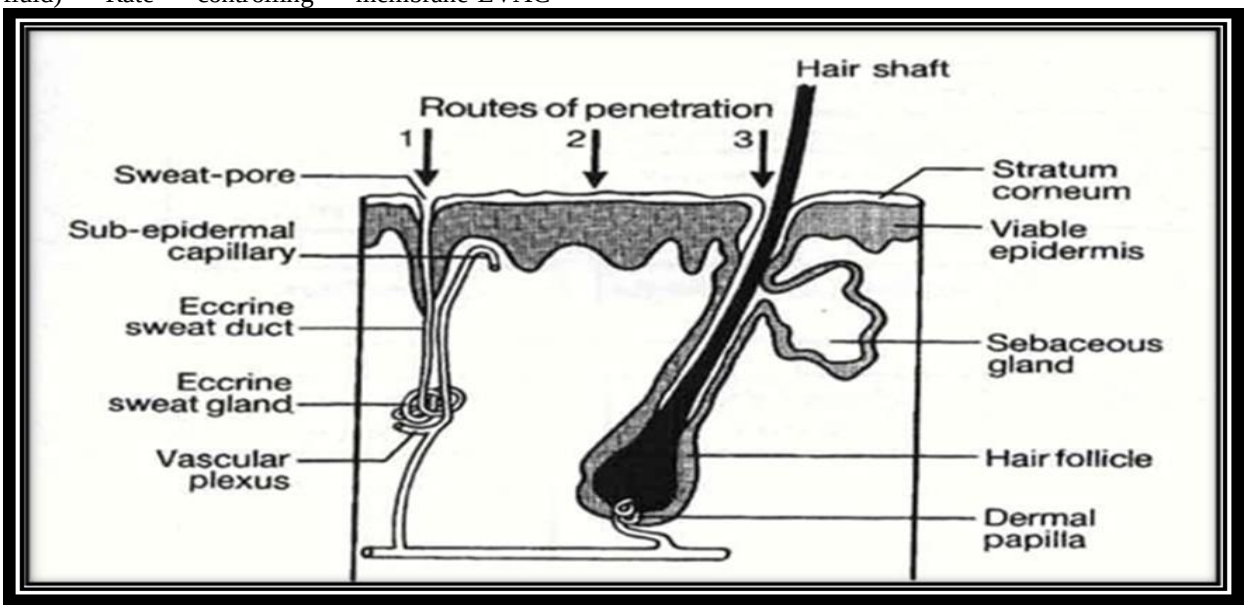

Figure 1: Simplified diagram of skin structure and macro routes of drug penetration (1) via the sweat ducts; (2) across the continuous stratum corneum or (3) through the hair follicles with their associated sebaceous glands.

Fractional appendage area obtainable for transport is merely about 0.1%; this route typically contributes negligibly to steady position drug flux. The pathway is essential for ions and large polar molecules that fight to cross intact stratum corneum. Appendages may be providing shunts, important at short times prior to steady state diffusion. Additionally, polymers and colloidal particles can target the follick. The intact stratum corneum thus presents the main barrier; its „brick and mortar" construction is analogous to a wall (Figure1.2). The corneocytes of hydrated kera bilayers of ceramides, fatty acids, cholesterol and cholesterol esters. These bilayers form regions of semi crystalline, gel and liquid crystals domains. Generally molecules penetrate through skin via this intercellular microroute and therefore many enhancing techniques plan to disrupt or bypass elegant molecular architecture. Viable layers may metabolize a drug, or stimulate a prodrug. The dermal papillary layer is so rich in capillaries that most penetrant clear within minutes. Frequently, deeper dermal regions do not considerably influence absorption, though they may bind e.g. testosterone, inhibiting its systemic removal (Kumar et al., 2007).

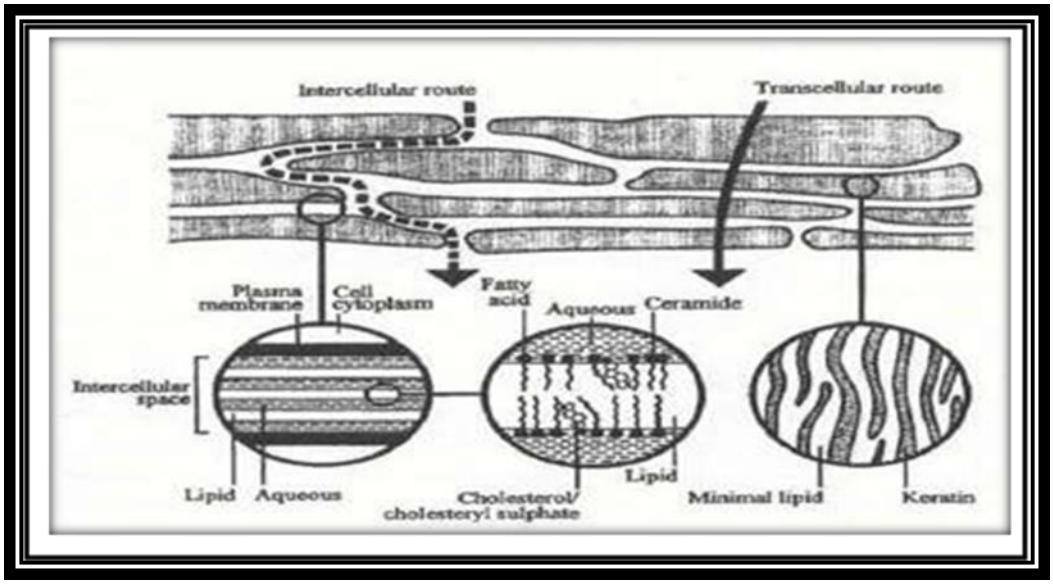

Figure 2: Simplified diagram of stratum corneum and two microroutes of drug Penetration.

1.5 Optimizing Transdermal Drug Delivery

Transdermal route offers several potential advantages over conventional routes like avoiding putrefaction due to hepatic "first-pass" effect, predictable and extended period of activity, minimizing side effects, utility of drugs having short half- life, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, reduced inter- and intra- patient variability, and most importantly, it improved patient compliance. But main major problems in transdermal drug delivery are the low penetration rate across the outer most layer of skin (Jain et al., 2001).

The non- invasive advance for providing transdermal drug delivery of diverse therapeutic substances are:

(1) Drug and vehicle interactions

(a) Selection of correct drug or prodrug

(b) Chemical potential adjustment

(c) Ion pairs and complex coacervates

(d) Eutectic systems

(2) Stratum corneum modification

(a) Hydration

(b) Chemical penetration enhancers

(3) Stratum corneum bypassed or removed

(a) Microneedle array

(b) Stratum corneum ablated

(c) Follicular delivery

(4) Electrically assisted methods

(a) Ultrasound (Phonophoresis, Sonophoresis)

(b) Iontophoresis

(c) Electroporation

(d) Magnetophoresis

(e) Photomechanical wave

(5) Vesicles and particles

(a) Liposomes and other vesicles

(b) Niosomes

(c) Transfersome

Vesicular systems are drug delivery system to deliver the drug dermally and transdermelly. Liposomes have the possible of overcoming the skin barrier, as the sears bilayered lipid vesicles, consisting primarily of phospholipids and cholesterols (Jain et al., 1997).

Liposomes were discovered by Bangham and colleagues (Bangham et al., 1965) and consequently became the most expansively explored drug delivery system. In early 1960‟s a great knowledge of vesicle

derivatives have been experienced for their abilities. Most experimentation, nevertheless, have centered on liposomes, since derivations only add to their basic property. Vesicles are closed, spherical membrane that separates a solvent from the surrounding solvent. Probable use of liposomes in topical drug delivery vehicles for both aqueous and lipid soluble drug has been examined. While it has been optional that the exterior envelop of a liposomes would allow it to pass through lipophilic skin, most researches show that liposomal vesicles become trapped inside the top layer of the stratum corneum cells. Usually liposomes are not expected to penetrate into viable skin, though occasional transport processes. This performance is useful both for local treatment of skin disorders and for cosmetic formulations, but not promising for systemic effect (Jain et al., 2004; Kumar et al., 2004).

1.6 Liposomes as Vesicular Drug Delivery System

Liposomes are small man-made vesicles of spherical shape that can be created from cholesterol and natural intoxic phospholipids. Liposomes are assured systems for drug delivery due to their shape, size along with hydrophobic and hydrophilic quality (besides biocompatibility). Liposomal properties change significantly with lipid composition, surface charge, size, and the method by which they are prepared. Furthermore, the choices of bilayers mechanism decide the „rigidity/fluidity" and type of the bilayers. For example, unsaturated phosphatidylcholine classes from natural sources (egg or soybean phosphatidylcholine) provide much additional permeability and less stable bilayers, whereas the saturated phospholipids with long acyl chains (for example, dipalmitoylphos phatidylcholine) form a rigid as well as impermeable bilayer structure (Gabizon et al., 1998).

It is shown that phospholipids precipitate and form clogged structures when they are hydrated in aqueous solutions. Such vesicles which have one or more phospholipid bilayer membranes can convey aqueous or lipid drugs, depending on the nature of the drugs used. Usually, liposomes are defined as spherical vesicles with particle sizes ranging from 30 nm to numerous micrometers. They consist of one or more lipid bilayers surrounding with aqueous units, where the polar skull groups are aimed at the pathway which is at the center and exterior aqueous phases. On the other hand, self-aggregation of polar lipids is not limited to conservative bilayers structures which rely on molecular shape, temperature and surrounding environment but may self-assemble into a variety of colloidal particles (Andreas et al., 2011).

Table 3: Advantages and disadvantages of liposome

Advantages of liposome	Disadvantages of liposome
Liposomes have increased efficacy and therapeuticindex of drug (actinomycin-D)	Liposomes have low solubility
Liposome have increased stability via encapsulation	Liposomes have short half-life
Liposomes are non-toxic, flexible, biologically compatible, completely biodegradable, and nonimmunogenic for systemic and non-systemic administrations	Sometimes phospholipid undergoes oxidation and hydrolysis-like reaction
Liposomes reducse the toxicity of the encapsulatedagent (amphotericin B, Taxol)	Leakage and fusion of encapsulateddrug/ molecules
Liposomes also help to reduce the exposure of sensitive tissues to toxic drugs	High cost of production.
Site avoidance effect	Fewer stables
Liposomes have flexibility with site-specific ligands to achieve active targeting	

Liposomes are amiable and are used as transporter for numerous molecules in cosmetic as well as pharmaceutical industry. Food and farming industries also have extensively studied the use of liposome encapsulation to produce as delivery systems that can deceive the compounds that are unbalanced (for example, antimicrobials, antioxidants, flavors and bioactive elements) and shield its functioning.

Liposomes can entrap both hydrophobic and hydrophilic complexes together, avoiding decomposition of entrapped substances, and release the entrapped substances at designated targets (Benech et al., 2002).

Because of their biocompatibility, biodegradability, low toxicity and aptitude to entrap both hydrophilic and lipophilic drugs together and short site-specific drug delivery to tumor tissues (Johnston et al., 2007), liposomes have enhanced rate both as an investigational scheme and commercial purpose. Liposomal encapsulation technology (LET) is the latest drug delivery method used by medical investigators to administer drugs that work as curative promoters to specific body organs. This application of delivery system is targeted for delivery of vital combinations to the body. LET is a technique of generating sub-microscopical foams called liposomes, which frequently encapsulate equipments. These „liposomes" form a barrier around their contents, which oppose the enzymes in the mouth and stomach, alkaline solutions, digestive juices, bile salts, and intestinal flora that are generated in the human body, as well as free radicals. The chemical substantes encapsulated in liposomes are, therefore, protected from oxidation and degradation. These protective phospholipids shield/barrier remains undamaged until the contents of the liposome are delivered to some specific targeted glands, organ, or system where the contents would be utilized (Himanshu et al., 2011).Also, drugs with different lipophilic values can be encapsulated into liposomes: strongly lipophilic drugs are entrapped totally in the lipid bilayers, powerful hydrophilic drugs are situated completely in the aqueous section and drugs with intermediary log divides between the lipid and aqueous phases, both in the bilayers and in the aqueous core (Maria et al., 2006).

1.6.1 Classification of liposomes

Various different techniques can be employed to classify liposomes, with size and structure being the most extensively used. The classification was titled as "Liposomes and Their Uses in Biology and Medicine". The categorization uses three letter acronyms to name the different classes (Betageri et al., 1993). Other classifications that are used are categorization according to production methods as well as classification according to the composition of the liposomes.

1.6.1.1 Classification of liposome according to size and shape

(a) Multilamellar vesicles (MLVs): These liposomes have more than one lamella, and can vary in size between 100 to 1000 nm.

(b) Small Unilamellar vesicles (SUVs): These liposomes are smaller than 0.1μm with just a single lamella. The composition of the membrane, as well as the aqueous medium has an influence on the minimum size that can be attained. The size variation of the population of SUVs is small when the liposomes approach the minimum size.

(c) Large Unilamellar vesicles (LUVs): These liposomes sizes start from 0.1μm and can reach sizes of up to 1000nm, which is close to the size of living cells. These liposomes have just a single lamella.

(d) Oligolamellar vesicles: These liposomes are composed of few concentric lamellae and are termed as oligolamellar liposomes. They are considered to be 2-5 bilayers and range in size from 50 to 250 nm.

(e) Giant vesicles: These are unilamellar liposomes of the average diameter reaching up to 100 μm. Since the size of these liposomes was approximately two-three order of magnitude greater than that of liposomes formed by other methods they quickly got the name of giant unilamellar vesicles (GUVs).

1.6.1.2 Classification of liposomes according to composition

The membrane of liposomes is usually constituted of natural components found in the membranes of regular living cells, but these constituents can be extensively varied and may even include artificial materials. Just tweaking the proportions of the ingredients can modify the properties of the membrane as well as the uses obtainable to the manufacturer.

(a) Conventional liposomes: These liposomes are collected of natural phospholipids (which may be neutral or negatively charged) and cholesterol. These liposomes are often used for targeting of the reticulo-endothelial system (RES). This shortens the circulation times of the liposomes substantially. Contents of these liposomes are most often intended for lysosomes (New, 1990).

(b) pH-sensitive liposomes: The membranes of these liposomes are composed of either cholesterol hemisuccinate (CHEMS), phosphatidyl ethanolamine (PE), oleic acid (OA) or dioleoylphosphatidyl ethanolamine (DOPE). These liposomes fuse with cells when the pH is low, thus discharge its content into the cell cytoplasm. These liposomes are perfect

for the delivery of macromolecules and weak bases (Sharma et al., 1997).

(c) Cationic liposomes: Cationic lipids make up the membrane of these liposomes with dimethyl-dioctadecyl ammonium bromide (DDAB), dioctadecyldimethyl ammonium chloride (DOGS), 2,3-dioleoyloxy- N - (2 (spermine carboxamido) - ethyl) - N, N- dimethyl – l - propanaminium fluoracetate (DOSPA), 1,2 dioleoyloxy-3-(trimethylammonio) propane (DOTAP), 1,2dimrystyloxypropyl-3-dimethyl- hydroxethyl ammonium bromide (DMRIE), and 1,2-dioleyloxypropyl-3-dimethyl- hydroxyethyl ammonium bromide (DORIE) joint with dioleoylphosphatidyl ethanolamine (DOPE). These liposomes tend to be toxic in high doses with a short lifespan, thus restricting them to local administration. They are most frequently used for the delivery of macro molecules that have a negative charge, this includes the delivery of DNA and RNA (New, 1990).

(d) Long-circulating liposomes (LCL): The lipids used for this type of formulation are neutral lipids with a high TC. Cholesterol is also included in these formulations (normally between 5 and 10%). These liposomes have a extremely long circulation half life, of up to 40 hours (Sharma et al., 1997).

(e) Immuno-liposomes: These liposomes are Conventional liposomes (CL) or Long Circulating Liposomes (LCL) with antibody or other recognition sequences fond of to the surface. These liposomes are formulated to bind to specific cells and to release the drug in that area, thus making it a targeted delivery system (Sharma *et al.*, 1997).

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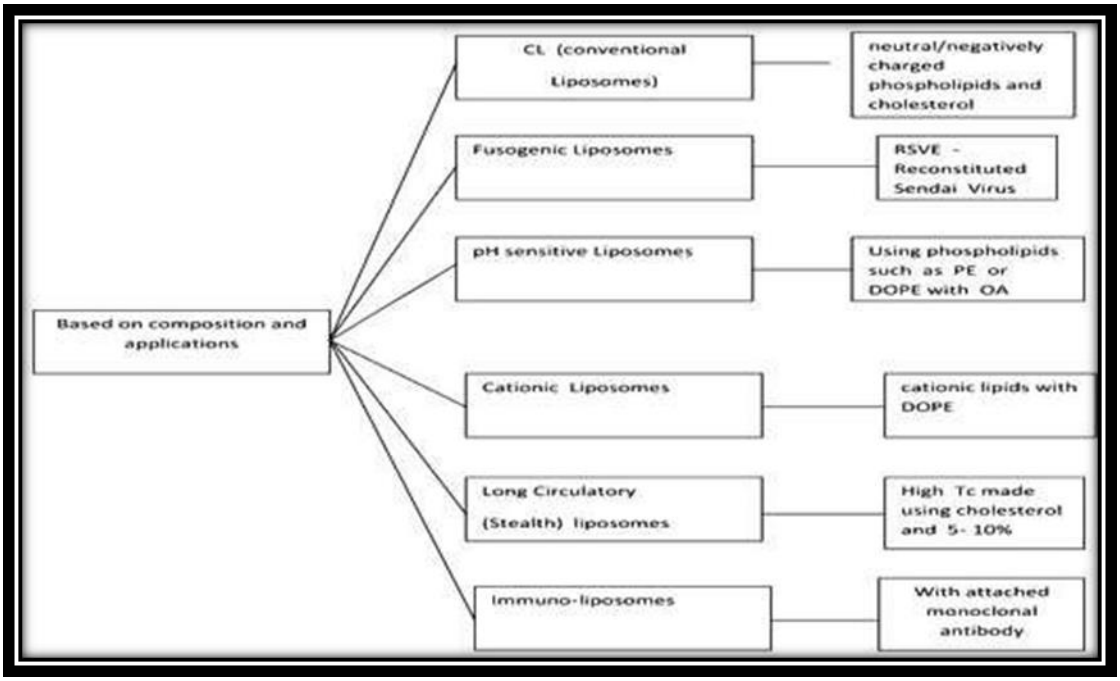

Figure.3: Classification of liposomes according to composition

1.6.1.3 Composition of Liposomes: The Major Structural Components of Liposomes are:

Phospholipids - Phospholipids are the major component of the liposome's membrane. The phospholipids used in liposomes are more classify into natural and synthetic phospholipids. The mainly phospholipid used is known as lecithin (also known as phosphatidylcholine) and is amphipathic.

1.6.2 General Method of Preparation

The accurate choice of preparatory method of liposomal system depends on the following grounds:

(1) The physiochemical nature of the material to be entrapped along with the liposomal ingredients.

(2) The nature of the medium in which the lipid vesicles are separated from each other.

(3) The effective concentration of the material to be entrapped and its potential toxicity

(4) Nature of all other processes involved during application/delivery of the vesicles.

(5) Optimum size, polydispersity and shelf-life of the vesicles for the intended application

(6) batch-to-batch reproducibility and possibility of large-scale production of safe and competent liposomal products (Mozafari et al., 2008).

Liposomes are manufactured in majority using various procedures(Figure 1.5) in which the water soluble (hydrophilic) substance are entrapped by using aqueous solution of these substance as hydrating fluid or by the accumulation of drug/drug solution at some phase during manufacturing of the liposomes. The lipid soluble (lipophilic) substances are solubilized in the organic solution of the constitutive lipid and then disappear to a dry drug containing lipid film followed by its hydration. These techniques involve the loading of the entrapped mediator before or during the manufacturing procedure (Dua et al., 2012).

1.6.2.1 Mechanical dispersion methods

(a) Liposomes prepared by lipid film hydration method: When liposomes are arranged in lipid solution of organic nature they end up into lipid dispersion in water. Especially this method is carried out by using chloroform /chloroform: methanol mixtures. The main purpose of this method is to gain a clear lipid solution for mixing of lipids completely. Normally these lipid solutions are prepared at 10-20mg/ml of organic nature, although these concentrations may be used if the lipid solubility and mixing are properly done. Once the lipids are mixed as per procedure in the organic solvent, the solvent is separated to yield a lipid film. For small volumes of organic solvent (<1mL), the solvent can be vanished by using dry nitrogen or argon stream in a fume hood. For larger volumes of the organic solvent, the removal process should be done by rotary evaporator yielding a thin film of lipid on the sides of a round bottom flask.The lipid films which are separated are dried to remove remaining organic solvent by placing the vial or flask on a vacuum pump overnight. If the use of chloroform is nauseous, the other solvents in which lipid(s) can be dissolved in tertiary butanol or cyclohexane. This lipid solution is transferred to containers and frozen by placing these containers into a block of dry ice or shaking the container in a dry ice-acetone or alcohol (ethanol or methanol) bath. Care should be taken while freezing that the container can withstand sudden temperature change without cracking. After totally freezing, this frozen cake was kept on a vacuum pump and was lyophilized until it was dry (1-3days depending on volume).The lipid cake‟s thickness should not be more than the diameter of container which was used for lyophilization. Vacuum pumps can be used to separate dry lipid films or cakes; the container should be stored tightly closed, taped and frozen until it is ready to hydrate (Danilo et al.,. 1997).

(b) Hydration of Lipid Film/Cake: Hydration of these stored lipid films/cakes is simply done by adding an aqueous medium to the container of dry cake and then agitated. After discharge of vacuums and elimination from the lyophilizer; the flasks are flushed with nitrogen and 5ml of saline phosphate buffer is added. The flask behaves as evaporator (flushed with n2), at room temperature and pressure at the speed below 60 rpm. The flask is keft rotating for 30minutes or till all lipids has been removed from the sides of the flask and has given milky-white suspension which is free of visible atoms. This milky white suspension is allowed to stand for a more 2 hours at room temperature or at a temperature above transition temperature of the lipid in order that total swelling process give MLVs. Appropriate hydration media comprises of distilled water, buffer solutions, saline, and non-electrolytes such as sugar solutions. Generally conventional solutions which meet these conditions are 0.9% saline, 5% dextrose and 10% sucrose (Dua et al., 2012). Through all the hydration process various lipids form compounds similar to their own structure. Lipids with high charges on experimention form a sticky gel when hydrated with low ionic strength solutions. The difficulty can only be increased when salt is added or by downsizing the lipid shelving. Poor hydrating lipids like phosphatidyl ethanolamine have a liability to self accumulate upon hydration. Lipid vesicles enclose more than 60% particles having a compact hydration layer surrounding the vesicle. As atoms move toward each another, there is no repulsion due to hydration to repel the advancing particle and then these two membranes fall in a well of energy where they all adhere together and form aggregates. They together settle in solution as large floccules which will scatter on crusade but develop upon sitting. The manufactured goods which are formed from hydration are a large, multi- lamellar vesicle (LMV) whose structure is similar to an onion and each lipid bilayer is separated by a layer of water. The spacing between layers of lipid is pressurized by poly-hydrating layers which being closer than highly charged layer which divides on electrostatic repulsion. Once a stable, hydrated LMV suspension has been produced, the economization of particles can be done by many methods, including sonication as well as extrusion (Batzri et al., 1973).

(c) Sonication: LMV suspensions when deranged by sonication method produces small, unilamellar vesicles (SUV) with diameters in the range of 20-60nm. Usually sonicated particles are prepared by using following instruments– (1) Bath and Probe Tip Sonicators and (2) Cup-horn sonicators. Although cup-horn sonicator is less used but successfully produces SUV. Probe tip sonicators gives high energy input to the lipid suspension but these sonicators suffer from overheating of the lipid suspension causing its degradation. The tips of sonicator also tend to liberate titanium particles into the lipid suspension which has to be removed by centrifugation prior to use. For this cause, bath sonicators are the most immensely used instrumentation for preparation of SUV. LMV dispersion is sonicated by placing a test tube containing the suspension in bath sonicators (or placing only the tip of the sonicator in the test tube) and sonicating it for 5-10 minutes above the Tc of the lipid and in this time period lipid suspension should begin to clarify and start yielding a somewhat foggy and transparent solution.This foggy appearance is due to scattering of light produced by residual large particles remaining in suspension. These particles are removed by centrifugation yielding a clear suspension of SUV. Mean size and distribution of particles of suspension is influenced by composition, concentration, temperature, sonication time and power, volume, and sonicators tuning.

(d) French pressure cell method: This method involves the extrusion of MLV at 20,000 PSI at 4°C through a small orifice. The method cause several damages as compared to sonication method. The technique is simple, fast and reproducible and involves gentle handling of delicate equipments (Hamilton and Guo, 1984). The liposomes resulting from this method are somewhat larger than SUVs sonicate. The disadvantages of this method are that the temperature is hard to achieve and the working volumes are comparatively small (about 50 mL max.) (Riaz et al., 1996).

(e) Membrane Extrusion Liposomes: This method involves firstly suspension of phospholipids in buffer saline solution to give large, multi-lamellar vesicles. So obtained vesicles are then again and again passed through a polycarbonate filter with 100 nm pores giving uniformly sized and "Large Unilamellar Vesicles (LUV), which are approximately 100 nm in diameter. This method is syringe-based membrane extruder method which is inexpensive and easy to use.

(f) Freeze-thawed liposome preparation method: SUVs are frozen quickly and slowly defrosted. The sonication is short lived and scatters collective materials to LUV. The unilamellar vesicles are formed as a result of the production of SUV by the method of freezing and defrosting. Growing phospholipids concentration is strongly inhibited by this type of synthesis and raising ionic power of the medium. The encapsulation efficiency is increased from 20% to 30%.

1.6.3 Application of Liposomes

(1) Medicinal applications of liposomes: Applications of liposomes in pharmacology and medicine can be classified as therapeutic and diagnostic applications of liposomes containing either drugs or various markers, and they are used as model/ tool/ reagent in the basic studies of cell, process of recognition, and to study the mode of action of +ve substances. Exceptionally many drugs have a very slender therapeutic window, means that the amount of drug between potent dose and lethal dose is very small. In a few cases the toxicity can be decreased or the efficacy can be increased by the use of an appropriate carrier for drug which changes the chronological arrangement and spatial sharing of the drug, i.e. its pharmacokinetics and bio-distribution. The indemnity and limitations of drug carriers used for liposomes seriously depend on the communication of liposomes with cells and their invivo fate after administration. In vitro and in vivo studies of the interactions with cells have shown that the interaction between liposomes and cells is done by simple adsorption or subsequent endocytosis. Fusion with cell membranes is much rarer. The fourth possible interaction is exchange of bilayer constituents, such as lipids, cholesterol and membrane bound molecules with components of cell membranes. The body protects itself with a complex immune system. Upon entering into the body, surface of larger objects like thrombus are eventually is passivated by coating with bio macromolecules while smaller particles, including microbes, bacteria, and colloids are eaten up by the cells of the immune system. This reaction of the immune system has triggered considerable efforts in the improvement of biocompatible and non recognizable surfaces and has also, on the other hand, narrowed the spectrum of application of micro particulate drug carriers only for targeting of the very small cells of the immune system.

(2) Improved solubility of lipophilic and amphiphilic drugs: Various examples of lipophilic and amphiphilic drugs include Porphyrins,

Amphotericin B, Minoxidil, some peptides, and anthracyclines, respectively. In some cases hydrophilic drugs, such as anticancer agent Doxorubicin or Acyclovir can also be encapsulated in liposome at various concentrations in no. of folds above their aqueous solubility. This is may be due to precipitation of the drug or gel formation in the liposome with appropriate substances encapsulated.

(3) Liposomes in parasitic diseases and infections: As conventional type of liposomes is digested by phagocytic cells in the body after intravenous injection, they are ideal vehicles for the targeting of drug molecules into macrophages. The best known example of this type of liposomes is „Trojan horse-like" mechanism. In this there are several parasitic diseases which normally reside in the cell of mononuclear phagocytic system. They include diseases like leishmaniasis and other fungal infections.

(4) Anticancer therapy by liposomes: The toxicity of various anticancer mediators as liposome formulations was shown to be less than the free drug. Anthracyclines are drugs which stop the growth of dividing cells by getting into the DNA and therefore killing fast dividing cells. These cells are usually present in tumors, but can also be found in gastrointestinal mucosa, hair, and blood cells and therefore this class of drugs are very toxic. They are mostly used and studied as Adriamycin. Above all, acute toxicities and dose of drug is limited by its cumulative cardiotoxicity.

(5) Liposome in immunology: For protein antigens, liposome behaves as excellent carriers as they can carry large amount of antigen in association with excipients. These liposomes are made to mimic the pathogen that stimulates the development of the immune system. There are numerous mechanisms which promotes their uptake by antigen presenting cells and exposure of encapsulated antigens to the lymphocytes of the immune system for the induction of reaction. In addition to the improvement of liposomes as immuno-potentiators. Earlier these types of liposomal vesicles have been used in investigation for wide range of immunological events. These comprise of lysis of foreign cells as a result of membrane damage and the aptitude of membrane sensitized haptenic antigens to start formation of antibodies and/or cytotoxic effector cells.

1.7 Acne vulgaris

Acne vulgaris or simply known as acne is a human skin disease characterized by skin with scaly red skin (seborrhea), blackheads and whiteheads (comedones), pinheads (papules), large papules (nodules), pimples and scarring (Thappa et al., 2009). Acne affects skin having dense sebaceous follicles in areas including face, chest and back (Benner and Sammons, 2013). Acne may be of inflammatory or non-inflammatory forms (Harper, 2009). Due to changes in pilosebaceous units lesions are caused by androgen stimulation. Acne occurs commonly during adolescence, affecting about 80–90% of teenagers in the Western world and lower rate are reported in rural societies. Acne is usually caused by increase in androgens level like testosterone mainly during puberty in both male and female. Acne reduces over time and tends to disappear over the age. The large nodules called as cysts and severe inflammatory acne called as nodulocystic. The cystic acne occurs on buttocks, groin, armpit area, hair follicles and perspiration ducts and affects deeper skin tissue than common acne. Acne causes scarring and psychological effects such as; reduced self-esteem and in rare cases depression or suicide (Goodman, 2006; Purvis et al., 2006). Reports showed the incidence of suicidal tendency in patients with acne as about 7.1%. Acne usually occurs during adolescence. The word acne refers to the presence of papules, scars, comedones and pustules. The common form of acne is known as acne vulgaris. Many teenagers suffer from this type of acne. Acne vulgaris shows the presence of comedones. Acne rosacea is synonym for rosacea and some persons not have acne comedones associated with their rosacea, hence prefer the term rosacea. Chloracne occurs due to exposure to polyhalogenated compounds.

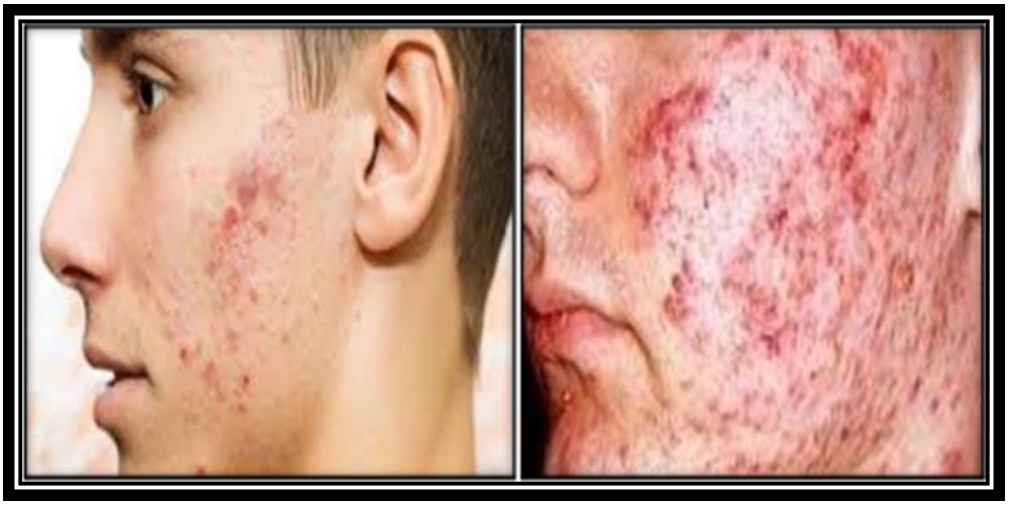

Figure 4: Acne on the face

1.7.1 Epidemiology

In 2010, it was reported that acne affects approximately 9.4% of the population. It affects about 90% of people during teenage years and sometimes in adulthood. About 20% people have moderate and severe cases. Acne rates are low in rural areas and it may not occur in the non-westernized people of Paraguay and Papua New Guinea (Spencer et al., 2009). It is more common in females 9.8% compared to males 9.0%. In over 40 years old subjects about 1% of males and 5% of females have problems (Dawson and Dellavalle, 2013). It affects all ethnic groups' people and it is not clear if race affects rates of disease. Acne affects 40 to 50 million people which is about 16% in the United States and approximately 3 to 5 million people which is about 23% in Australia. In the United States, it is more severe in Caucasians than African descent people .

1.7.2 Signs and Symptoms of Acne

It includes papules, nodules (large papules), seborrhea (increased oil-sebum secretion), comedones, pustules and scarring (Thappa et al., 2009).The appearance of acne varies with skin color and it is also associated with psychological and social problems (Dawson and Dellavalle, 2013).

1.7.3 Etiology

Acne develops due to blockage of follicles, hyperkeratinization and keratin plug formation and sebum (microcomedo). With increased androgen production, sebaceous glands are enlarged and sebum production is increased. The microcomedo may enlarge to form an open comedo (blackhead) or closed comedo. Comedones occur as a result of clogging of sebaceous glands with sebum, naturally occurring oil and dead skin cells (Benner and Sammons, 2013). The naturally occurring commensal bacterium Propionibacterium acnes can cause inflammation and inflammatory lesions like infected pustules or nodules and papules in the dermis around the microcomedo or comedone resulting in redness, scarring or hyper pigmentation (Benner and Sammons, 2013; Simpson and Cunliffe, 2004).

1.7.4 Environmental Factors

It includes various factors like High-humidity, Prolonged sweating, Increase in skin hydration, Exposure to dirt or vaporized cooking oil or certain chemicals like petroleum derivatives.

1.7.4.1 Hormonal

Menstrual cycles and puberty may also causes acne. During puberty, increase in androgens level causes the enlargement of follicular glands and sebum production is also increased (Benner and Sammons, 2013). Anabolic steroids produce similar effect (Melnik et al., 2007). Several hormones are linked with acne like the androgens testosterone, dihydrotestosterone, dehydroepiandrosterone sulfate and insulin like growth factor 1 (IGF -I). In later years development of acne vulgaris is uncommon but rosacea incidence will increase which is having similar symptoms in older age groups. Acne vulgaris in adult women may be due to underlying condition such as; pregnancy, Cushing"s syndrome, hirsutism or polycystic ovary syndrome. Acne climacterica refers to menopause associated acne, occurs as production of the anti-acne ovarian hormones estradiol and progesterone allowing the acnegenic

hormone testosterone to continuously exert its effects.

1.7.4.2 Genetic

The genetics of acne susceptibility is polygenic as the disease does not follow classic Mendelian inheritance pattern. There are multiple candidates for genes related to acne which includes polymorphisms in Tumor necrosis factor-alpha, Interleukin-1 alpha, CYP1A1 (Taylor et al., 2011).

1.7.4.3 Infectious

Propionibacterium acnes (P. acnes) are anaerobic bacterium species that mainly causes acne. Staphylococcus aureus has been discovered to play an important role since normal pores colonized only by Propionibacterium acnes . Specific clonal sub strains of P. acnes are also associated with normal skin health and long term acne problems. These strains have the capability of changing, perpetuating or adapting to the abnormal cycle of inflammation, oil production and inadequate sloughing activities of acne pores. For at least 87 years, one virulent strain of Propionibacterium acnes has been circulating around Europe Antibiotics resistance has been continuously increasing to P. acnes in vitro.

1.7.5 Diagnosis

Scales used for grading the severity of acne vulgaris are as follows:

a) Pillsbury scale: It classifies the severity of acne ranging from 1 (least severe) to 4 (most severe).

b) Cook's acne grading scale: It sees the images to grade severity of acne ranging from 0 (least severe) to 8 (most severe).

c) Leeds acne grading technique: It counts and classifies inflammatory and non- inflammatory lesions ranging from 0 to 10.

(i) Acne, grade I; multiple open comedones (ii) Acne, grade II; closed comedones (iii) Acne, grade III; papulopustules (iv) Acne, grade IV; multiple open comedones, closed comedones, and papulopustules, plus cysts.

1.7.5.1 Differential diagnosis

a) Acne rosacea: It is commonly observed in middle or later age of life.

b) Folliculitis and boils: It may present with pustular lesions and are similar to acne.

c) Milia: These are small keratin cysts that may be confused with whiteheads. They may be whiter than acne and most commonly seen around the eyes.

d) Pityrosporum folliculitis: It predominates on the trunk.

1.7.6 Management

Various medicines are used for treatment of acne which includes benzoyl peroxide, antibiotics, antiseborrheic medications, sulfur and sodium Sulphacetamide, anti-androgen medications, salicylic acid, hormonal treatments, alpha hydroxy acid, retinoids, azelaic acid, keratolytic soaps and nicotinamide (Ramos-e-Silva and Carneiro, 2009). Laser and light devices and minor subcision surgery is also performed. Benzoyl peroxide is first line treatment for mild and moderate acne due to its effectiveness and mild side effects like irritant dermatitis, dryness of the skin, redness and peeling. It helps to prevent formation of comedones caused by P. acnes bacterium and has anti-inflammatory properties. Topical application increases sensitivity to the sun and sunscreen is combined to prevent sunburn. Benzoyl peroxide is often combined with antibiotics. Benzoyl peroxide is found to be equally effective as antibiotics at all concentrations, although it does not produce bacterial resistance (Sagransky et al., 2009).

1.7.6.1 Antibiotics

Antibiotics are used in more severe cases due to their antimicrobial activity against P. acnes along with anti-inflammatory properties. They are becoming less effective with increasing resistance of P. acnes worldwide (Sagransky et al., 2009). Antibiotics including Clindamycin, erythromycin and tetracycline‟s such as; Doxycycline, oxytetracycline, lymecycline and minocycline are topically applied or orally administered for treatment of acne.

1.7.6.2 Antiseborrheic Drugs

Sulfur is used in concentrations varying from 1 to 10% and act as an antiseborrheic and mild keratolytic but it produces bad odor and the staining of clothes. Alcohol-ether in equal parts and zinc sulfate also act as sebum reducing agents .

1.7.6.3 Topical Sulfur and Sodium Sulphacetamide

Sulfur is used as a drying agent and antibacterial agent. It is present in washes, lotions, creams, foam formulations, prescription and nonprescription

masks. It can be useful for treatment of rosacea and seborrhoeic dermatitis. Sodium Sulphacetamide is often combined with sulfur and has anti-inflammatory properties. Sodium Sulphacetamide can treat acne and used for the sensitive skin acne patient (Gupta and Nicol, 2004).

1.7.6.4 Salicylic acid

Salicylic acid has bactericidal and keratolytic properties and hence lessens acne. Salicylic acid open obstructed skin pores and promotes shedding of epithelial skin cells but it causes hyperpigmentation of the skin in individuals with darker skin types (Benner and Sammons, 2013).

1.7.6.5 Anti-androgen treatment

In females acne can be treated with the use of combined oral contraceptives (Rubin, 2001). Third or fourth generation progestins such as norgestimate, desogestrel or drospirenone combination product may be more beneficial. Oestrogenic oral contraceptive is an effective for acne (Karrer-Voegeli et al., 2009). Due to androgenic properties of oral contraceptive norethisterone is contradicted in acne. Anti-androgen cyproterone combined with 50 µg of ethinylestradiol is available as Dianette® which is most effective hormonal intervention (Tan, 2004). A combination of ethinylestradiol with drospirenone available as Yasmin® has been found to be effective (Joish et al., 2011). Spironolactone has been shown to be effective for older women (Kim and Del Rosso, 2012).

1.7.6.6 Topical retinoids

Topical retinoids possess anti-inflammatory properties and act by normalizing the follicle cell life cycle and prevent hyperkeratinization of these cells that can create a blockage. It includes tretinoin, adapalene and tazarotene. They are related to vitamin A and similar to isotretinoin and have much milder side effects like skin irritation and flushing (Benner and Sammons, 2013). Retinol a form of vitamin A has mild effects and is used in many over the counter moisturizers and other topical products.

2. SUMMARY AND CONCLUSION:

The purpose of this research work is to develop and evaluate topical liposomal gel of Farnesol for treatment of acne. In the clinical management of acne, topical formulations are the preferred route of drug administration. In addition, combination therapy often proves more efficacious and better tolerated than mono therapy with a single drug so combination of Farnesol and Hydroquinone has been attempted via delivery by liposomal gel formulation. Farnesol is a widely used drug in the topical treatment of Acne, and other skin disorders. Farnesol synthetically produced is retinoid commonly used in the treatment of acne.

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4. CONFLICTS OF INTEREST

Authors have no conflicts of interest to declare.

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