1. **PREAMBLE**

**INTRODUCTION**

1.1. **DRUG DELIVERY SYSTEM AS A TRANSDERMAL FORM**

One of the chief aims in delivery of drug in body successfully in research was the discovery that acceptable them through skin. Transdermal drug delivery system play is vital because this route is a free from invasive methods. Further, trouble of drug largely affected by GUT enzymes when we take drug through oral route and uneasiness related with non oral as parenteral drug. For systemic supply of drugs for a number of diseases topical route is first choice. Hence, topical preparation is the best patient compliant manner of drug deliveries in the body (Kanitakis J., 2002). Transdermal drug delivery system is that related to manner of drug supply as sustained release manner (i.e. constant plasma drug concentrations), over an extended time period (Basak S.C et al., 1997).

1.1.1. **Conventional dosage forms of drug are better**

The transdermal or topical routes of drug have following advantages:

1. Overcome problems related with gastro-intestinal route due to enzymatic degradation, pH, drug-food interactions etc.
2. In case of vomiting, diarrhoea, etc. oral preparation are unsuitable.
3. Overcome the effect of “hepatic first pass”.
4. Possibility and inconveniences of parenteral remedy will be avoided.
5. Short plasma half-life drugs properties extends via the reservoir of drug present in the therapeutic delivery system and release drug as controlled manner.
6. Reaction of drug terminated rapidly by exclusion of drug from the skin surface.
7. Unconscious/coma patient have fast accessibility of medicament then compare to oral.
8. Decrease side effects and improve remedial effect.
9. Provide predictable activity over extended duration of time
10. Improved control of the concentration of drug with small therapeutic indices.
11. Minimize inter and intra-patient variation.

This route is a good substitute to buccal, sc (subcutaneous), intravascular and trans mucosal routes for delivery and move toward drugs into the skin for treatment of many disease.
Transdermal includes the following kinds of drug management:

1. Apply locally e.g., transdermal gels
2. Drug transporter, e.g., liposomes and nanoparticles
3. Penetration enhancers
4. Electrotransport at transdermal route
5. Patches applying transdermally
6. Physical modalities with the purpose of transdermal drug carrier
7. Overcome invasive technique by transdermal delivery of drug e.g., injections or needle-free treatment

Biopharmaceutically, several advantages may offer over injection preparation, across mucosal surfaces

1. Therapeutic efficiency improved
2. Escaping of an injection preparation
3. Rapid absorption than compared with other route
4. Patient acceptance more than parenteral preparation
5. Hepatic first pass metabolism by the liver is bypassing
6. Low price when compared with parenteral preparation

1.1.2. Difficulties of transdermal drug delivery system

(1) Permeation of drug via skin of human:
Human skin is a chemical as well as physical barrier of body; Stratum corneum is a vital superficial obstacle layer of human skin, put off every external agent as well as drugs. The transdermal drug delivery system will be complicated when a drug requisite is greater than 10 mg / day. Merely comparatively effective drugs can be supply via this path.

(2) Irritation effect of Skin:
Percutaneous absorption is very necessary step for drug action in transdermal preparation. It’s possible with help of different additives or excipients, but it may be caused skin irritation and sometimes contact dermatitis.

(3) Clinical reception:
Previous to mounting a transdermal preparation, it has to be make sure carefully.
1.2. TRANSDERMAL ADMINISTRATION OF DRUG VIA SKIN

1.2.1. Permeation via skin: (Banker GBS and Rodes CT, 1979)

Skin has covered about 2-3 square meter area of body as major protective organ of human body. Most of transdermal formulations are to be applied on the skin surface. That’s by fundamental information of human skin, physiological role and biochemistry of skin is very essential. The single organ of the body exists in larger size which separates the internal body organ from the external surroundings. It’s joint mucosal lining of the tracts of digestive, respiratory, and excretory as well as reproductive system and makes a defensive casing. The presence of sweat gland and sebaceous glands (contain fatty acids secretion sebum) control the pH of the skin is ranged from 4 to 5.6. Growth of micro-organism and pathogen on the surface of skin are dependent upon acidity of the skin. It may helps in restricting and preventing them.

1.2.2 Physiology of Skin:

Three layer are epidermis, dermis, and subcutaneous tissue (Kanitakis, 2002) present in skin. Several layers make the internal structure of skin (fig. 1). The outer coat of skin is recognized as epidermis and the beneath the epidermal layer is well identified as dermis. This layer of skin dermis contains blood vesicular system, hair follicles, and dermal glands as sweat gland & sebaceous gland etc. Below the dermis fatty tissues subcutaneous are present; bulbs of hair protrude in to these fatty tissues layer. Cornifiede (corneocytes) covering of skin is making high dense cross linked construction of protein which decreases absorption of drug in to body (Maya W. and Ashar S. 2012). Skin of human is most significant and targeted area/site for treatment of local skin diseases. Skin act as rate limiting barrier for entering or penetrating of drugs in body. There are a lot of approaches or method for penetration enhancement across the skin. In which vesicular and provasicular system is one of them most promising system fulfilling of this requirement. (Touitou E, et al., 2000, Jain S, et al., 2003)
1.2.3 Epidermis

The layers of epidermis are:

I. Basel layer (Growing Layer)
II. Squamous cell layer (Prickly cell Layer)
III. Granular cell layer (Str. Granulosum)
IV. Stratum Cornified Layer (Str.Corneum)

Two cells one of them keratinocytes and second dendritic cells are chiefly made up of upper layer of epidermis which is squamous and stratified in nature. The epidermis generally is separated into four layers basis on morphology and position of keratinocyte cells as they set apart into horny cells, following decreasing order forth one is horny cell layer or the cornified layer outer coat (stratum corneum), third the granular cell coat (stratum granulosum), second the squamous cell coat (stratum spinosum), first the basal cell cover (stratum germinativum), (James et al., 2006 Murphy). The three inferior layers are living in nature stratum malpighii is nucleated cells of the skin.
The epidermis is a renewing repetitively and pilosebaceous cells, nails; sweat glands are derivative structures of this layer. Approx 70-80% of cells in the skin layer are the ectoderm resultant keratinocytic in nature. The keratinization is separation progression which occurs as the cells transfer from the basal layer to the exterior of the skin.

(1) Basel layer (Growing Layer)
Column-shaped keratinocytes cells are bind with basement covering region with their long axis upright to the dermis. Another name of this basal layer is Stratum germinativum. Individual layers form by these basal cells and adhere to one another with two more outward squamous cells layer from side to side desmosome junctions (Murphy, 1997).

(2) Squamous cell layer
Six to ten layer broad stratum spinosum or squamous cell are present above the basal cell epidermis (Murphy, 1997). A variety of cells are containing by this cell layer which differ their character depending on their position in their shape, structure, and sub-cellular labels.

(3) Stratum Granulosum
Living cells of the epidermis which is exists as outer most layers called stratum granulosum or the granular layer. It is composed of flattened cells containing plenteous kerato-hyaline granules in their cellular cytoplasm.

(4) Stratum Cornified Layer
Outermost non-nuclear, translucent, thin layer cells on the palm and sole of the hand and foot respectively. This layer made a mechanical shield to the skin, Horny cells (Corneocytes) layer to maintain water loss and foreign attack (Jackson et al., 1993). Most of anti-inflammatory and analgesic drugs are used as transdermal preparation because of these drug are reason of many adverse effects when administered as orally form as GIT trouble such as irritation and ulceration in mucosa. These drugs via skin as transdermal systems provides controlled manner which have short lives in blood with discard oral disadvantage for osteoarthritis and rheumatoid arthritis disease (Bhargava T. et al, 2011).
**Subcutaneous layer**
Layer of this tissues composed of fat loaded areolar sheet, recognized like superficial fascia linked with the dermis of the skin. Vascular system such as arteries and veins are present in this region.

**Skin appendages**
Skin is scattered by hair follicle and related numerous gland such as sebaceous gland, sweat gland, mammary gland etc. It is the region of containment of body fluids and tissues.

**1.2.4 FUNCTIONS OF SKIN**
1. Protector from exterior stimuli example as chemicals, light, radiation, heat, cold etc
2. Reply of stimulus as pressure, heat, pain etc
3. Metabolites wastes clearance through skin
4. Temperature regulator of body
5. Regulate blood pressure
6. Prevented penetration of poisonous foreign material and radiation
7. Mechanical shock absorber
8. Promote Sexual appeal and recognition

**1.3 NOVEL DRUG DELIVERY SYSTEM**
Different methods are recently used for development of novel preparation such as liposomes, niosomes and provascular system (Proniosomes, Aquasomes, and Ethamosomes etc.), nanoparticles, microsphere etc.

**1.4 VESICULAR DRUG DELIVERY SYSTEM**

**1.4.1 LIPOSOMES**
Liposomes are prepared in varying sizes beginning from 25 nm to some micrometers. Liposomes consist of a single or multiple lipid double layers thus forming vesicles which may be unilamellar or multilamellar. They are capable of getting transported to both hydrophilic and lipophilic form of lipid layer or in the hydrophilic core. They are supposed to guard and/or to prevent to degradation the active ingredients. Whenever liposomes come to contact with the skin, it was liable to break down into its constituent components. For that reason, liposomes at most excellent can transform drug transport to
stratum corneum of skin, but absorption of drug via skin will need more stable form such as SLNs (solid lipid nanoparticles) (Cevc G and Blume G. et al., 2004).

When the drug enter in the body as form in liposome preparation then compared to conventional dosage form the concentration of drug in the epidermis may be raise up to 5- times more (El Maghraby GM et.al., 2008). In cosmetic area an aqueous cream of liposome in water can easily prepared for better performance. Examples of different preparation of liposomes cream formulation as antioxidants, vitamin A and E and its derivatives.

![Fig. 2 a) Model of a unilamellar liposome b) Representation of Niosomes.](image)

**Fig. 2 a) Model of a unilamellar liposome consisting of one double lipid bilayer b) Representation of Niosomes.**

**Applications of liposomes**

- Localized drug effect
- Enhanced drug uptake
- Cancer chemotherapy

Liposomes are used as a carrier for different pharmaceutical preparation e.g. immune agents, vaccine adjuvant, and eye preparation, Cranium targeting drug, other infection and present time for treatment of life threatening cancer chemotherapy. In the skin for the improvement of local effect they can be used as topical or transdermal drug delivery system and overcome the adverse effect of systemic or oral administration of drug and improve the patient acquiescence.
Some of applications related to liposomes are described as follows:-

- Liposome to create Stable Plurilamellar Vesicles was integrated 5-Flurouracil for the topical delivery of drug. Freshly prepared liposome was direct incorporated in hydroxyl propylmethyl cellulose gel (HPMC) polymer in 5-FLU liposomal dispersion for increment enhances its stability.

- Lyophilization technique was used for preserving drug in its dry form and easily reconstituted instantly prior to its application into its ultimate dosage form therefore increasing the shelf life of liposomes. The lipid nature of the vesicles enhanced drug transfer into the skin, which provide as carriers for the supply of drug.

- Fluconazole categorized in antifungal drug was used as topical liposomal gel for candidiasis by incorporating in base of carbopol 934 gels shown an excellent release of drug by liposomal form. Skin penetration rate and deposition in skin was in the form of liposomal gels or dispersion more in contrast its commercial gel along with stable for two months.

- Gel liposomal preparation of diclofenac sodium was shown more anti inflammatory action this was prepared by thin film hydration technique which showed increased sustained release of drug.

- Lidocaine liposomal gel for local anesthetics action was prepared by mixing in carbopol base and this also shown that the incorporated drug release for the longer period through liposomes.

- Tretinoin liposomal gel prepared by the amalgamation of carbopol 934 had shown enhanced efficacy. This gel compared with plain tretinoin gel drug diffusion showed 4-5 times decrements in flux and almost two-three fold increment of drug retention on skin.

- Carbopol 940 base used for converting of ketoconazole antifungal drug as liposomal gel and the shown the amplify release reaction ability on skin. At refrigerated temperature the stability of liposomal preparation shown maximum drug retention percent
1.4.2 TRANSFEROSOMES

When “edge activator” is adding with diverse amounts of surfactant for example sodium cholate, sodium deoxycholate etc to the bilayer of traditional liposomes with a small concentration of ethanol these tailored vesicles are called Transferosomes. The edge activators are making an ultraflexible structure by destabilizing the membrane. Transferosomes, are penetration enhancers scientifically is assume that ultra deformable 10 times that of an unchanged liposome which pinch through pores between the corneocytes which is less than one-tenth of liposomes diameter, therefore these liposomes 200–300 nm pores sizes be capable of passes easily. Encapsulated drug enter inside deep in the epidermis not to the blood circulation (Benson HA et al. 2006).

Transferosomes perform perform as vectors of drug, which are left behind intact after incoming to the skin. They can be active as penetration improvers, disturbing extremely ordered ordered intercellular lipids from Stratum corneum of skin and consequently provide availability of the drug particles penetration in skin. The current studies recommend that the incorporation and infiltration of these vesicles through the skin involves two basic mechanisms. First is hydrophobic or hydrophilic nature of the API another is transferosome content. Several drugs for example NSAID as well as local anesthetics in form of transferosomes have been used in animal experiments showing amplified dermal and clinical result compared to conservative formulations (Benson HA et al. 2006).

Transferosomes is aggregate of self flexible and optimized lipid drug having low and high molecular mass, transfer easily through intact vesicles, gives better penetration in addition to behave as depot, release drug slowly and gradually. Its membrane flexibility is obtained by integration of suitable surfactants in the appropriate ratios. Insulin is mainly administered subcutaneous but that is not convenient to patient suffering from diabetics. Insulin is also converted into transferosomes e.g. transfersulin which overcomes these problems related with subcutaneous. Interferon’s have also been encapsulated with transferosomes work as a carrier for example naturally occurring protein INF-α (interferon-α) is a having immun-modulatory effects, antiviral, antiprolifertive etc.
Application of Transferosomes

- Polypeptides as well as protein like drugs e.g. insulin, various vaccines, bovine serum albumin and are transport in body easily with the help of transferosomes as a carrier. They get better the site targeted of API along protection and healing of skin disorder.

- Transfersomes of Telmisartan using were formulated by usual rotary evaporation sonication technique and improved dermal administration of drug. Transfersomes of Telmisartan exhibits elevated entrapment, drug efficiency with elevated permeation of drug across skin.

- Insulin transfersomal gel was made by using reverse phase evaporation technique which showed extended hypoglycemic action and was recommended that insulin transfersomal gel can be use for the treatment of insulin dependent diabetes

- Paromomycin sulfate (PM) was prepared as transfersomal preparation with respect to transdermal delivery for probable dermal therapy of cutaneous leishmaniasis and helpful against candidate treatment of leishmaniasis.

- Indinavir sulphate transfersosomal gel were formulated by using conventional rotary evaporator which was finally incorporated into a gel base and shown good result when compared formulation of liposome which containing indinavir sulfate as blank drug solution.

- Almost 26 to 86% of curcumin drug taken orally do not absorbed and is excreted by fecal material. When it is taken orally occupy reduced bioavailability because of its less GUT absorption. When drug converting as transfersomes of transdermal delivery, it showed elevated entrapment efficiency as well as higher permeation of drug and showed potential approach enhancement in permeability of drug for longer period.

- Carries system was also incorporated of interferon’s in form of transfersomes e.g. naturally present protein, interferon-α (INF-α) derived from leukocyte. It having properties of antiproliferative and antiviral with immune-modulators property. Transfersomes was possible for given that sustained liberate of the taken drug and rising the stability of incorporated drugs moieties.
Interleukin-2 (IL-2) and interferon-α formulation as transdermal transferosomes intended for better administration of drug. IL-2 and INF-α trapped drug incorporated by transferosomes in sufficient level for immunotherapy of API.

Transferosomes had also shown corticosteroids delivery based drug and increase targeted specificity and overcome of adverse effect of corticosteroid delivery into cutaneous penetration of drug. A form of transferosomes drug was biologically active and dose of drug was a number of times less than that which is being used presently.

DNA vaccine carriers for successful topical vaccination use transferosomes in cationic stage was using of DNA encoding of plasmid for surface antigen (HBsAg) in hepatitis B loaded for topical applied preparation in contrast nude DNA give better result.

1.4.3 PHARMACOSOMES (Vaizoglu et al., 1986)

To remove the problem related to transferosomes can be overcome by the alternative approach is called "pharmacosome". Pharmacosomes drug dispersed in collide which is covantly bond with lipid and show ultra fine vesicles, hexagonal aggregates micelle based on the structure of chemical composition of lipid drug compound (Vaizoglu and Speiser., 1986). Pharmakon means drug, soma means carrier, link to each other for the reason that the system they are called pharmacosomes. It can transfer through cell membranes effectively and take compensation on the use of liposomes, transferosome and niosomes.

Pharmacosomes are having high entrapment efficiency for the reason that here drug itself is conjugated with vesicles which is made of lipids. Pharmacosomes does not require any monotonous long step for separate, make rid and unentrapped the drug from the preparation. Covalently linkage with drug prevents deterioration of drug but some time it’s possible due to hydrolysis. Release of drug from pharmacosomes is either hydrolysis or enzymatic degradation

1.4.4 ETHOSOMES

Ethosomes is ethanolic liposome’s which are used for low penetration power drugs via biomembrane specially dermis. It is made up of phospholipids; ethanol (ethyl alcohol and isopropyl alcohol) at lofty proportion (30-50%) along with water is called ethosomes.
They were delivered of encapsulated drugs to the deeper layer of skin with high penetration rate and reaches drugs in the systemic circulation. In case of lipophilic nature of drugs it is highly loaded then classic liposomes in this form. Ethosomes encapsulated anti viral drugs are used for treatment of hepatic infection as acyclovir with significantly improved proved through clinical trial in humans compared to the established commercial cream with same concentration of active drug such as Zovirax™. Insulin and different antibiotics has been also loaded as ethosomes with effective for systemic transdermal supply and penetrate the different layers of the dermis in animal. In contrast to additional transdermal & dermal delivery systems Improve drug permeation is seen by this dosage form.

- Easily transfer large macro-molecules such as peptide, polypeptides, protein, etc.
- They can be used for incorporation of non-toxic materials.
- Patient compliance is greater as the drug is available solid as well as semi solid form (gel or cream).
- Drug delivery system with ethosomes can be widely useful in different field such as pharmaceutical, veterinary and cosmetics. In future transdermal drug delivery system with ethosomes may play an important role. Different cosmeceuticals preparations using as ethosomes e.g. Lipoduction™ and Noicellex™

**Application of Ethosomes**

Ethosomes are mainly used as replacement of liposomes. They can be used for a lot of purpose in drug delivery system. A variety of functions of ethosomes as a carrier of wide range of drugs are

**AIDS / HIV drugs Delivery**

- Herpes labials treatment by ethosomes of acyclovir as antiviral drug was shown elevated curative competence with shorter therapeutic time in the treatment of in contrast ordinary topical cream Zovirax cream which contains 5% of acyclovir shown short therapeutic efficiency due to less permeation.
As compared with solution of lamivudine, ethosomal was in form of lamivudine as model antiviral drug showed 25 times elevated transdermal permeation across in the rat skin.

Stavudine in form of ethosomes shown eight to nine folds better transdermal permeation across rat skin when incorporated into HPMC gel as compared to solution of plane drug.

Ethosomes of Zidovudine transdermal delivery showed better action in contrast as taken zidovudine orally which has strong side effects.

**Delivery of NSAID drugs**

- Gel of Diclofenac potassium were prepared by incorporating in carbopol base with improve its efficiency compared with the commercial gel of this drug. As compared to liposomal, ethosomes of Diclofenac potassium gel increase permeation and improve skin retention.
- Aceclofenac gel in form of ethosomes efficiency was superior than plain aceclofenac gel and ordinary commercial gel of aceclofenac which evaluated in vitro and in vivo evaluation.
- Ketoprofen were loaded as ethosomal preparation subjected in vitro release through the skin showed elevated transdermal flux compared to hydroalcoholic drug solution. This is accomplished that ketoprofen ethosomes is a more valuable carrier for transdermal drug preparation.
- Ethosomal gel loaded with Ibuprofen applied transdermally remained in blood plasma for a extensive period of time in contrast to extra vesicular administration and it also stated an elevated comparative bioavailability.

**Delivery of Anti-Fungal drugs**

- Ethosomes loaded with Clotrimazole as the transdermal form had shown improved flux and enhanced penetration as matched with ultra deformable liposomes. Ethosomes also showed large zone of inhibition in difference to ultra deformable liposomes preparation.
- Ethosomes of fluconazole were formulated in appropriate topical base and drug diffuses two times more than liposomal and three times more than hyper ethanolic solution of fluconazole.
**Delivery of Other drugs**

- The treatment of acne or alopecia, pilosebaceous parts have been used for local effect of drug therapy, predominantly minoxidil, which is a lipid soluble drug prepared as ethosomal form in treatment of baldness, that gather into exposed skin of mice, in vitro ethosomal preparation improved the skin permeation of minoxidil when matched with either ethanolic or hydroethanolic of minoxidil solution and targeting improved clinical effectiveness.

- Treatment of atopic dermatitis, an immunosuppressant drug tacrolimus was used as loaded in form of ethosomes to explore inhibitory achievement upon allergic reactions and improving pharmacological effect for tacrolimus. Ethosomes loaded drug had minor size of vesicle and more encapsulation of tacrolimus along with more successful skin retention of drug.

- Melatonin loaded ethosomes manage improved permeation, lesser lag time, elevated drug entrapment and minimum irritancy on skin, this is offers an appropriate facilities for transdermal delivery of this drug.

- Methotrexate, which has insufficient transdermal permeation of drug is a highly hydro-soluble, antipsoriatic, anti-neoplastic drug. This was encapsulated within ethosomes and loaded in ethosomes transporter provided enhanced permeation across skin in form of transdermal route and decrease lag time.

### 1.4.5 SPHINGOSOMES

Sphingosomes resolve the main drawback related to liposomes and other vesicular system such as less stability, minimum tumor holding efficiency in antineoplastic cells, less in vivo circulation time. Due to size flexibility and constitution of materials, diverse kinds of sphingosomes have been prepared (Saraf et al., 2011). In addition the qualities of liposome have certain problems related with degradation, oxidation and hydrolysis, sedimentation, leaching, aggregation or fusion of drug during storage. The hydrolysis of vesicles may be prevented overall by use of lipid which holding, ether or amide linkage in place of ester linkage as in sphingolipid or derivatives of phospholipid such as 2-ester linkage changed by carbomoyloxy group.

Concentric bilayer vesicle which is the aqueous material was wholly surrounded through double layer of lipid membrane, mostly containing natural or synthetic sphingolipid.
Liposomal preparation derived from sphingomyelin based cholesterol has numerous advantages comparatively to other formulation. Stable to against acid hydrolysis and better drug retention is characteristics of sphingosomes. Route of administered of sphingosomes include parental such as intravenous, intramuscular, subcutaneous, and intra-arterial. Usually it will be intravenous administered and sometimes by inhalation as well as may be orally or transdermally. It is composed of sphingomyelin (sphingolipid) and cholesterol and an acidic in nature.

**Advantages of sphingosomes (Vyas and Khar, 2002)**
- Offer selective unreceptive targeting to tumor cells
- Enhance efficacy along with therapeutic index
- Augment stability through encapsulation
- Decrease in toxicity of the encapsulated agent
- Develop pharmacokinetic effect means circulation time increased
- Providing facilities to couple with targeted specific ligands

Prolonger circulation time in blood plasma transferred most of the healing agent for over longer time period at specific target organ or site. It is achieved by this new technology of sphingosomes.

**Method of preparation**
- Mechanical dispersion method or Classical method
- Film method

**Applications of sphingosomes**

Biodegradable, innocuous nature and being indistinguishable to biological membrane sphingosomes may establish to be efficient carrier for targeting the drug at targeted site.
- In tumor therapy, semi-synthetic vinca alkaloid (Vinorelbine) was used in treatment of in cancer at pre-clinical and clinical stages use as phase I clinical trials in form of sphingosomes. This amplified amount of drug at site of tumor cell was related augmented pharmacological action. Connection between drug effective action for killing tumor cells by interfering with mitosis at an accurate stage of cell cycle e.g. vincristine, vinorelbine and topotecan. Proprietary of sphingosomal drug delivery for encapsulation of anticancer drugs has improved the therapeutic effect.
Marqibo™ preparation of sphingosomal loaded with anticancer drugs act on active cell cycle-specific which may help amplified targeting at site of action.

- Sphingosomes used in cosmetic preparation
- Antimicrobial, Antifungal and Antiviral Sphingosomes preparation
- AIDS treatment or Anti-HIV therapy e.g. ciprofloxacin, oflaxacin, vancomycin, Amoxicillin, Amphotericin B, Iodoxuridine.

- Gene delivery with help of sphingosomes

**1.4.6 NIOSOMES:**

Niosomes is a non-ionic surfactant vesicle and a substitute of liposomes which are prepared by mixture of surfactant (non ionic), phosphate, cholesterol with following hydration in hydrophilic medium. Cholesterol works as stabilizing agents which have been used for preparation of niosomes (Singh C.H. et al., 2011).

They can encapsulate both hydrophilic and hydrophobic drug, improve the delivery in to skin, and sustain the release of the drug. They may effort as a storehouse of drug and discharge the drug in sustained or controlled manner.

It consists of amphiphilic moieties which provide a wide solubility range (Dhiman S. et al., 2012). In psoriasis patients concluded that phase I and II study niosomes of methotrexate are more effective than marketed non niosomal methotrexate gel. (Lakshmi P et al. 2007).

In contrast liposomes, niosomes are superior vesicles because more stable and relatively least price but for the period of dispersion, both preparation has the possibility of aggregation, union, and discharge of encapsulated drug (Hu C and Rhodes DG et al., 2000).

Applications of Niosomes

This drug deliverance is extensively adopted in different pharmaceutical preparations. Work as a transporter for a lot of biomolecules e.g. protein, peptides, haemoglobin, vaccines etc. Deliverance of most of drug as topical route such as NSAID and other frequent drugs to avoid gastric irritation, targeted, decreased side effects and small dose
than the presently available dosage form for cure of different local skin disorders as along
improved acquiescence of patients.

a) Anti-Fungal Agents

- Fluconazole loaded niosomes with help of different grade of surfactant were
  prepared and evaluated and shown localized drug storehouse in the skin, and has
  increase cutaneous drug retention.
- Non alcoholic naftifine hydrochloride an antifungal drug as niosomal formulation
  of the drug were prepared to conquer the problem of detrimental effect of skin due
  to repeated exposure of presence of half concentration of alcohol in marketed
  preparation.

b) NSAID'S

- Aceclofenac topical niosomal preparation has integration with carbopol gel. It
  showed better diffusion and healing effectiveness.
- Nimesulide niosomal gel delivery by incorporating into carbopol gel base showed
  extended release of drug thus increasing the anti-inflammatory action.
- Topical application of ketoprofen was in niosomes encapsulated form which
  shown sustained release pattern of drug.
- In spite of having high oral bioavailability, rofecoxib had to be reserved due its
  side effects in gastrointestinal and heart toxicities. To overcome its adverse effects
  encapsulation of drug was made in niosomes. It showed extended as well as
  controlled drug release of drug.
- Ibuprofen in form of oral administration shows reduced aqueous solubility and
  restrictions of drug access in blood therefore improve gel of ibuprofen as
  niosomes had been ready as topically application.
- Niosomal gel of lornoxicam was ready with use of carbopol base as transdermal
  preparation with rational drug encapsulation at appropriate size along better drug
  permeation.

c) Anti-acne drug

- Niosomal gel of erythromycin has prepared and incorporated into carbopol gel
  base the method of film hydration applying topically with extended release,
improved retention into skin and increased infiltration across the skin and reduced adverse action.

- Tretinoin (TRT) was prepared as niosomal gel formulation using of span-60 surfactant of and then incorporated in 971 gel base of carbopol. The in vitro discharge of drug niosomal gel showed the sustained pattern.

**d) Cosmetics**

- N-acetyl glucosamine is used for treatment of hyper pigmentation disorders prepared as niosomes was reported in topical form improved permeation in to the skin. It was inhibiting thyrosinase enzymes in skin cells. This formulation was shown better degree localization of drug in the melanocytes, which desired in hyper pigmentation of skin condition.
- Minoxidil were incorporated in niosomes shown better action and diffusion as contrast to usual dermal drug carrier.
- Due to low solubility and permeability ellagic acid (potent antioxidant, phyto-chemical) was used as limited. Niosomal preparation of this acid was improved the penetration along improved effectiveness.
- Finasteride drug used for effective treatment of alopecia as topical niosomes have been formulated.
- Present time niosomes are extensively used in the antiaging cream and other products related to delay ageing similar to “LOREAL CREAM”

**e) Muscle Relaxants**

A muscle relaxant baclofen formulated as niosomes is has ready to find better diffusion and bioavailability character of this drug as topical carrier. In the form of noisomes offer some importance as in more entrapment of drug, increase stability and better muscle relaxation action.

**f) Bioactive agents targeting**

**i) To reticulo-endothelial system (RES)**

First of all, vesicles take up primarily through RES system. Circulating serum factors “opsonins” cells quickly uptake of niosomes which is marker of drug clearance restricted drug accumulation was utilized in curing of cancer cells. This process was recognized as metastasize to the organ as hepatic tissue.
ii) To organs other than RES

This was suggested that transporter system be able to be intended for specific targeted location in the body cells with help of antibodies. Binding of immunoglobulin’s quite eagerly on lipid surface of vesicles appears to consequently present a suitable way for targeting of drug carrier. A lot of cells have inherent capability distinguish as binding with determinants of specific polysaccharides and will utilized to direct carriers arrangement to targeted cells.

g) Neoplasia

i) Methotrexate

Administration of methotrexate anticancer drug was intravenous route for treatment of S-180 tumor bearing mice as entrapped niosomal drug, outcomes in entirety tumor declination with elevated blood plasma level as well as lower removal of drug.

ii) Doxorubicin

*Doxorubicin* is a broad spectrum antibiotic which categorized in anthracyclic group. Antitumor properties produced as dose dependant but cause permanent heart toxicity adverse outcome. Drugs prepared in form of niosomes and apply mice bearing S-180 neoplastic cells improved span of drug life and the decreased proliferation rate in sarcoma. This preparation was better the half-life of the drug, protracted its flow as well as changed metabolism of encapsulated drug.

h) Leishmaniasis

This drug was used for targeted microorganism which is present containing organ reticulo endothelial system with help of niosomes. Parasite of leishmaniasis invades cells of liver and spleen and antimonials are normally approved drugs for incorporating arsenic which on elevated concentration its damage the tissue of visceral organ such as heart, liver and kidney.

i) Immunological application of Niosomes

It was observed that niosomes is powerful adjuvant concerning immunological activity and shown minimum toxicity along improve stability. This has been active through antigen because the immune nature of the reaction aggravated.
j) **Delivery of peptide drugs**

Niosomes encapsulated of vasopressin in administered as form of oral preparation and shown intestinal loop model in-vitro experiment and observed higher stability of these drugs extensively.

**k) Transdermal delivery of drugs by Niosomes**

Transdermal route delivery of drug has related to main problem is delay penetration of drug through skin. Drug incorporated in form of niosomes was an amplified in the penetration rate.

**l) Niosomes as carriers for Hemoglobin**

Niosomes is being able to use as means of transportation of oxygen via hemoglobin. Free haemoglobin was shown spectrum in visible region as niosomal suspension.

**m) Other Applications**

**a) Sustained Release**

It was recommended that niosomes of anticancer drug methotrexate are taking by the hepatic cells and liver act as a storehouse. Sustained release actions via niosomal encapsulation of drugs maintain with short therapeutic index and little solubility in water this drug manage in the circulation.

**b) Localized Drug Action**

Localization and penetration through skin epithelium of drug was totally dependent on their size. When drug supply with niosomal forms, it was required to fulfill above criteria. This is best technique to attaining the localized drug action. After localization of drug its pharmacological action improved and increase potency of the drug and overcome its possible systemic toxicity for example antimonials drug as form of niosomes are captured by mononuclear cells consequential in drug is localized and potency of drug is increase as well as reduce dose of drug and possible toxic condition. Development of niosomal drug delivery is tools for early life stage, and play important function in chemotherapy of tumors cells and leishmaniasis treatment etc.

**1.4.6.1 DISADVANTAGES OF NIOSOMES**

1. On storage they aggregate with each other.

2. Whenever it’s taken orally, bile salts and phospholipase enzyme of body act against this formulation.
3. Limited hydrolysis and leakage properties of drugs

![Fig. 3 Showing structure of Niosome](image)

**1.4.6.2 PROBLEM WITH VESICULAR SYSTEM**

![Fig. 4 Problems with vesicular system](image)
1.5 PROVESICULAR SYSTEM

1.5.1 PRONIOSOMAL GEL

Proniosomes gel is liquid crystal laminar structure which is made up of surfactant, cholesterol and lecithin. It is a very popular because it is easy to apply and absorption via skin is also better than other preparation (e.g. ointment, cream) of semisolids. It is a drug preparation which can be converted into niosomes by hydration (Ram A. et al., 2012). With the addition of water Proniosome dissolves and converted to niosomes suspension. Surfactants are mainly employed for coating of proniosomes (Malakar J. et al., 2011). Proniosomes are more effective preparation to improve stability concern related to physical properties i.e. aggregation, blending and leak out and or hydrolysis of encapsulated drug above niosomes. It also provides easiness of carrying, distribution, dosage and storing of drug.

1.5.2 Advantages of proniosomes gel: (Singla S. et al., 2012)

1. Bioavailability and permeation of drug is enhanced.
2. Transdermal/Topical preparation of drug delivery system can be developed by proniosomal preparation.
3. Physically (aggregation, fusion, leaking) and chemically they are more stable than niosomes and liposome.
4. It is having an optical flexibility, packaging and processing are very easy than conventional vesicular system
5. Do not require any special storage and handling condition.
6. Improved biocompatibility, non immunogenicity and non toxicity.
7. Improved permeation of drug via skin with protection of drug with biological components

A range of examples of diverse component of proniosomes are tabulated in Table 1 along with their use.
Table 1: Commonly used materials for proniosomes preparation

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactants</td>
<td>Span 20, 40, 60, 80, 85, Tween 20, 40, 80</td>
<td>To increase drug permeation across the skin</td>
</tr>
<tr>
<td>Lecithin.</td>
<td>Soya Lecithin</td>
<td>Penetration enhancer</td>
</tr>
<tr>
<td></td>
<td>Egg Lecithin</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Cholesterol</td>
<td>To prevent leakage of drug formulation</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>Maltodextrin</td>
<td>Provides flexibility in surfactant and other component ratio.</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>Sorbitol</td>
<td>Alters the drug distribution</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Isopropyl, ethanol and methanol</td>
<td>Maintain the quietness of vesicle membrane and penetration enhancer</td>
</tr>
</tbody>
</table>

1.5.3 Methods for preparing 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. Coacervation phase separation
2. Slurry method
3. Slow spray technique

1.5.4 Separation of unentrapped drug

Separation or removal of entrapped drug moieties in proniosomes from unentrapped drug was necessary to performed removal of unwanted or undesirable side effects of other excipients as well as maintain physical stability of dosage form. It may be performed by an assortment of methods:

1. Dialysis

In this technique proniosomal dispersion was dialyzed in the aqueous phase with help of dialysis tube with buffer and 0.9% of NaCl saline or solution of glucose.
2. Gel Filtration

Whole unentrapped of API present in dispersion of proniosomes was separated by this filtration technique. It was performed by sephadex-G-50 column with the help of eluted solution of phosphate buffer and 0.9% of NaCl solution.

3. Centrifugation

Proniosomal suspension is centrifuged at particular RPM for specific time period and the separated of supernatant. Free from unentrapped drug by washed the pellet is rapidly and then re suspended to get a niosomes.

1.5.5 Application of proniosomes: (Waghmode M and Shruti A, 2012)

Proniosomes are primarily work as substitute of niosomes chiefly as transdermal pathway. Hydrophilic and hydrophobic active moiety has been successfully entrapped in proniosomes delivery system. Table 3 shows drugs have been used with proniosomes carrier for preparation of many active pharmaceutical ingredients.

a. Drug targeting (Sudhamani T et al., 2010)

- The ability to target drugs concept by niosomes useful aspects for target the reticuloendothelial system. Niosome vesicles are takes up by reticulo-endothelial system (RES) preferentially. Circulating serum factors opsonins controlled the uptake of niosomes. Opsonins work as marker for clearance of niosomes.
- In cancer of liver and spleen, it is very necessary to localization of drugs and beneficiary to cure of tumors which is recognized to metastasize in these tissues. Localization of drugs also helpful in parasitic infections of the hepatic cells.
- Excluding RES, other organ can also be targeting by niosomes such as Antibodies (immunoglobulin) a carrier system can be attached to lipid surface of the vesicular system to targeted particular cells.

b. Anti-neoplastic (Jain N.K. et al., 2004)

- The main drawback of most anti-neoplastic/anti-cancerous drugs generates rigorous side effects. Provescular system of anti-neoplastic drug can alter the metabolism; extend circulation and half life of the drug, therefore lessening the side effects of these drugs.
- Antineoplastic drugs Doxorubicin and Methotrexate were successfully entrapped as niosomal preparations with slower elimination and more drugs stored in cancer cells along elevated plasma levels of drugs.
- Proliposomes of Podophyllotoxin-dipalmitoyl phosphatidylcholine were more stable than liposome of PPT-DPPC, and these dosage forms showed better encapsulation efficiency of PPT (72.3%) and can be stored at low temperature for several months with better stability (Lin Zhong-fang et al., 2004).

c. **Peptide drug delivery**
- Proniosomes bypass the possible enzymatic degradation of oral peptide drug delivery systems and breakdown the peptide structure drug. Protection of peptides in GIT intestinal peptide breakdown is being investigated by the use of proniosomes effectively.
- Oral delivery of a vasopressin hormone prepared by Yoshida et al. and they conducted more drug entrapped in vesicles of niosomes and decided significantly stable of peptidal drug in vesicles form greater than before.

d. **Immune Responses**
- Properties of immunological selectivity of niosomes manage their low toxicity and better stability properties. Aggravation by antigens niosomes are used to information for the nature of the immune reply. Immunological selectivity, low toxicity, and greater stability are the reasons for better immune responses of Proniosomes.

e. **Haemoglobin release carriers**
- Haemoglobin (oxygen carrier) within the blood, encapsulated as niosomal preparations reported since 1989 by Moser P. and Marchand A. M. In anaemic patients, the niosomal vesicle haemoglobin carrier is better permeable to oxygen in cellular level (Moser P et al., 1989).

f. **Transdermal Drug Delivery Systems (TDDS)**
- Proniosomes are that they to a great extent improve the uptake of drugs through the dermis. In cosmetics industries firstly uses of the proniosomes as transdermal drug delivery system.
Antibiotics proniosomes preparation use to treatment of acne as topical preparation. Provesicular system is use as penetration enhancer of the drugs through the dermis in contrast to other preparation.

g. **Sustained Release (SR) delivery**
   Liver of body work as depot for many drugs for example methotrexate when apply as niosomes suggested by Azmin et al. for low therapeutic index and low water soluble drugs encapsulated, for release of drug sustained manner.

h. **Localized Action of Drug (LDA)**
   - Size of proniosomes maintained dosage form for less epithelium penetrability and more drugs limited at the site of application. Drug release via vesicular system is techniques to get restricted action of active moiety.
   - Localized drug achievement consequences in improvement of efficiency of strength of the API along with lessen systemic toxicity e.g. mononuclear cells are taken up within niosomes of antimonials drug encapsulate therefore more drug localized in targeted tissue therefore increase effectiveness as well as reduce dosing frequency. Proniosomal formulation system of API has revealed assure in anti-leishmanial and chemotherapy of neoplas (Elsie Oommen et al., 1999).

i. **Leishmaniasis**
   - Genus Leishmania were caused Leishmaniasis disease in which a parasite attacks on the liver and spleen cells. But with the help of proniosomes activity elevated levels of the drug reaches on targeted cells devoid of any adverse effects and manage potential consequently permissible enhanced effectiveness treatment of disease (Perrett S. et al., 1991).

j. **Management of cardiac Disorders**
   - Treatment of hypertension by captopril drug, as proniosomal carrier system able of competently distribute entrapped drug over and prolong period of time. Transdermal proniosomal gel preparation of captopril was encapsulated the drug through Coacervation phase separation technique with various formulations by different ratios of span, cholesterol and lecithin (Uchegbu IF et al, 1995, Murdan S et al, 1999).
**k. Antibacterial rehabilitation**

- Proniosomes of Amphotericin-B can be stored for long period of without remarkable transformation in size of vesicle along maintain internal integrity of pharmacological action (Lawrence MJ et al., 1996).

**l. Cosmeceuticals /Cosmetics formulation**

- Present time huge numbers of cosmetic preparations existing in the market are turn to account as vesicular preparation for carrying cosmetics preparing active components (Thakur R. et al., 2009). It is proved that proniosomes delivery system is a more effective than noisome and liposomes, and their additional properties superior over others e.g. formulation, carrying, storage and transportation.

- Carrier of different active moieties by incorporated into proniosomal form as consist of nutritional cream, moisturizing agent, anti-ageing cream, anti wrinkle preparation, cleansing cream or gel, sunscreen cream or gel (Varshosa J et al., 2005).

- Proniosomes at the duration of storage and shipment created as physically stable of drug molecules. The applications of proniosomes gel is primarily used for topical/transdermal preparation.

- In cosmetics and Cosmeceuticals proniosome gel preparation may be handled as successful release systems for due to their unique properties (Blazek-Walsh AI et al., 2001, Souto EB et al., 2008).

**m. Hormonal Therapy**

- Transdermal drug delivery system (TDDS) of proniosomes as levonorgestrel (LN) characterized. The contraception properties of drugs were successfully transferred by use of patch of proniosomal transdermal levonorgestrel.
Table 2: Cosmeceutical’s Preperations and route of delivery

<table>
<thead>
<tr>
<th>Therapeutic category</th>
<th>Therapeutic agent</th>
<th>Delivery system</th>
<th>Delivery route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-wrinkle</td>
<td>Pseudo-ceramide</td>
<td>Liquid crystal</td>
<td>Topical</td>
</tr>
<tr>
<td>Sunscreen agent</td>
<td>Benzophenone -4 / octyl methoxycinnamate</td>
<td>Liquid crystal</td>
<td>Percutaneous</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Vit. A</td>
<td>Liquid crystal</td>
<td>Topical/Transdermal</td>
</tr>
<tr>
<td>Skin cleansing agent</td>
<td>Cosmetic composition</td>
<td>Liquid crystal</td>
<td>Topical</td>
</tr>
</tbody>
</table>

n. **NSAID Formulation**

- A Ketorolac tromethamine is a nonsteroidal (NSAID) agent which is a category in analgesic and anti-inflammatory drug. In post operative pain this drug is presently administered intramuscularly (IM injection) as well as oral preparation provided as multiple doses for short-term administration. Half-life of this drug is very short approx. 4 to 6 hr so that repeated dosing requisite, which is unacceptable patient compliance therefore, a substitute noninvasive manner of delivery of the drug is desired.

- Piroxicam (NSAID) is another example of potent analgesics which are treating of dysmenorrheal problem in female and different acute and chronic musculoskeletal disease as osteoarthritis, rheumatoid arthritis etc but numbers of gastrointestinal disorders are related to piroxicam therefore dermal delivery is an another better route of choice, but it’s necessary to formulation which ensures the deep skin penetration (Chandra A, et al, 2008).

o. **As Aniallergic**

- Carboplatin proliposomes were prepared by film extrusion method. Mannitol used in liposome is preventing aggregation of vesicles. Allergic reactions of proliposomes of carboplatin were evaluated in animal (Guinea pigs). Not any
allergic reactions such as hemolysis, hemagglutination and vein irritation were found in Guinea pigs (Halsall, JA *et al.*, 2005).

**p. Vitamins Preparation**

- Enhance stability of vitamin A by prepare proliposomes by Freeze drying method. The entrapment efficiency of vitamin A was found 98.5% along with more stabile.

**q. Co-Enzyme preparation of Proliposome**

- Coenzyme Q10-proliposomes was also prepared by freeze-drying technique and maintain it’s to enhance the stability. Different excipients used as cryo-protectant e.g. sucrose, lactose, mannitol and trehalose etc (Yoshioka T *et al.*, 1994).

**Table 3: Applications of proniosomes as drug carrier**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Category</th>
<th>Drug</th>
<th>Drug delivery system</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Antipsychotic effect</td>
<td>Haloperidol</td>
<td>Proniosome</td>
</tr>
<tr>
<td>2.</td>
<td>Antifungal</td>
<td>Griseofulvin</td>
<td>Proniosome gel</td>
</tr>
<tr>
<td>3.</td>
<td>NSAIDS</td>
<td>Flurbiprofen</td>
<td>Proniosome gel</td>
</tr>
<tr>
<td>4.</td>
<td>NSAIDS</td>
<td>Ketorolac</td>
<td>Proniosome gel</td>
</tr>
<tr>
<td>5.</td>
<td>NSAIDS</td>
<td>Ibuprofen</td>
<td>Proniosome</td>
</tr>
<tr>
<td>6.</td>
<td>NSAIDS</td>
<td>Aceclofenac</td>
<td>Proniosome</td>
</tr>
<tr>
<td>7.</td>
<td>NSAIDS</td>
<td>Piroxicam</td>
<td>Proniosome gel</td>
</tr>
<tr>
<td>8.</td>
<td>NSAIDS</td>
<td>Indomethacin</td>
<td>Niosomes,</td>
</tr>
<tr>
<td>9.</td>
<td>Antihypertensive</td>
<td>Alprenolol</td>
<td>Proniosome gel</td>
</tr>
<tr>
<td>10.</td>
<td>Antihypertensive</td>
<td>Losartan Potassium</td>
<td>Proniosome gel</td>
</tr>
<tr>
<td>11.</td>
<td>Antihypertensive</td>
<td>Captopril</td>
<td>Proniosome gel</td>
</tr>
<tr>
<td>12.</td>
<td>Antiasthmatic and antiallergic</td>
<td>Cromolyn Sodium</td>
<td>Proniosome</td>
</tr>
<tr>
<td>13.</td>
<td>Antihistamine</td>
<td>Chlorpheniramine Maleate</td>
<td>Proniosome</td>
</tr>
<tr>
<td>14.</td>
<td>Contraceptive agent</td>
<td>Levonorgestrel</td>
<td>Transdermal Proniosome gel</td>
</tr>
</tbody>
</table>
PROBLEM ON HAND

1.5 AIM OF THE STUDY

At the present time the most familiar form of drugs delivery is the oral administration. Whereas this has the remarkable benefit of easy administration and a requirement for the growth of novel drug delivery system to overcome difficulties related to other route therefore get better the therapeutic effectiveness and supply of drugs by more specific site. The method most often utilized is transdermal drug delivery which way the transport of therapeutic drug materials via the skin for systemic outcome as well as local action. With the help of proniosomes create beneficial choice these could be hydrated without delay previous to use thus would stay away from various tribulations related among hydrated niosomes and troubles of aggregation, fusion, and leak out of active moiety (physical stability) may possibly reduce. Further expediency of the proniosomes are related to carrying, delivery, storage, and dosing would construct easy by some time as dry niosomes or proniosomes shows potential industrial manufactured dosage form. Dithranol is used for the dealing of skin disease (psoriasis) due to various factor mentioned earlier.

It normally exists as many an antipsoriatic drug but various dosage forms create different side effects as alone or as a combination of drug. The majority frequently shown side effects are skin rash, itching, peeling, redness, blistering, burning, stinging, swelling, or extra sign of skin irritation etc. The most extensively established topical dosage form as cream e.g. dithranol (micanol 1 % w/w cream) was used but a localized and staining effect of drug such as irritation and pigmentation of skin by short contact period of time need to repetitive application of drug. Overcome this type of frequent dosing problem for patient compliance is very necessary.

To overcome these inherent drawbacks associated with conventional drug delivery of dithranol, try to do making or designing substitute drug release arrangement by means of proniosomes form following compensation over the other dermal preparation.

1) They minimize physical constancy problems related to niosomes e.g. aggregation, blending, and leak out drug tendency provide additional convenience in transportation, distribution, storage and drying.
2) By use of non ionic surfactant along with phospholipids in proniosomes, be able to more penetration across cell membrane.

3) Troubles associated with liposomal vesicular system as degradation or oxidation by hydrolyzing of API in addition to other tribulations of active ingredients for example sediment, aggregate and blending of active moiety during storage of drug.

Psoriasis is a non-communicable ailment that apparent chronic inflammatory disease of skin. Psoriasis generate arthritis was seen in about 10% of disease affected persons, which possibly will involve the various body parts e.g. neck, hands, wrists, feet, ankles, and lower back. The global occurrence of this disease is approximately 2-3%, however it prevalence rates is about 4-6% in developed countries. The behavior of affected individuals may be changed by this disease consequential in obesity, augmented alcoholism and more frequency of smoking. Almost two thirds of disease suffered population has a conciliatory form of the disease, with below 3% of the skin surface of the body, excluding others have more wide participation skin.

The treatment of psoriasis included corticosteroids and topical preparation as cream lassar’s paste of dithranol. Most of corticosteroids produce undesirable effects e.g. skin atrophy, telangiectasias, absorption as systemic manner cause (HPA) hypothalamic-pituitary -adrenal axis suppression on prolong use while cream causes irritation on lesional and perilesional, staining of skin and clothes.

Dithranol has auto-oxidized and oxidized by different agents such as UV/visible light, temperature increase, pH increase, presence of metals traces (as Zn) and O₂ gas.

So in the present study we are developing an alternative dosage form transdermal proniosomal gel of dithranol which would be overcomes the above mentioned Problems. Hence in present work, a challenge is been prepare proniosomes transdermal gel of dithranol.

Vesicular system prepares as transdermal drug delivery such as liposomes, niosomes etc perform as drug carriers with inexpensive along with chemically stable but they are not to physical stabile. Above and beyond traditionally way of formulate vesicular preparation (liposomes and niosomes) are required specialized equipment’s and time consuming.
IMPORTANCE AND SCOPE OF THE PROJECT

1.6 OBJECTIVES OF THE STUDY

In present time we were need to use of inexpensive as well as low toxic excepients to full fill the desire nanopreparation, PTG were suitable to this criteria because of the absence of excessive use of solvents in the production procedure. This preparation can also increase therapeutic achievement of the drug. Preparation of the DTH proniosomal transdermal gel (PTG) was perform “Coacervation Phase separation” procedure by means of various types of non-ionic surfactants e.g. Span 40, 60, 80 and Tween 60, 80 along with lecithin, cholesterol and ethanol etc. PTG could guard of dithranol from degradation caused by external factors such as UV irradiation. This research was also to develop a mathematical model using $3^2$ factorial designs in order to assume the adequate condition for preparation of DTH-loaded PTG with preferred character capable to get better the localization of dithranol in skin for treatment of psoriasis. Optimized formulations were examined through maximum drug entrapment efficiency (EE) and minimum particle size and ex-vivo diffusion and localization of DTH.

The following objects are required for desired preparation of PTG by DTH:

- To be develop a physically and chemically stable transdermal drug delivery system.
- To lessen adverse effects of drug along augmented the effectiveness of API.
- To amplify residence time of active moiety at the targeted tissue.
- Increased skin penetration of the drug.

1.7 THE PROBLEM

Introduction and History of Psoriasis

Psoriasis diseases distinguish from other common skin diseases firstly by two dermatologist’s Drs. R. Willan and T. Bateman in the late eighteenth century and this disease was identified as Willan’s lepra. Name of this disease they were decided on the basis of appearance of lesions and recognized two categories leprosa graecorum and psora leprosa. In 1841 F.V Hebra dermatologist was proposed a new Latin word “psoriasis” originated from the psorian name Greek word “to have the itch.”
Inflammatory skin disorder which is differentiated by hyperproliferation and abnormal differentiation of the stratified epidermal cells of skin correspond to psoriasis disease. This disease is also attack on joints in several patients. It generally causes distinct, red, scaly plaques to become visible on the skin, and consequently is grouped as a papulosquamous disorder (Fig 5 and 8).

A lot of type of an immune mediated skin disorder are occurs in humans for examples psoriasis, contact dermatitis, angioedema, urticaria, atopic dermatitis, autoimmune blistering etc. These problems are related to proliferative and chronic condition which is dependent on genetic and environmental character. It is allergic contact dermatitis in IV cell mediated hyposensitivity reaction. Allergens conjugate with skin protein and produce cytokines (Fonacier L. S. et al., 2009). This is a chronic, long life, type skin disorder in which body immune system is mainly responsible. It is characterized by hyper proliferation of keratinocytes (Saraceno R. et al., 2008). Psoriatic patient suffers from inflammation, local itching with pain in affected area. Sometimes approx. more than or up to 40-50 % of psoriatic patient associated with this disease and involves pain in joint along with swelling (Gordon K.B. 2006, Racz E. 2009, Clark, A.R. 2000)

In 1876, psoriasis treatment is discovered accidentally but luckily by Baumann Squire, using a tree extract Goa powder which contained dithranol (anthralin), which is still used to the present era as topical therapies.

In 1925, a dermatologist Dr. William Goeckerman proposed a highly valuable, skin treatment regimen that combination of ointment of crude coal tar with progressively increasing exposure of radiation of ultraviolet B (UVB) through hot quartz, mercury vapor lamps. This remedial regimen still bears his name and this is most successful topical treatments administered in therapy for psoriasis.

In the 1950s, Dr. John Ingram prepared the “Ingram regimen,” combination of UVB radiation and anthralin to the plagues. late 1950s, after the discovery of cortisone a decade earlier, formulation of topical corticosteroid started to be developed and applied to affected lesion of psoriasis (Pittlekow M. et al.,).

1.7.1 EPIDEMIOLOGY

The frequency of psoriasis varies extensive among world populations and geography, particularly latitude. It is basically a disease of Caucasians (2% to 3%) being much less
common in Asians (0.1%) and native Africans. Approximately 2% of the population is affected in the US (Lomholt G et al., 1964). Certain race such as the Japanese psoriasis occurrence is low and may be not present in indigenous Australians along South American Indians (Green AC. 1984).


The mean age for initial onset of psoriasis is a from 15 to 20 years, Clinically type I and II on basis of onset age of disease Henseler and Christophers proposed two type appearances of this disease. Psoriasis of (Type I) is starts at before age of 40 years whenever second commenced after the age of 40 years (Type II). More than 75% of patients related to Type I disease. Type I, psoriasis is more common and brutal disease than type II (Henseler T. et al., 1985). Different types of systemic and topical treatment of psoriasis are available in present time but its treatment is totally dependent on following nature of disease (Menter A, et al., 2007).

a) Severity
b) Cost of drug and Convenience of patient
c) Relevant co-morbidities
d) Effectiveness
e) Individualization of patient response.
Psoriasis is distinguished by cells containing T lymphocytes exhibits hyper-proliferation and unusual differentiation of epidermal keratinoytic cells and lymphocytic infiltration particularly CD4+ cells in the skin (dermis) and helper T cells, type 17 (Th17) and CD8+ cells within the epidermis, in conjunction with the characteristic cytokines and chemokines released by these cells (Guenther LC et al., 2002, Cameron AL et al., 2002).

Abnormal differentiation and hyper-proliferation of skin cells (keratinocytes) characterized in psoriasis. In addition, psoriatic arthritis is commonly associated with psoriasis in up to 40-50% patients and suffered from joint pain and swelling. Psoriasis is chronic inflammation with unidentified etiology. This disease was predictably dependent on genetic and environmental factors. However, perform the first-line treatments of psoriasis is dithranol, vitamin D and its analogs example as calcipotriol, and topical corticosteroids (Racz, E et al., 2006).

For treatment of psoriasis, topical and dermal route of drug administration preferred. Additionally, it is established that combination of two therapies than compare mono-therapy are more potent towards action and well tolerated (Gillard, S.E. et al., 2005).

Psoriasis type skin disease which is an autoimmune and non-contagious disorder is affected around 2 to 3% of the total world population. This disease is creating serious problems in term of psychological, physical and social parameter. Through this disease rarely or not kills anyone. In systemic therapy or phototherapy mainly concerning with the possible tissues toxicity beyond the various presently existing management options of psoriasis, topical therapy is the most widely used approach, circumventing (Katare et al., 2010). The topical treatments of the disease by Dithranol refer as a ‘Gold Standard’ for antipsoriatic action (Agarwal R et al., 2001).

1.7.2 HISTOPATHOLOGY OF PSORIASIS

a. Epidermal Hypothesis

There is a great speeding up of the transportation time of cells from layer of the basal cell to the topmost line of cell layer of squamous from about thirteen days in normal epidermis of active psoriatic lesions. Stratum Corneum antigen (SCag) has leak from pores of Stratum corneum in psoriatic skin. After that stratum corneum antibody (SCab) binds made SC antigen-antibody complexes for bind to complement. This complex
triggers infiltration of polymorphonuclear WBC from the dermis into the epidermis and stimulate epidermopoiesis.

b. Histopathological features
Basal cell is migrated to surface movement from the basal cell layer to the granular and cornified layers by incurable differentiation of keratinocytes cell present in the epidermis. Epidermal thickening is seen in persistent plaque lesions. Thickening of epidermis is an outcome of basal keratinocytes cells hyperplasia. Simultaneously, parakeratosis condition in histopathology was shown of abnormal keratinocytes differentiation with absent of granular layer. Psoriatic lesion of epidermal lymphocytes was improved and composed of helper (CD4+) and killer (CD8+) T lymphocytes cells.

c. Genetic Hypothesis
The psoriatic phenotype and the HLA-Cw6 locus have shown a Strong involvement. Approximately 70% incidence of the gene in patients for psoriasis compared with an occurrence of 10% in the usual people. Class I antigen B13, B17, B37 as well as class II antigen D27 also involve HLA systems connected with psoriasis.

d. Immune System and Psoriasis
There are three main theories of pathogenesis of Psoriasis are as given below related to T-cell mediated inflammatory skin disorder:
1) Cytokines which is epidermal keratinocytes-derivatives, trigger T-lymphocyte activation epidermal keratinocytes.
2) Immunologic cytokines in turn activating epidermal keratinocytes generates from antigen dependent T-cell activation.
3) CD8+ ‘killer’ T-lymphocyte is auto-reactive with epidermal keratinocytes and trigger epidermal activation by autoimmune reactions according to third theory suggestion.
1.7.3 TYPES OF DIFFERENT PSORIASIS

- **Erythroderma**: In this type psoriasis cover whole of body make possible, hypothermia and heart failure etc.

- **Guttate Psoriasis**: Minute <1cm water drop appearance sores on chest, legs arm etc. more common amongst children and teenagers more common amongst children and teenagers, characteristically plaques psoriasis of 1 cm width in exanthematous allocation subsequent infections of streptococci, particularly in throat.

- **Psoriasis Inversa**: Huge flat red scraps take place in this areas mainly folded area of body such as buttocks, under the breast, arm pits, groin etc.

- **Psoriasiform Hyperplasia**: hyperplasia in epidemic area evocative or like to psoriasis.

- **Psoriatic Plaque**: Dry, red lesions (Plaques) cover with a silver scale on the knees, elbows, scalp as well as lower back. Plaques are itchy, sore or sometimes both pointed distinguish erythematos.

- **Pustular Psoriasis**: contrasting than psoriasis vulgaris, local or dispersed formation of pustules in clinical study, fingers and toes represent 3 special appearances, palms and soles also affected.

All of psoriasis treatments are not necessary the same on all parts of the skin. Limbs and trunk psoriasis all preparations use safely but some areas need unique treatments such as the skin folds and face required low potency drug e.g. a weak corticosteroid cream or
related preparation and a once or twice a day tar preparation may be also accepted. It is necessary to make sure that the quantities or dose of drug used should be safe or within limits. Scalp type psoriasis a medicated tar or coconut oil shampoo approved besides to a steroidal or vitamin D scalp lotion along with a tar or coconut oil. Medicinal shampoo may be used for treatment of very mild flaky scalp psoriasis.

In case of nails psoriasis there is not any effective topical treatment occurs. Prescribe topical treatments such as vitamin D, Vitamin A, corticosteroid but more time consume to work and reduce rather than clear the problem. Different types of psoriasis with symptoms and curable drug are shown in table 6.

1.7.4 **PSORIASIS TRIGGERS**

Several group with related to this disease discover that symptoms commence or develop into lesser for the reason that presence of a definite trigger factors. Frequent triggers may consist of

- Diet
- Immunological factors
- Environmental factors
- Alcohol
- Smoking
- High fat diet can triggers chemical mediator release
- Koebner response (Sunburn)
- Scrapes
- Biting of insect
- Certain drugs like lithium, antimalarial, anti-inflammatory etc
- Stress
- Some of drugs NASID (ibuprofen), ACE inhibitors (antihypertensive drug), and beta blockers (for congestive heart failure treatment)
- Other factors such as Physical factors (Trauma, Abrasions, Contusions, Lacerations, Burns), Infections (Viral bronchitis Streptococcal pharyngitis, Human immunodeficiency, virus (HIV) infection) and Medications (above mentioned and Corticosteroid withdrawal etc)
<table>
<thead>
<tr>
<th>S.N.</th>
<th>Psoriasis subsets</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Psoriasis vulgaris</td>
<td>Minute &lt;1cm water drop appearance sores on chest, legs arm etc. more common amongst children and teenagers</td>
</tr>
<tr>
<td></td>
<td>(a) Guttate psoriasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(b) Plaque psoriasis</td>
<td>Dry, red lesions (Plaques) cover with the knees, scalp, elbows and lower back as silver scale. Plaques are itchy, sore or sometimes both</td>
</tr>
<tr>
<td>2</td>
<td>Pustular psoriasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(a) Pustulosis palmo-plantaris</td>
<td>Germ-free Eruption happen on soles and palms linked with 90% case is smoking and sometimes associated with chronic Plaque psoriasis</td>
</tr>
<tr>
<td></td>
<td>(b) Acral pustular psoriasis</td>
<td>Appears on fingers and toes produce bright red area it may ooze or scaly and painful nail deformities</td>
</tr>
<tr>
<td></td>
<td>(c) Generalized pustular psoriasis</td>
<td>Acute illness associated with fever in pustules occur in or around painful red area of skin</td>
</tr>
<tr>
<td>3</td>
<td>Arthritis Psoriasis</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Erythrodermic psoriasis</td>
<td>Cover whole body surface initiate hypothermia, and heart failure</td>
</tr>
<tr>
<td>5</td>
<td>Nail psoriasis</td>
<td>Nails causing them to pit, become discolored and nycholyysis and subungual hyperkeratosis, grow abnormally, lose and separate from your nail bed.</td>
</tr>
<tr>
<td></td>
<td><strong>Plaque psoriasis</strong></td>
<td>Dry and red skin lesions, Recognized as, plaques and enclosed in silver scales, usually itchy, sore, or both</td>
</tr>
<tr>
<td>---</td>
<td>----------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>7</td>
<td><strong>Scalp psoriasis</strong></td>
<td>Mainly affect the back portion of head red scraps take place in these areas of skin enclosed by thick silvery white scales. severe condition it can cause alopecia, but temporary</td>
</tr>
<tr>
<td>8</td>
<td><strong>Inverse psoriasis</strong></td>
<td>Huge flat red scrap present, mainly folded area of body such as buttocks, under the breast, arm pits, groin etc.</td>
</tr>
</tbody>
</table>

### 1.7.5 TREATMENTS FALL INTO THREE CATEGORIES

- **Topical or Dermal Preparation**
  These preparations are based on applied to skin or outer layer of body epidermis as preparation are creams, ointments and gel etc.

- **Phototherapy or Light therapy**
  Skin of body which is infected by psoriasis is exposed to certain types of light such as Ultraviolet light (UVA or UVB).

- **Oral and injected medication** – Medicines are be appropriate diminish the production of abnormal skin cells but this type of treatment applied whenever above treatment not produce desirable result.
(A) Plaque psoriasis

(B) Guttate psoriasis

(C) Flexural psoriasis

(D) Generalised pustular psoriasis

(E) Palmoplantar pustulosis

(F) Erythrodermic psoriasis

Fig. 7: Shown different types of psoriasis
### Table 5: Management of psoriasis in normal practice

<table>
<thead>
<tr>
<th>Delivery System</th>
<th>Drugs</th>
<th>Efficacy/Safety</th>
<th>Main side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| a) Corticosteroids | Clobetasol 0.05%  
Betamethasone valerate 0.1% | Low potency to very potent/safe when use short period | Skin atrophy |
| b) Chrysarobin derivative | Dithranol (Anthralin) | Moderate to severe psoriasis (Short contact regimen)/ low toxicity | Local irritation, Staining |
| c) Vitamin D and these analogs | Calcitriol, Calcipotriol, Tacalcitol | More effective when use combination with other Mild to moderate psoriasis | Irritation and Burning sensation, More expensive |
| **Systemic**    |       |                 |                   |
| a) Immunosuppressive | Methotrexate, Cyclosporine | Less effective/ sometime Organ-toxicity | Hepatotoxicity, Folate deficiency, |
| b) Calcineurin inhibitor | Tacrolimus, Pimecrolimus | Limited because size of molecules, low skin penetration | Malignancy, Itching, Stinging etc |
| **Radiation**   |       |                 |                   |
| a) Phototherapy | Ultraviolet B (UVB) combined with Either coal tar or dithranol | Scalp psoriasis | Pruritus, headaches |
| b) photochemotherapy | UVA (long wave) combined with Psoralen, Methtreaxate. Etretinate etc. | Notable decrease in erythema, scaling | Cancer risk, Folate deficiency, Liver enzymes level elevated |
1.7.6 MANAGEMENT OF PSORIASIS IN NORMAL PRACTICE

A. Topical Corticosteroids

Adrenal cortex of adrenal gland mainly secreted steroidal hormones of corticosteroids which is participate a lot of physiological action related to carbohydate metabolism immunity, stress response, catabolism of protein blood electrolyte balance, protein and fat metabolism. Different parts of body absorb topical corticosteroid at different rate and extent suppose some of steroid more efficacies on the palm may be in ineffective on the face.

Some of example different body part shown different absorption percentage Such as:-

- 1% for fore arm
- 4% of axillla
- 7 % of face
- 30 % for eye lids and genitals
- 0.1% for palm and 0.05% for sole

Anti-inflammatory and antiproliferative effects of corticosteroid based upon their efficacy as well as rapidity of action in table 6 is showing different therapy as manage mild or moderate of disease (Van de Kerkhof PC et al., 2003)

Efficacy

- Early phase of management of psoriasis apply potent or very potent corticosteroids particularly e.g. clobetasol propionate and betamethasone dipropionate excluding on certain area of body for example the face and flexures, it was confirmed by clinical trials experimentation it also grade A recommended drug (Liden S. 1992).

Safety

- When applying small time periods this corticosteroids as topical preparation are regards as protected, but prolong employed of steroidal API produce lot of side effects i.e. skin atrophy, striae, telangiectasia and dermatitis, etc. additional infrequently steroidal drugs is related acneiform, eruption, hypo-pigmentation, hypertrichosis, infections in skin, ecchymosis, along allergic contact dermatitis etc, are common side effects (Miller JJ et al., 1999).
- Systemic absorption of corticosteroids has been produce iatrogenic Cushing syndrome but only very infrequently. In pregnant women, it causes teratogenic effects in foetus seen. Accordingly, during pregnancy the use of topical corticosteroids should be limited with caution and use recommended dose of drug (Tauscher A.E. et. al., 2002).

**Table 6: Classification of Corticosteroids as topically apply**

<table>
<thead>
<tr>
<th>Category</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Very potent)</td>
<td>Decloban, Clovate 0.05%</td>
<td>Clobetasol</td>
<td>Potent 600 times than Hydrocortisone</td>
</tr>
<tr>
<td></td>
<td>Synalar forte 0.2%</td>
<td>Fluocinolone acetonide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Halog 0.1%</td>
<td>Halcinonide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sicorten 0.05%</td>
<td>Halometasone</td>
<td></td>
</tr>
<tr>
<td>Class II (Potent)</td>
<td>Betnovate, Celestoderm</td>
<td>Betamethasone valerate</td>
<td>Potent 50 to 100 times than Hydrocortisone</td>
</tr>
<tr>
<td></td>
<td>Diproderm, Diprolene, 0.05%</td>
<td>Betamethasone dipropionate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Menaderm</td>
<td>Beclomethasone dipropionate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dereme 0.025%</td>
<td>Beclomethasone salicylate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Demotest, Olfex 0.025%</td>
<td>Budesonide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flubason 0.25%</td>
<td>Desoximetasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Claral 0.05%</td>
<td>Difluortolone valerate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Synalar, Gelidin, Cortiespec, 0.025%</td>
<td>Fluocinolone acetonide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cutanit 0.025%</td>
<td>Fluocinolone acetonide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cusigel, Novoter 0.05%</td>
<td>Fluocinonide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Utralan M 0.2%</td>
<td>Fluocortolone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elocon ointment 0.1%</td>
<td>Mometasone furoate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topicort gel 0.05%</td>
<td>Desoximetasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mexivate ointment 0.05%</td>
<td>Betamethasone dipropionate</td>
<td></td>
</tr>
<tr>
<td>Class III (Moderate potency)</td>
<td>Betnovate, Celestoderm 0.1%</td>
<td>Betamethasone valerate</td>
<td>Potent 2 to 25 times than Hydrocortisone</td>
</tr>
<tr>
<td></td>
<td>Emovate 0.05%</td>
<td>Clobetasone butyrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Locorten 0.02%</td>
<td>Flumethasone pivalate</td>
<td></td>
</tr>
</tbody>
</table>
### B. Vitamin D and analogues of vitamin D (Calcipotriol)

Vitamin D use for treatment of mild to moderate psoriasis is the safest and most efficient treatments and it is a grade A recommendate therapy are perform by synthetic analogs of vitamin D. The vitamin D derivatives are present in form of calcipotriol, tacalcitol, and calcitriol. Vitamin D acts on keratinocytes cells of skin to stimulate differentiation and reduce proliferation. On the other hand, it was also shown immunosuppressive effects and action of down regulation of the Th1 response by receptor polymorphisms (Takahashi H. 2003,).

#### Efficacy

After eight weeks of treatment effectiveness of calcipotriol was equivalent to that of effective corticosteroids and more than of another vitamin D analogue, dithranol and coal tar. It is prove in a systematic quantitative randomized controlled trials of moderate plaque psoriasis patients (Ashcroft DM et. al., 2000). Vitamin D derivatives efficacy of was sustained over prolonged time period without tachyphylaxia type side effect (Camarasa JM et al., 2003, Ramsay CA et al., 1994).

#### Safety

The common side effect of vitamin D derivatives in 10% - 20% of patient was irritation around the lesion at face or flexures of affected area. Sometimes another side effect associated with therapy is hypercalcemia and hypercalciuria (Berth-Jones J et al., 1993).

<table>
<thead>
<tr>
<th>Class IV (Low potency)</th>
<th>Mild Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synalar capilar 0.01%</td>
<td>Flucinolone acetonide</td>
</tr>
<tr>
<td>Isdinium, Ceneo 0.1%</td>
<td>Hydrocortisone butyrate propionate</td>
</tr>
<tr>
<td>Suniderma 0.1%</td>
<td>Hydrocortisone acetate</td>
</tr>
<tr>
<td>Elocom cream 0.1%</td>
<td>Mometasone furoate</td>
</tr>
<tr>
<td>Batmen cream, Peitel cream 0.25%</td>
<td>Prednicarbate</td>
</tr>
</tbody>
</table>

| Hydrocortisona Isdin, 1%, 2.5% | Hydrocortisone |
| Vaspit 0.75%                   | Fluocortin    |
| Aclovate                      | Aclometasone dipropionate |
| Tridesilon cream 0.05%        | Desonide      |
Children of age below 6 years, therapy of calcipotriol is not recommended however it was observed effectiveness and safety of this treatment in children similar as adults (Darley CR et al., 1996).

C. Association of Corticosteroids with Salicylic Acid
Penetration of topical corticosteroids was amplified 2-3 fold with salicylic acid decided in experimental performance. A Keratolytic property of salicylic acid is responsible for treatment.

Efficacy
Concentration 0.05% of betamethasone dipropionate plus 3% salicylic acid produced quick reply than treatment with combination of clobetasol and calcipotriol (Guenther LC, 2004)

Safety
Some time very mild or moderate adverse effect observed in clinical trials and restricted application site. During treatment not any adrenal participation or more salicylate blood concentrations were noticed. Burning and itching sensations type adverse reactions were reported in some patients. It has been recommended that particularly in patients with renal failure use of the combined formulation and to above should avoided 20% of the body surface for the reason that of the systemic side effects by the absorption of salicylic acid (Koo J et. al., 1998, Katz HI et al.,1998)

D. Phototherapy
Radiation therapy is very useful for treatment of this disease particularly ultraviolet (UV) radiation standard valuable in lesions. Summer months are very valuable times for treatment of psoriasis and frequently observed recover their skin lesions for the duration of this periods. UV radiation may well take action by reduce keratinization through anti-proliferative property via interfere of T-cells in plaques psoriasis. Phototherapy, thought must be given to the capability of UV radiation to stimulate photo-damage of skin and amplify the hazard of skin cancer with tanning (hyper pigmentation).
A different UV band use for different type psoriasis treatment such as

- UVB radiation at 311 nm is an option to standard substitute 290 to 320 nm for Apoptosis of T cells
- UVB radiation at 290 to 320 nm shown immunomodulatory action
• Photo-chemotherapy (PUVA) use for treatment with either oral administration of drug occasionally after ultraviolet A (UVA) radiation (320 to 400 nm) under expert medical supervisor’s bathing of psoralen. But main troubled with PUVA is hazardous to skin and cause cancer or melanoma.

The American academy of dermatology was provided proper strategy or guideline for treatment of psoriasis with radiation of UV light (Menter A et al., 2010).

Predominantly psoralen plus UVA (PUVA) are initially now considered to work as locally acting immunosuppressive and inhibition of keratinocytes proliferation (Beissert S. and Schwarz T. et al, 2002).

E. Vitamin A Derivatives or Retinoids

Tazarotene is a gel formulation which is derivative of acetylenic retinoid existing in a different concentration of 0.1% and 0.05% finally it is converted active form tazarotenic acid when apply on skin. The topical retinoid such as tazarotene and etretinate systemic agents perform binding with retinoic receptors in the nucleus and transformed transcription of gene, consequential in differentiation and proliferation of keratinocytic cells returning to normal cells (Menter A, et al 2007).

Efficacy

After successful clinical trials have improved signs and symptoms of plaque psoriasis within 6-12 weeks demonstrate in the knees and elbows by once-daily tazarotene application. In 70% psoriatic patient taking tazarotene 0.1% diagnosed with moderate psoriasis test by randomized trial of 334 patients, a good response was obtained but the slower the therapeutic onset action than that seen with potent corticosteroids (Weinstein GD., 1996)( Koo JY.,2001).

The use of combination with moderately as well as potent topical corticosteroids is a superior treatment alternative for the reason that the effect therapeutic response accelerates and minimizes the tazarotene irritant effect along with dose requirement of corticosteroid minimum (Gollnick H and Menter, 1999).
Safety
Approx in 20% - 40% patients of tazarotene application lengthen associated with inflammation, irritation and itching, burning type sensation, erythema, like side effects problems.

➢ Acitretin
It is a retinoic ring aromatic compound and control severe pustular psoriasis. Topical treatments through acitretin amplify the management of psoriasis. Moreover, its highly teratogenic possiblelity, mucocutaneous actions are related with treatment include some other side effects be fond of xerosis, cheilitis, peeling of skin, and alopecia.

➢ Tazarotene
It is also a topical form of retinoid derivatives accepted for the dealing in psoriasis in adults, except in children.

F. Dithranol or Anthralin (Pittlekow M et al.,)
Therapy by dithranol has been employed to healing of psoriasis for over one century. Anthralin (dithranol) are still characterized a significant therapeutic alternative in child to old psoriatic patients although its mechanism of action is not understood properly. Probable its show toxic effect on psoriatic cells and mitotic inhibitors character responsible dithranol action. Long-contact therapy was mange in hospitalized patients where anthralin petrolatum base used but it in OPD patients a short-contact treatment used for reduce its probable property of irritation, perilesional staining, along with stable staining of garments. Anthralin in concentration of 0.1% to 3% apply as half an hour and then a washed not seen trouble along washable formulation psoriatic plaques patient. Combinations of DTH therapy with other topical formulation or UVB phototherapy are to get better the response.

Anthralin or dithranol drug as cream form Dithrocream, Micanol, Psorlin etc, is an anthracene derivative (hydroxyanthrones) drug use for treatment of psoriasis. Anthralin is obtainable in dose of 0.1 to 2% strengths as different form creams, ointment, or pastes. A lot of action mechanisms have been recognized by Dithranol, it was collected in mitochondria (cell power house), and where it obstructs with the transfer of energy to the cell, possibly by releasing liberated radicals from oxidation of anthralin.
It was delay DNA replication and disturbed cell division that happens in psoriasis plaques. Considerably greater sensitivity of DTH with keratinocytes and effectively eliminating these pathogenic immune-inflammatory cells than from lesional skin it was shown to cause cell apoptosis and death of lymphocytes. Additionally, Anthralin may act as falling the high levels of cyclic GMP (cGMP) that occurs in psoriasis. Anthralin has a lower onset of action in regulating psoriasis disease normally some weeks compared to steroidal drugs, but has ease to recover reactions on withdrawal or tachyphylaxis etc. this drug cannot be used on the soft organ of body such as face or genital part of body. It is stains the skin a yellowish brown colour in the short time and sometimes permanently and also stains clothing fabrics. Anthralin may cause a local sensation of burning along with irritation this drawback can be regulated by cautious awareness to the information of treatment guidelines and regularly increasing the potency of drug.

Dithranol (DTH) / anthralin have been used in the treatment of psoriasis over a century years, a de-methylated derivative of chrysarobin. (Naldi L and Carrel C.F.,1992).

**Efficacy**

Moderate to severe psoriasis will be treated 75 percent perfection in PASI score about 66 percent psoriatic patients within 3 months through short-contact regimen. Combination of this drug with phototherapy UVB (ultraviolet light B) was shown better expressions results in effectiveness as well as time of remission.

**Safety**

Highly effective and working as first line therapy because it’s not produce any systemic toxicity and other skin side effects such as skin atrophy which is associated with corticosteroid because this drug moiety hardly penetrate the epidermis. Principal negative aspect associated by means of anthralin is local irritation noticed estimated 72 percent patients and the staining occurs in sometimes clothing and furniture.

**G. Calcineurin Inhibitors**

Tacrolimus and pimecrolimus are model drugs as calcineurin inhibitors for therapy or management of atopic dermatitis as topical application, approval of these drugs for particular this disease are not proper recognized. Although in numerous researches was shown proved successful in adult psoriasis as topical application of calcineurin inhibitors
due to absent risk of atrophogenic. Calcineurin inhibitors are mainly helpful and efficient in inverse psoriasis. Nonsteroidal immunomodulators such as tacrolimus and pimecrolimus are widely used in recent years.

**Efficacy**

Therapeutic outcome of these calcineuin inhibitors as topical application is restricted by the dimension of molecules and their inadequate capability to penetrate the dermis (Zonneveld I M *et al.*, 1998, Yamamoto T *et al.*, 2003). Tacrolimus and pimecrolimus treatment or therapy decided for constructive as management of psoriasis on face and inter-triginous areas. An experiment was performed about 57 patients as Double-blind randomized controlled producing good results with pimecrolimus in inverse psoriasis treatment (Gribetz C *et al.*, 2004).

**Safety**

At the area of application some treatment associated side effects should be anticipated in approx 15% of patients, such as itching, stinging, and erythema.

**H. Methotrexate**

Its acting inhibition of folic acid antagonist enzymes such as dihydrofolate reductase and down regulates purine synthesis with inhibition of DNA synthesis. This inhibition result on epidermal keratinocytes. In folate metabolism and thymidylate synthase provide immunosuppressor properties of methotrexate act as for T cell actions additionally, it is regulate keratolysis of epidemis. Catalytic alteration of deoxyuridylate to deoxythymidylate was possible by presence of above enzymes along with production and restoring of DNA. Its inhibits the duplication and functions of T and B lymphocytes and restrain the secretion of numerous cytokines like interleukin-1, interferon $\alpha$, and tumor necrosis factor $\alpha$. For treatment of psoriasis methotrexate drug used as the first systemic drugs along with extensively used to treatment of psoriasis in young patients and superior clinical trials was achieved in various cases. Nausea and vomiting are related to treatment of therapy with methotrexate otherwise not any severe side effects occurred with methotrexate but constant observation is required to avoid recognized acute hepatotoxicity or hematotoxicity.
I. **Cyclosporin**

It is first renowned drug for treatment of psoriasis. It is more effective in psoriasis related arthritis disease. Psoriasis is keratinocytic and an immune response disease. In recent times this is distinguished and reported, this was interact with p21, NFA-1, 2, calcineurin, and Sp-1/Sp-3-dependent transcripted factors and affect epidermal keratinosis.

J. **Rosiglitazone**

It is reported that to this drug also restore to health of psoriatic patient although it’s categorize an insulin resistance anti-diabetic drug. Rosiglitazone was act on binding with a specific receptor (PPAR) and (PPARγ) and decrease level of kappa B nuclear factors (Ellis, C.N. et al., 2007).

K. **Leflunomide (DMARD)**

Leflunomide is disease modifying anti-rheumatic drug which is work as pyrimidine synthesis inhibitor. This is an immunomodulatory drug which is inhibiting dihydroorotate dehydrogenase (pyrimidine synthesis enzyme). Additionally leflunomide was shown anti-proliferative as well as anti-inflammatory for curing of disease and performed upgrading treatment of psoriatic arthritis (Nash, P. et al, 2006).

L. **Infliximab**

Infliximab is one type monoclonal antibody which exhibit elevated attraction and specific binding with TNFα cells (Knight D.M. et al, 1993). It is assistance moderate to rigorous plaque psoriasis without any adverse effect along immediate response. This drug is mange quick response accessible of drug at target tissue than other biologic agents. It is also show binding with TNFα of both circulating and cell surface and neutralize its action (Scallon, B.J., et al, 1995).

Multicenter randomized trial was established the Infliximab efficacy for psoriasis of two hundred forty nine patients in severe plaque psoriasis and approximate 75 % upgrading score of PASI within ten weeks when placebo compared with drug.

M. **Adalimumab**

It is also monoclonal IgG1 antibody connected to complete human TNFα which binds with high affinity and highly specific with soluble as well as membrane bound TNFα. It
is block interaction of cell surface receptors of p55 and p75 by neutralizing biological activity of TNFα. Additionally adalimumab lyses of cells correspond to surface TNFα. Subcutaneous dose 40 mg given in alternate weekly. FDA is approved use of Adalimumab for healing in growing person suffered disease in form of moderate to rigorous persistent plaque psoriasis. Example etanercept, adalimumab is frequently used as self administered (Papoutsaki, M. 2007).

N. Golimumab

Subcutaneous injection of golimumab which is belongs to family of TNF antagonist’s choice with a supplementary interested dosing regimen after applying few months. This is done by etanercept, adalimumab when given two week, as subcutaneous injectable preparation respectively, as well as eight week IV infusion of infliximab. To perform large phase three placebo-controlled trial of four hundred five patients of psoriasis with low toxicity by use of Golimumab.
RELEVANT LITERATURE REVIEW

1.8 LITERATURE REVIEW:-

1. **Jain N.K. *et al.*, (1996), reported niosomes is a drug carrier for better sustained release and stable than liposomes for treatment of different disease including cancer.

2. **Udupa N *et al.*, (1999), prepared β cyclodextrin containing mithotrxate entrapped niosomes for tumour treatment. They use lipid layer hydration method for Preparation of MTX –BCD complex is to niosomes and concluded MTX –BCD complex noisome shown high entrapment effecting about 84% then with plain dry and impure anticancer activity.

3. **Ong P.Y. *et al.*, (2008), studied atopic dermatitis which is barrier defect by filaggrin protein deficiency make in skin disease exaggerated 17% of children is US. They concluded that genetic factors and immune disturbances are responsible for pathogenesis of AD.

4. **Kapoor A *et al.*, (2011), prepared niosomes with use of different sorbitan esters for anticancer drug aclovir as span 20, 40, 60 and 80 by reverse phase separation method and maximum efficiency of drug release shown by use of span 60 with acyclovir as sustained release pattern.

5. **Vadlamudi H. C. *et al.*, (2012), Enlighten of niosomes drug delivery are lot of advantages and their different method of preparation for example ether injection, hand shaking, microfludization, reverse phase evaporation, sonication, formation from proniosomes etc. it will be shows most powerful tool for diagnosis as well as treatment of disease.

6. **Aggarwal D *et al.*, (2005), prepared mucoadhesive niosomal by use of ophthalmic preparation for increased effect of timolol maleate as decreased IOP, by used two different polymers as chitosan and carbopol coated niosomal of timolol maleate by reverse phase evaporation method. Chitosen based preparation was shown more sustained release preparation approximate eight hour than carbopol which sustain six hour produce lesser side effects than timolol solution. Release of drug was considerably through preparation up to 91% within 2 hour.
Evaluation of drug permeation was on albino rabbits as pharmacodynamics parameter pneumatonometer use for calculating intraocular pressure (IOP).

7. Barakat H S et al., (2009), prepared naftifine hydrochloride alcohol free niosomes gel because alcohol by repeated exposure to skin shown experimental effect. Niosomes gel provided two benefits first drug formulated with cosolvant and secondary, localization of drug at fungal infected area. The antifungal drug naftifine hydrochloride preparation was containing half percentage of alcohol in the form of co-solvent in marketed topical gels but frequent revelation to alcohol could be unfavorable effect to skin. Goal of niosomes preparation a free of alcohol gel having 1% drug. Optimization of prepared formulation was performing by use of different variables to attaining maximum entrapment as well as stability parameter. Gel preparation was formed through incorporation of niosomes with hydroxyl-ethyl cellulose gel. The 1% weight by weight preparation of entrapped in the niosomes final gel. The consequences advise the probable use of the gel of niosomes.

8. Chwada H S et al., (2011), formulated nimesulide niosomes with characterization by evaluation of size of particle, entrapment encapsulation, as well as in vitro release of nimesulide and performed stability testing. They describe niosomes prepared by –different non ionic surfactants such as different grade of span and phophatidycholine in different molar ratios through lipid film hydration and ether injection method, prepared multilamillar and unilamillar vesicles respectively higher entrapment of drug efficiency by span 60 and cholesterol in 80:70 molar ratio with slow release relatively through mechanism of zero order and Higuchi diffusion controlled. In the physical stability concerned confirm that this preparation stored at low temperature for two months by maximum retention of drug.

9. Boguniewicz Mark et al., (2003), reported that in AD (atopic dermatitis) characterized by loss of ceramides in horny layer of skin which is not responsible for loss of permeability barrier in skin but also increase sensitivity and susceptibility to colonization of staphylococcus aureus
10. Hughes J and Rustin M.H.A., (1999), reported topical corticosteroids although first choice of drug as mono therapy since 1952 but its side effects as skin atrophy, striae, allergic contact dermatitis etc. iv ts use is limited or use with other antipsoriatic drug with combination as vitamin D₃ analogue etc.

11. Zemtsov A. et al., (2013), reported cream of desoximethasone with citrizine in emu oil base give better result for treatment of psoriasis atopic and stasis dermatitis than other cream which contain propylene glycol as base.

12. Goudanavar P et al., (2012), prepared perindopril erbumine (ACE inhibiter) loaded proniosomes gel by phase conservations techniques by using different ratio of surfactants. In vitro study shown decrease release of peridopril erbumine from gel formulation with surfactant lipophilicity increases. Permeation of drug through rat skin of optimized preparation was formed to be 70.26% and formulation which contain 900:100mg ratio of Tween 20:60 with 0.5ml alcohol and 0.18 ml water shown greater drug released with controlled rates.

13. Pardakhty A. et al., (2013), reported niosomes for vaccine and gene delivery decided nanoniosomes delivered gene in cells for treatment of cancer and other disease at hereditary level and enhance the immunogenicity by protection through prevention of antigen degradation in body and side specific.

14. Alsarra I. A. et al., (2005), prepared proniosomes of transdermal preparation of ketorolac and performed drug permeation by use of Franz diffusion and concluded improved drug permeation and reduce lag time. If use of span 60 surfactant more drugs permeate through skin than Tween 20 surfactant. In preparation of niosomes nonionic surfactant are used for transport of hydrophilic and hydrophobic drugs easily in body. HPLC and SEM (scanning electron microscopy) methods was used for encapsulation efficiency as well as size of niosomal vesicles. Proniosomal composition was directly affected the vesicle size.

15. Khanam N et al., (2013), reported niosomes was shown encapsulated capability for equally hydrophilic and lipophilic type drug for long period of time. Niosomes mainly prepared by surfactant as ether linked, ester linked, sorbitan esters, alkyl amides, fatty acids and amino acids, cholesterol etc. Different niosomes prepared different techniques.
16. **Gupta A et al., (2007)**, prepared captopril an antihypertensive drug proniosomes transdermal system for extend release time by use phase separation Coacervation technique. Proniosomes is encapsulated 66.7 to 78.7 % of captopril by this metod.

17. **Chandra A et al., (2008)**, prepared piroxicam proniosomes based delivery system which is NSAID for various musculoskleton disorders. Piroxicam can produce GIT disorder when taken orally. Proniosomes showed maximum permeation through skin, and then it may be given alternative route through skin.

18. **Sudhamani T. et al., (2010)**, enlighten proniosomes a promising drug carrier overcome physical stability of niosomes. It is formulated by spraying and slurry method after that proniosomes converted in to niosomes. They focus the new nano drug technology of the improvement in the formulation of proniosomes originate niosomes. It is a smaller colloidal material that possibly hydrolyzes instantly previous to apply converted dispersions of niosomes. Proniosomes derived niosomes are characteristics by different parameter such as size and size distribution of particle, release of active moieties. Characteristics related niosomes was produced by proniosomes are better than predictable niosomes.

19. **Malakar J et al., (2011)**, reported proniosomes is better carrier for drug delivery system, these are coating of non ionic surfactant and quickly converted into niosomes on applying site with much better then niosomes by providing optimal flexibility, unit dosing as well as stable than conventional niosomes. They was reduce the troubles connected with niosomes by use of proniosomes as physical stability e.g. fusion, aggregation, as well as leak out, to offer suitability for conveying, distribution and storing of API. These are high-quality as or still better than usual niosomes.

20. **Aggarwal G et al., (2011)**, reported proniosomes more effective designed at sustained release pattern, stability related API carrier also more at these systems. In future scope, primary in the area of transdermal delivery of drug arrangement will be extra capable release coordination.

21. **Shamsheer AS et al., (2011)**, formulated & evaluated proniosomal gels of lisinopril dihydrate as transdermal preparation with use of lecithin, cholesterol, surfactants. Prepared proniosomal gels have shown physical characterization with
in permissible limits with zero order release pattern evaluation of drug by
different method include by FTIR spectrum and proniosomal gels evaluated by
pH determination, Viscosity, size of Vesicle, spontaneity rate, entrapment
efficiency, as well as in vitro permeation through skin and stability studies. The
compatibility between drug and excipients conducted exposed that there no
interaction which was as confirm that from FTIR spectrum. All the physical
parameter of proniosomal gels was observed that the gel proniosomes showed
superior thixotrophy behavior. Vesicle size was set up to be 20.10-26.23\(\mu m\) range
and in optical microscopy studies showed spherical and homogenous structure of
vesicles. Proniosomal gels were stable at 4 to 8 \(^\circ C\) and 25±2 \(^\circ C\) in stability
studies. Drug release was exhibiting mechanism of diffusion process as zero
order. At 4-8 \(^\circ C\) and 25 ± 2 \(^\circ C\) temperature of proniosomal gels in which it was
stable. The proniosomal gels are appropriate for controlled release of lisinopril
drug OD (once day) formulation.

proniosomes gel (Gugulipid is a guggul resin ethyl acetate extract which is
acquire from “Commiphora wightii”) for bypass of systemic side effect and
increased their therapeutic activity. It is contain guggulsterone steroid and shown
a strong hypolipidemic action. Despite of its hypolipidemic character it contains
other therapeutic behavior e.g. antimicrobial, antioxidant, anti-inflammatory,
antiarthritic and antihelmintic. They was improves therapeutic character by
Separation of unwanted pharmacological action at the site of inflammation.
Systemic side effects may be overcome by topical application of anti-
inflammatory agents along with therapeutic activity improvement.

carrier particle which are coated with surfactant. These dehydrate product
converted in to niosomes immediately when agitated with hot aqueous medium.
These systems overcome vesicular problem for instance aggregation, blending
and leakage of API along with improve oral bioavailability of Cyclosporine A and
targeting drug to particular specific site. These preparation easily cross the
stratum corneum layer of skin and increase time of existence of drug in systemic
circulation with low toxicity. Cholesterol and lecithin was used in proniosomes for role as membranes stabilizer as well as lipid nature of skin it provide better bilayer stability & permeability through. Stability associated with traditional liposomes and niosomes as usual vesicular system are facing problem. A novel vesicular approach is famous as proniosomes solve these type problems.

24. Dubey A. et al., (2012), prepared of proniosomes loaded lornoxicam by lipid hydration technique at different ratio of cholesterol and surfactant and evaluated of proniosomes by performed IR, angle of repose and SEM. Testing of niosomal suspension through in-vitro release and efficiency of drug entrapments etc. they concluded that the molar ratio of span 60 and cholestrole is 170:80 shown better entrapments efficacy (72:69%) and release percentage (85:37%) at the end of one day among all seven formulation.


26. Sambhakar S. et al., (2012), prepared sorbitol based proniosomes of cephalosporin for better permeability and stability of oral dosage form. Preparation of drug free flowing dry proniosomes of Cefuroxime axetil with help of polymer sorbitol or maltodextrin. These provesicular systems are characterized by Scanning electron microscopy, flow character, efficiency of drug entrapment, drug release patter and ex-vivo permeation study. Size of vesicle was found to be below 5µm and lower the value of angle of repose shown the niosomes coated by suitable carrier as sorbitol. Preparation Span 60 polymer was shown high entrapment efficiency release of drug as controlled manner. Permeation of drug was more with Span 60 with bile salt than Span 60 only and Span 40. Physical property of proniosomes gel and the entrapment efficiency after storage shown no change and found to be more than 90% respectively, proniosomes indicating not any leakage or degradation of drug while slight sedimentation and aggregation of particles occurs by niosomes. These factors designate the commercial feasibility and effortless develop of proniosomes.
27. Mishra S et al., (2013), formulated and optimized of proniosomal gel for transdermal delivery of naproxen which is used as NSAID for rheumatoid disease. She was used $3^2$ factorial designs for optimization of various formulation variables. They were taken independent variable such as amount of surfactant A and cholesterol B. while entrapments efficiency and drug permeation as dependent variable. They were concluded proportion related to surfactant and cholesterol directly affected entrapment efficiency as well permeation.

28. Pazoki et al., (2003), performed the outcome of various agents like indomethacin, diazepam, and extract of garlic on mice skin at persuade dithranol effects through the skin biopsy of topical applied dithranol examined after 48 hr. or 96 hr. and suggested all of these drugs reducing dithranol induced damaged on skin.

29. Tencomnao T. et al (2009), investigated epidermal growth factor receptor (EGFR) is responsible for psoriasis pathogenesis and shown a human keratinocytes cell has induced down regulation of the EGFR by Dithranol preparation.


31. Mokhtar M et al., (2008), prepared flurbiprofen proniosomal gel with use of presence and absence of cholesterol and different type of spans surfactant. The flurbiprofen entrapment efficiency in niosomes which is prepared from proniosomes was depended on different process variables such as drug separation method, content of cholesterol, total concentration of lipid, hydration medium pH and concentration of drug. Prepared proniosomes after hydration converted niosomes. Flurbiprofen a poorly soluble drug which entrapped efficiency of drug in proniosomes depend with influence of different variables of processing as well as formulation such as chain length of surfactant, pH of the dispersion medium, amount of cholesterol, amount of drug, lipid level, and charge on surface of lipids. The % EE was more with span 60 than other sorbitan ester such as span 40 and span 80. The highest entrapment efficiency was observed 94.61% at pH of the hydrating solvent was 5.5. Proniosomes are recommended a stable precursor for
the instantaneous preparation of niosomal transporter systems according to present research.

32. Thakur R et al., (2009) formulated losartan potassium transdermal preparation system as proniosomes with the help of different grade of nonionic surfactants span and tween for example 20, 40, 60, and 80. The optimized proniosomal gel prepared by polymer HPMC gel as a suitable base. Surfactant span 40 proniosomal preparations showed best in vitro skin permeation.

33. Amusa A. S. et al., (2012), prepared niosomes by thin film hydration methods by entrapped fluoroquinolones in non ionic surfactant vesicles. Fluroquinolones niosomes produced approx two folds lessening in MIC’s in opposition to microorganism pseudomonas aerceginosa along with E.coli. Different fluoroquinolones encapsulation efficiencies were ciprofloxacin, gatifloxacin, and levofloxacin, norfloxacin 71.11%, 19.11%, 34.23% and 70.09 % respectively. Stability is temperature-dependent such as highest stability of formulation is happening at 5°C furthermore the lowest at 37°C. Slow diffusion of API across dialysis cell membrane was extended release of drug from vesicles. Drug release kinetics follows first-order, it means dependent concentration term.

34. Dhiman S et al., (2012), describe niosomes is a novel drug delivery system. Explain that it is an admixture of surfactant among alkyl or dialkyl ether of poly glycerol as well as cholesterol which is consequent hydration. It’s more effective for numerous lives threatening disease.

35. Udupa N et al., (2000), prepared sumatriptan succinate niosomes use for nasal administration which is selective 5-hydroxy tryptamine receptor agonist treat for headache in acute migraine attacks, release of drug from niosomes of sumatriptan was release 58.7% for a period of 6 hr.

36. Kamath R. et al., (1998), suggested that withaferrin A which is isolated from witania-somnifera (ashwagandha) niosomes produce better antitumor efficiency of a long period of time than plain withferrin A which is dispersed in saline of phosphate buffer.
37. Jain N.K. et al., (1995), reported niosomes is a drug carrier for better sustained release and stable than liposomes for treatment of different diseases including cancer.

38. Sharma P et al., (2013), investigated drug delivery as niosomes is novel approach for treatment of leishmaniasis, neoplasia, different vaccine, hormone, TDS (transdermal drug delivery system), SR (sustained release), etc. They concluded drug delivery through niosomes provided better targeting for appropriate tissue destination.

39. Jesubel R. B. et al., (2013), suggested niosomes form of drug more stable than conventional at different temperature and pH scale in during storage. Niosomes which is carrying drug in to the body parts by oral system can overcome GIT barrier, then shown better absorption enhancement of ampicillin antibiotics in biosystem by niosomes. They describe therapeutics performing an essential role for the management of diseases with a lot of route for administering the drug in to the body. In the field of pharmaceuticals niosomes play role as drug carrier. These are preparation useful in transport the drug to the intention site, devoid of any modification in drug composition and configuration. The microbial culture of drug showed a very good activity along with high-quality in the drug on pH. All the parameters that create problem for drugs activity and delivering of drugs was tested. The necessary extent of the drug was transferred to the target organ without any modification of the ampicillin. Niosomes have enormous potential as drug delivery carriers on the basis of work performed.

40. Singh P. K. et al., (2012), prepared proniosomes act as sustained release delivery of drug. Slurry method was used with diverse surfactant and cholesterol proportion. Release of drug from proniosomes dependence on CMC ratio of cholesterol : surfactant and coating will be smooth & uniform as well as consistent hydration, with the help of SEM study detected maltodextrin power coated with surfactant uniform or not.

41. Radha G.V. et al., (2013), suggested that proniosomes drug delivery system play important role for targeted drug action. Span & Tween (surfactant) play key role as sustained hydrophilic lipophilic balance. Another components cholesterol and
lecithin which is behave as stabilizers of membrane influence permeability along with vesicles stability. They use as enhancing of penetration activity through membrane and maltodextrin, lactose, sorbitol and manitol use as carrier.

42. Walve J.R. et al., (2011), suggested preparation of proniosomes act as surrogated carrier for important topical transdermal drug vesicles, as penetration enhancer, biodegradable, non toxic amphiphilic in nature. These preparation are improve is cosmetics / cosmeceuticals permeation through the lipid layer, drug proniosomal system was hydrated with effortlessly in hydrated medium or through itself contact with skin when topically applied.

43. Allam A. N. et al., (2012), reported proniosomes as a stable carrier of acyclovir when they are taken orally. Ex-vivo experiment was shown drug diffusion in form of proniosomes preparation in intestine of guinea pigs exhibit greater permeability then from acyclovir solution. Prepared niosomes of acyclovir is stable at 4± 1 °C temperature then 25 °C ± 2.

44. Rao R et al., (2011), formulated proniosomes by Coacervation phase separation technique along with characterized proniosomes of valsartan as angiotensin –II inhibitor for heart failure treatment. High entrapment efficiency of proniosomes EE (71%) and drug release DR (88%) with span 60 type surfactant. In Stability characterization was performed for leaking of drug from the proniosomal preparation for the duration of storage. A proniosomes for particular (9:9:2) proportion of Span 60, lecithin and cholesterol respectively, shown highest drug entrapment efficiency about 71.50% and 75% drug release. At low refrigerated temperature as about 4 to 8°C proniosomal showed elevated withholding of valsartan within the vesicles up to one month.

45. Pardakhty A et al.,(2007), reported delivery of insulin niosomes during in vitro experiment. Polyoxyethylene alkyl ethers (Brij) were used for niosomes preparation for delivery of insulin by method of film hydration. Cholesterol and different grade of Brij (35 and 58) are necessary for niosomes formulation. Quantity of cholesterol, charge or hydrophilicity of surfactants is affecting the size of vesicles. Proteolysis action of α-chymotrypsin, trypsin and pepsin on degradation of insulin can be controlled by entrapment in bilayer structure of
niosomes of insulin. The maximum defensive action was seen in Brij 92 and cholesterol at 7:3 molar ratios and release of insulin was 26.3% entrapped during 24 h in similar fluid intestinal. These research outcomes showed that release pattern as sustained release niosomes of insulin as for delivery of peptides and proteins.

46. Krueger JG. (2002), describe psoriasis vulgaris is the mainly established as ailment of T-cell mediated inflammatory infection. Psoriasis pathogenesis associated toward number of leukocytes cell activation which control cell mediated immunity and T cell dependent activity which promotes the development psoriasis lesions and chemokine release in inflammatory skin lesions are critical paths in immunologic activation. Engineered biologic therapies recommend a prospect for involvement with of all of these paths.

47. Sabat R et al., (2007), describe psoriasis is typical microscopic and macroscopic skin changes. Lesions in psoriasis are sharp border, red and little lesions through silver white scales. They describe reality that the pathogenesis of psoriasis depended on immune system of body additional, different Th17 T-cell, regulatory T cells, macrophages cells, dendrite cells, along with new cytokines with interleukin IL-22, 23, 20 are responsible for psoriasis. Loci of chromosomes have been also responsible in support of psoriasis susceptibility. The major histocompatibility complex (MHC) area (PSORS1) was on 6 (6p21) chromosome presences to be linked with the majority patients of psoriasis.

48. Divakara P. et al, (2013) reported the bark of “Pongamia Pinnata” shown the Anti-psoriatic activity in herbal ointment containing aqueous extract performed in rat ultraviolet ray photo-dermatitis model. The present research was performed to estimate the plant of “Pongamia pinnata” bark (aquous extract), a marketable SUEX GEL preparation which used for cure disease. P. pinnata bark part of this plant was used for treatment of UV radiated rat skin by SUEX GEL and exhibit considerable reduction in epidermal thickness, Str. granulosum retention, and control changes of skin due to irradiation. The efficacies of the ayurvedic ointment (SUEx GEL) were improved with “Pongamia Pinnata” bark extract for the treatment of psoriasis.
49. Tsai TF et al., (2012), suggested type 17, T helper responsible in psoriasis immune perform. Immune system and keratinocytes are playing a specific key part in disease. After successful psoriasis treatment with cyclosporine was confirmed that this disease was proliferation/differentiation of keratinocytes and an immune dysregulation. Primary clinical pathological characteristics of psoriasis cells of Th17 create interleukin IL-17 and IL-22 and other significant factors for pro-inflammatory effects on skin.

50. Reich K et al., (2007), describe treatment aim in psoriasis by biologics not only describe the therapeutic facility of psoriasis but also encouraged suggestion about the treatment of this widespread skin disorder. Important safety and practical aspects of psoriasis treatments are describe in newly existing psoriasis guideline in German S3 which contains comprehensive knowledge on related to a verity of preparation. In this research, least healing of psoriasis that should be accomplished by an independently selected healing regimen accessible. If, subsequent to a particular period of time, Dermatology Life Quality Index and PASI is not reached reduce at least 50 % of the baseline and ≤ 5 respectively, patients should be switched to a different therapy.

51. Ellis CN et al., (2001), performed experiment improvement in psoriasis. Use of alefacept for twelve weeks is connected with perfection in chronic plaque psoriasis and signifying with the purpose of specific task in psoriasis pathogenesis.

52. Dwarampudi LP. et.al, (2012) reported ethanolic seed extract of Psoralia corylifolia shown as anti-psoriatic as well as cytotoxicity activity. This seed extract were analyzed by HPTLC. In- vitro anti-psoriatic activity performed by Sulpho-rhodamine-B analyze human keratinocytes cell (H₄CaT). Finger printing of HPTLC disclosed the Gallic acid presence. Good anti-proliferative activity shown with ethanolic extract of IC50. Extract of “Psoralia corylifolia” seed was shown a largely Anti-psoriatic activity.

53. Asadullah K et al., (2002), reported treatment of psoriasis intended to better action. This recurrent immune illness treated by a number of novel systemic immunomodulatory therapies are in clinical improvement at new approaching
based at the pathophysiology. Purpose of targeting antigen costimulation and presentation, leukocyte adhesion and T cell activation, action of pro-inflammatory mediators, and modulating the cytokine balance. Even if mainly only preface data are accessible, these trials give to an additional appreciative of the disease and will ultimately direct to new therapeutic choice for psoriasis. In present study the justification and the early clinical data of these significant current investigational treatments.

54. Abdelnoor AM (2013) describe psoriasis related factors which involved in the Pathogenesis of diseases and describe it is an autoimmune disease. Innate as well as adaptive both immune factors are concerned in pathogenesis of diseases. Antigen presenting cells (APCs) also called dendritic cells, Neutrophils, Mast cells, keratinocytes along with different receptors that they convey and cytokines are example of innate immune response. The T-lymphocyte subsets and their cytokines are related to adaptive immune response. Cytokines generated in together of the immune factors and produced TNF and IL-17 in psoriasis pathogenesis.

55. Thorleifsdottir RH (2012) reported Psoriasis become well on after remove of tonsil (Tonsillectomy) is connected with minimize in the incidence of flowing T Cells with the aim of recognize determinants of streptococcal along with determinants corresponding to skin. Bacteria genus of streptococci related to throat infection along with T cells linked chronic psoriasis can be react to peptide sequences in M proteins of streptococcal and patient’s of psoriasis blood keratins have also identified. In the primary blinded probable research to evaluate the result of tonsillectomy on psoriasis in 29 patients and 13 patients’ approx 86% exhibit continued progress following tonsillectomy about 30 to 90% decrease in psoriasis severity.

56. Vijayalakshmi A. et al, (2012) reported the rhizome of Smilax china has anti-psoriatic properties. This research the methanolic rhizome extract of smilax china with isolation “quercetin” flavonoid was used for Anti-psoriatic activity. To performed anti-psoriatic action of drug use on Swiss albino mice by Methanol extract about 100 to 200 mg per kilogram of body weight. Carrageenan induced
pleurisy mice were intended for testing of anti-inflammatory activity of methanol extract and isolated quercetin flavonoid. In vitro anti-proliferant action was also performing in HaCaT. This separated flavonoid of S. china produced considerable orthokeratosis in the mouse tail test (P<0.01). They concluded that “quercetin” flavonoid shown better response for psoriasis.

57. Mitra A et al., (2012) reported Psoriasis and psoriatic arthritis ailments have unidentified etiology with chronic inflammation, disturbing 2 to 3% population of the world. This disease was consideration to be a hyper-proliferation of keratinocytes, along with immune system of body also involved that by it was considered disorders of autoimmune system. Now present study of different interleukin (IL)-23/Th17 was involvement also responsible its patho-physiology of disease. Different cytokine antagonist’s was used in treatment of psoriasis. The new monoclonal antibody ustekinumab was used against interleukin-12 plus interleukin-23. Important role of these cytokines responsible in psoriasis pathophysiology and to develop a deliberate approach to new healing armaments of psoriasis treatment.

58. El-Darouti M et al.,(2010), reported highlights of psoriasis with pathogenesis, adjuvant healing and management of resistant. Psoriasis is disease of skin and joints which is common inflammatory condition. Psoriasis etiology has been associated to genetic and the factors of environment. Patho-physiology of disease was revealed through hyper-proliferation of epidermis, production of helper T 1 cytokine, enhanced antigen presentation, T cell expansion, and T lymphocyte activation. Remarkable advances development of novel treatment in this disorder.

59. Chennam J V et al., (2012) describe niosomes vesicles formed on mixture of cholesterol and surfactant by means of successive aqueous medium hydration. This system is carry of amphiphilic as well as lipophilic drugs in vesicular systems like to liposomes. The liposome technology is used for method of preparation of niosomes. The fundamental process of preparation is probably used a mixture of surfactant along with cholesterol by hydration of aqueous phase in the lipid phase. Gel filtration or centrifugation methods were used for separation of unentrapped drug. In-vitro release rate was performed in dialysis tubing.
Niosomes are reduced amounts of toxic in drug with get better the therapeutic index through act as vehicle for drug delivery by prevents unwanted action to target tissue. There are two type vesicles such as unilamellar and multilamellar prepared by non-ionic surfactants (span and Tween). Niosomes are similar to the liposomes for potentially appropriate to many pharmacological action against a variety of diseases.

60. **Fadda AM *et al.*, (2002)** describe preparation of tretinoin-loaded niosomes by span, mixture of octyl/decyl polyglucosides, polyoxyethylene lauryl ether with of dicetyl phosphate along with cholesterol. Evaluation of vesicle of tretinoin was determination of different parameter such as dimension distribution of particle, percentage entrapment of API along in vitro release. Observation of result was shown that with or without tretinoin with amphiphiles mixture with cholesterol made stable vesicle dispersions.

61. **Ryan C *et al.*, (2013)**, studies pathogenesis of psoriasis and extensive development availability of original situation as high degree effectiveness for targeted specific organ or system. They talk about the mainly significant gaps in investigation of this disease at presently appearance and give suggestions for performed research for further study. These include studies of science along with clinical research for disease epidemiologic to establish the right incidence and expected the past of psoriasis. The studies in molecular level for psoriasis and psoriatic arthritis at recognize hereditary character responsible for disease and to recognize new treated targets.

62. **Yu X *et al.*, (2014)**, describe double filtration plasmapheresis for efficient healing of psoriatic arthritis and psoriasis. They describe psoriasis has a lifelong burden of affected patients and permanent cure has not possible. They give information in this research article describe a better therapeutic techniques for psoriatic arthritis with broad expended diseases with help of double filtration plasmapheresis (DFPP) techniques in a twenty five year-old female patient. After two months the first DFPP treatment a outstanding clinical normalization was attained. The patient has no visible disease after the three years treatment DFPP therapy and led
to the absolute falling off of the severe disease. Consequently they consider this therapy as hopeful in psoriatic arthritis treatment.

63. Nasr M (2010), prepared proniosomes of celecoxib (cyclooxygenase-2 inhibitor) and evaluated oral bioavailability of the celecoxib. Celecoxib is a poorly water-soluble drug and proniosomal drug delivery of this drug evaluated at in vitro and in vivo parameter. Spraying method used for preparation of proniosomes by use of surfactant Span 60, dicetyl phosphate and cholesterol. Total 95% of celecoxib drug was entrapped in prepared proniosomes formulation. Dissolution of celecoxib showed noticeable enhancement.

64. Manconi M et al., (2006) reported in vitro cutaneous delivery of niosomes carriers for tretinoin III. The thermodynamic activity effect of drug and different evaluation parameter of niosome such as size, composition, and charge on the transdermal preparation of tretinoin was determined. octyl-decyl polyglucoside and decyl polyglucoside was mixtures of alkyl polyglucosides used for tretinoin incorporation in multilamellar (MLV) and unilamellar (UV) vesicular preparation.

65. Benoit S et al., (2007) describe psoriasis at child stage initial in regarding 33% of patients associated to disease of psoriasis began in the first or second ten year of life. In the commencement of disease participation is often uncharacteristic or mild as well as set up of a certain identification may be difficult. The most common type psoriasis is plaque at childhood. In child age treatment can be confront because drawbacks associated with many therapeutic alternative and adult treatment. Additionally, it is not accepted in age of child. They focus on the characteristics of clinical performance and of the supervision of patients of psoriasis in children and young people.

66. Chaturvedi SP et al., (2012), formulated as lipid nanoparticle of dithranol by hydrogel base and develop of RP-HPLC method. This is a simple, specific and correct, accurate and reproducible technique of evaluated of dithranol. Dithranol was evaluated by using of phenomenex ODS C18 column and mobile phase of this elucidation is acetonitrile: methanol: buffer in ratio of 20:20:60 as at 258 nm wave length which had revealed intense peak. The concentration of dithranol was
in range of 20-100 µg/mL shown linearity. The percentage drug estimation was found near to 100 % confirm the precision of the method.

67. **Feletar M et al., (2008)**, describe developments in diseases of psoriasis and related psoriatic arthritis. Current mechanism of this disease is the immune and genetics level and help to the buildup new-fangled method for psoriasis management. They discuss present pathogenesis of this disease and existing therapies for the psoriasis.

68. **Nestle F. O. et al., (2004)** describe psoriasis mechanism and explain the disease of psoriasis and it is characterized as an autoimmune, persistent degenerative inflammatory illness, dependent on antigen-presenting interaction in dendritic cells of skin, keratinocytes along with T cells producing characteristic mark on lesions of skin distinctively sharply boundaries with blush and scalated plaques.