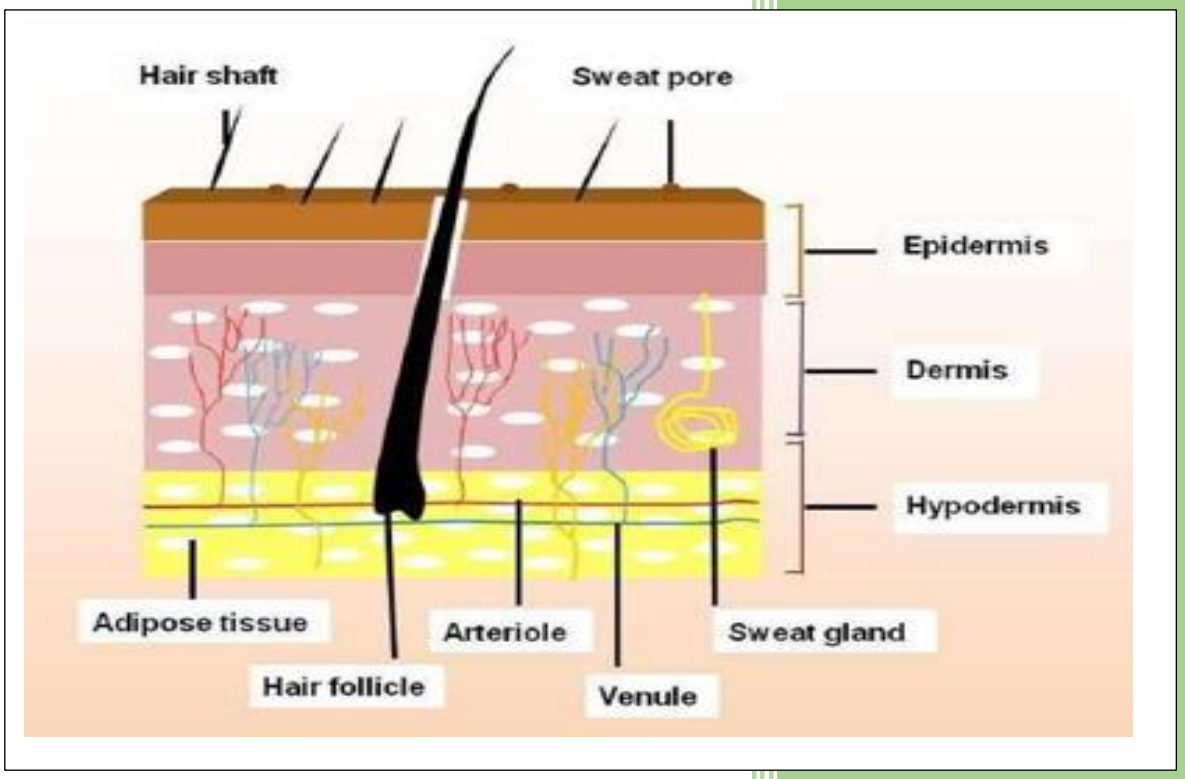
CHAPTER 1: INTRODUCTION



CHAPTER 1: INTRODUCTION

1.1 PSORIASIS

Psoriasis is a psychosocially, and on occasion therapeutically, weakening issue that influence 1 to 3% of the populace all around. It is an immune-mediated disorder with hyperkeratosis and other inflammatory reactions. It essentially includes deviant differentiation and exorbitant growth of ketatinocytes. Infection including T helper 1 (Th1) and T helper 17 cells (Th17) are closely linked with the pathogenesis of psoriasis. There are around 80% of patients who are suffering from psoriasis vulgaris are topically treated (Peeters *et al.*, 2005). Psoriasis can be categorized as mild, moderate and severe conditions. Mild psoriasis leads to the formation of rashes, and when it becomes moderate, the skin turns into scaly.(Peeters *et al.*, 2005; Proksch, 2008). In severe conditions, red patches may be present on skin surface and becomes itchy.

With the discovery of novel carriers the limitation arises in the traditional topical pharmaceuticals for the treatment of psoriasis are bypassed with protected and long term utilize (Proksch, 2008). Novel carriers, for example, liposome, niosome, nanoemulsion, nanostructured lipid carriers (NLCs) , microemulsion, emulsomes, invasomes, dendrimers, nanoparticles, hydrogel, etc.(Katare, O. *et al.*, 2010; Nickoloff, 1999; Suresh *et al.*, 2013a) and ethosomes have for sure conveyed us nearer to the objective of safe and effective treatment of the disease (Katare, O. P. *et al.*, 2010). Stratum corneum (SC) is the major challenge for the drug to get into the target tissues, via skin layers. Penetration enhancers added in the drug carrifiers help to increase the penetration capacity of drug through the outermost layer of the skin. The most favorable drug delivery should provide high penetration through SC and should not cause any irreversible changes to the skin barrier.(Creamer, D *et al.*, 1997; Hern *et al.*, 2001; Xia *et al.*, 2003).

There are many challenges in transdermal delivery of drugs. There will be variability in percutaneous absorption due to site, disease, age, etc. Skin irritation may happen and if the toxicities due to drug are more, the skin gets damaged. The first pass

metabolic effect of skin is also one of the challenges for topical delivery.(Bhushan *et al.*, 1999; Creamer, Daniel *et al.*, 2002; Krueger and Ellis, 2005). Novel drug delivery systems have lot of advantages. They increase safety and efficacy levels. Drug targeting specificity and lowering systemic drug toxicity are the important merits of NDDS. Also they have the ability to improve absorption rates and will prevent biochemical degradation of pharmaceuticals.(Colombo *et al.*, 2014a; Smith and Barker, 2006a).

Table 1.1 Difference between normal skin cells and psoriatic skin cells (Kim, E. S. and Frampton, 2016)

Sr. No.	Normal Cells	Psoriatic Skin Cells
1	Skin cells are smooth.	Skin characteristics typical for psoriasis are scaly, erythematous plaques, papules, or patches of skin that may be painful and itch.
2	Skin cells replaced usually after 28 – 30 days.	Skin cells replaced every 3-5 days.
3	There is no premature maturation or abnormal proliferation of keratinocytes.	Premature maturation of keratinocytes induced by inflammatory cascade in dermis involving macrophages and T cells.
4	Penetration potential is high.	Penetration potential is low comparatively.

Reduced quality of life, depression, higher cardiovascular risk, type 2 diabetes mellitus, metabolic syndrome, cancer, Crohn's disease, and psoriatic arthritis are all connected with psoriasis. Cancers, particularly skin cancer and lymphoma, are unknown to be linked to psoriasis or its treatment. Nonmelanoma skin cancer can be

exacerbated by phototherapy and immunosuppressive therapy (Kim, E. S. and Frampton, 2016). The differences between healthy skin and psoriatic skin cells are depicted in Table 1.1.

1.2 SKIN A ROUTE FOR NOVEL DRUG DELIVERY

Skin is considered to be the largest and outermost organ of the human body. Among three important layers of skin, epidermis functions as a protective barrier of the body.(Jain, Sima, 2017; Prieto-Pérez *et al.*, 2013) There are a lot of blood vessels and layers present in the epidermis. Sub layers are also present in this outermost layer such as stratum lucidum, stratum corneum, stratum spinosum, stratum granulosum, and stratum germinativum.

Dermis is present beneath the outermost layer, which is composed of connective tissues.(Guerra and Gisbert, 2013b; James, W. *et al.*, 2015). Hypodermis is situated under the dermis layer. For the treatment of psoriasis, percutaneous absorption of drugs is one of the widely accepted ways of drug delivery. The challenge that offered by topical treatment is the presence of SC as a barrier.(Cox *et al.*, 2010a; Fisher, 2005; Menter *et al.*, 2008; Richard *et al.*, 2013b) Conventional forms of drug delivery through skin have come across with many side effects and other application difficulties. Disruption of SC and targeting to the deeper layers of skin are not possible with ointments, creams etc. So, novel dermal delivery systems help to overcome these limitations, thereby enhance the bioavailability and potential of drug and are widely used for the treatment for psoriasis recently.(Naldi and Gambini, 2007).

Importance of topical medication for the treatment of psoriasis, topical treatment is mostly prescribed method since transdermal delivery of drug is the first line of defence for psoriatic skin. Psoriasis occurs when there is excess growth of skin cells due to faulty signals produced by immune system. These rapidly growing skin cells can be easily controlled by the novel topical medications which are meant for manipulating the functions of skin barrier.(Chen *et al.*, 2013b; Swanson *et al.*, 2007)

Direct administration of drugs to dermis and epidermis can be achieved by these drug delivery methods.(Fiorentino, 2007; Hadgraft, 1996; Morganti *et al.*, 2001b)(Figure 1.1)

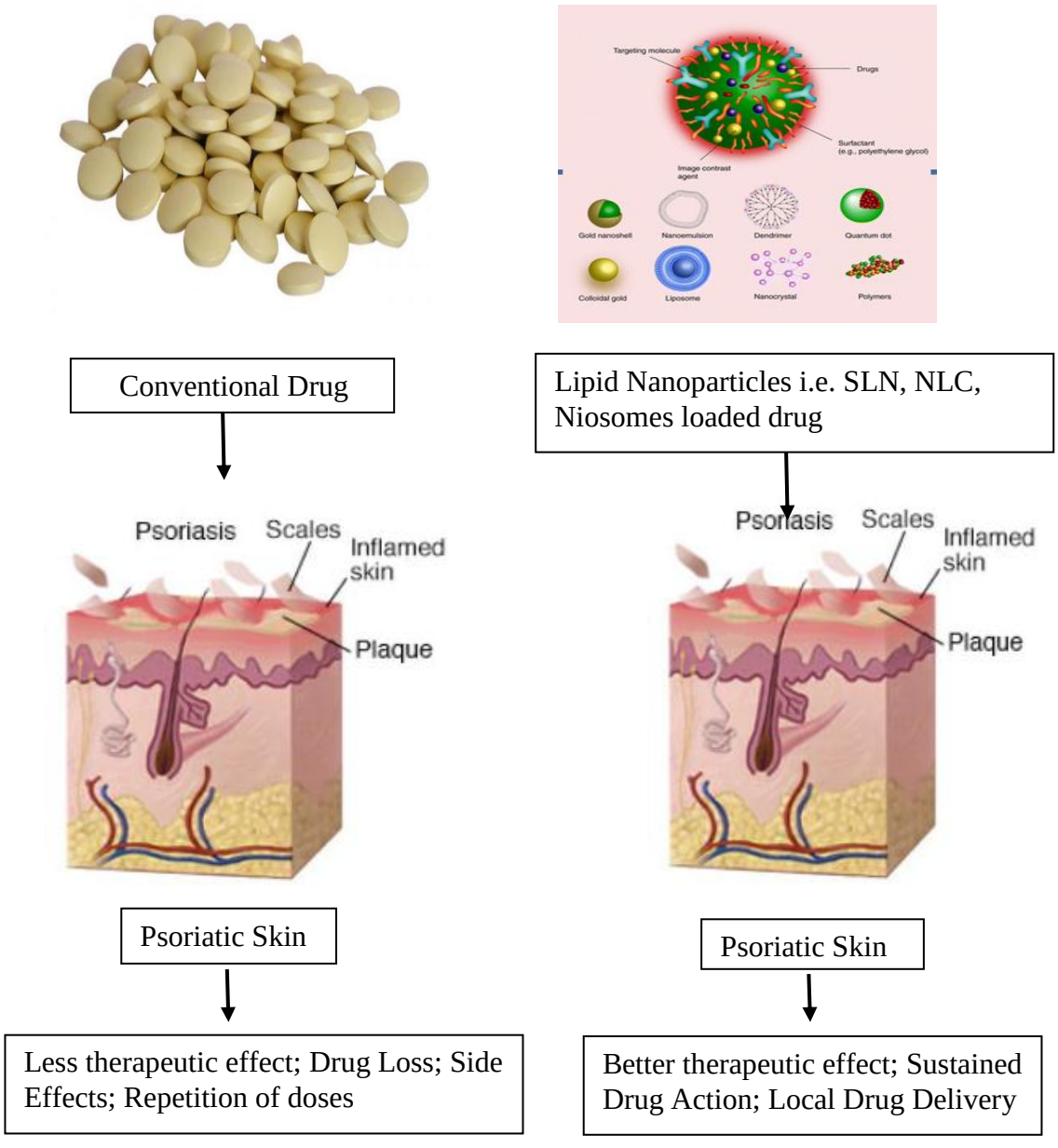


Figure 1.1: Penetration of conventional drug and nano-formulations through psoriatic skin.

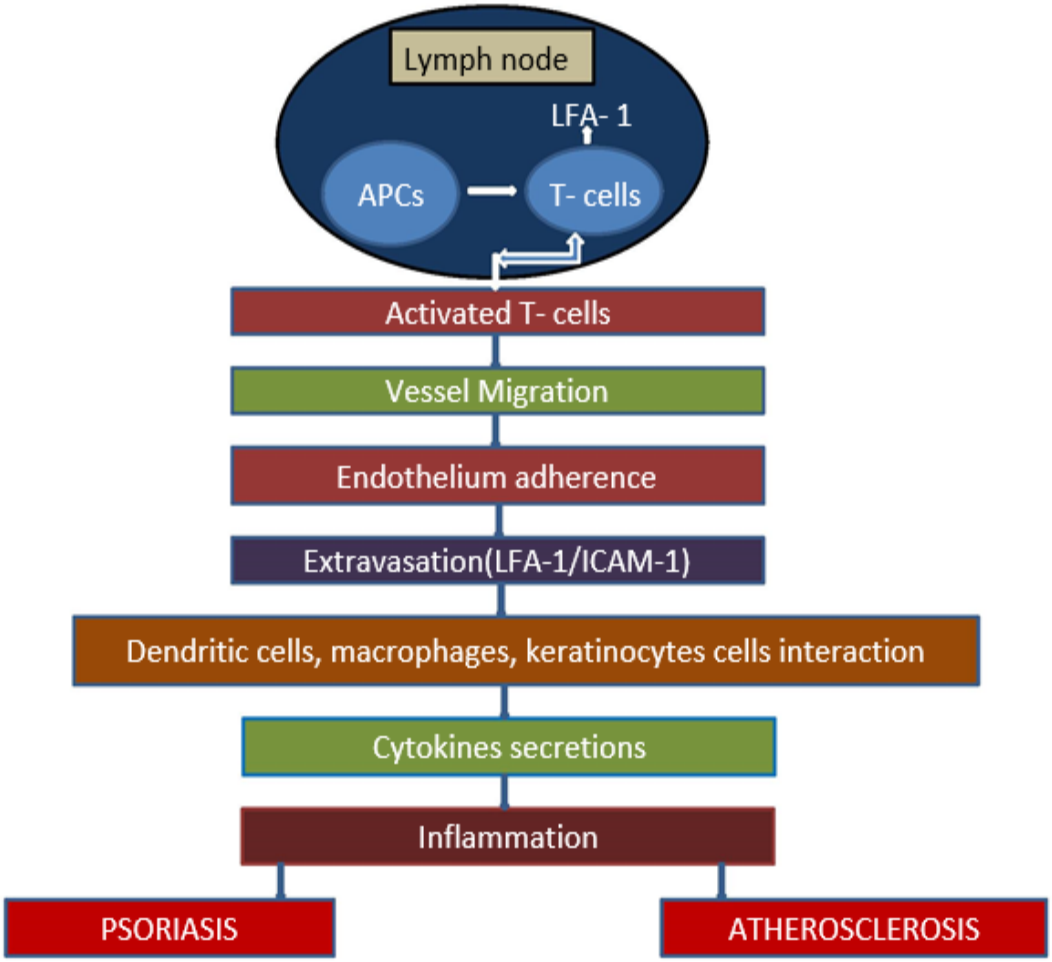


Figure 1.2 Pathophysiology of psoriasis

1.3 PATHOPHYSIOLOGY OF PSORIASIS

Activation of T lymphocytes in dermis (fundamentally CD4+ cells) and epidermis (predominantly CD8+ cells) are responsible for the initiation of Psoriasis which is an autoimmune disease (Nickoloff, 1999). T-cell when binds with Antigen presenting cells (APCs) they get activated. This process is mediated by surface molecules utilized for attachments; including cluster of differentiation (CD2) on the T cells and leukocyte function associated (LFA)- 1 and intercellular adhesion molecule (ICAM)-

1, and lymphocyte function-associated antigen-3 (LFA-3) on the APCs this is appeared in Figure 1.2.

For the specific T-cell there is a T-cell receptor (TCR) which recognizes an antigen presented on the major histocompatibility complex (MHC I or II) by the APC. Interaction between LFA-1 and ICAM-1, and extravasate responsible for the propagation of activated T-cells and enter the circulation via diapedesis through the endothelium in the skin at site of inflammation. At this point, by secretion of pro-inflammatory (type 1 or Th1) cytokines, which include, tumor necrosis factor (TNF)-α, interferon (IFN)-γ and interleukin (IL)-1 T-cells show the immunologic process. These cytokines secretions results in the production of Th2 cytokine including IL-11, IL-10 and IL-4. Each cytokine are responsible for down regulation of other's responses (Suresh *et al.*, 2013b).

The final outcome of this process is the keratinocyte proliferation, migration of other inflammatory cells, an increase in activity and vascular changes which results in the formation of the plaque psoriasis (Hern *et al.*, 2001).

Psoriasis is fundamentally a disease of the keratinocyte, because of its major quantifiable highlights of unusual epidermal thickening and scaling. Clinically, the vascular nature of psoriasis is noticeable by the erythematous plaques which indicate pinprick bleeding on evacuation of scale (Auspitz sign). Four times increment in surface area of the superficial vascular plexus in psoriasis, and an expansion in endothelial cell growth has been seen in histological investigations (Creamer, D *et al.*, 1997). In angiogenesis in psoriasis vascular endothelial growth factor (VEGF) specifically, seems to assume a fundamental part. This cytokine is likewise show up as a powerful mediator of irritation and increments vascular penetrability. Over communicating VEGF in the epidermis in transgenic mouse were accounted for to build up a psoriasis-like condition (Xia *et al.*, 2003). In erythrodermic psoriasis serum concentration of VEGF are expanded (Bhushan *et al.*, 1999), and a connection

between plaques VEGF, values of psoriasis area and severity index (PASI) and serum VEGF was also reported (Creamer, Daniel *et al.*, 2002).

The primary variables in charge of psoriasis are, over-articulation of VEGF in the psoriatic epidermis, diminished TNF concentrations, move in bone marrow transplants from affected people, angiogenic factors, and expanded concentrations of natural killer (NK T) cells.

1.4 EPIDEMIOLOGY

- Psoriasis, a chronic proliferative skin illness is a standout amongst the most well-known immune mediated issue happening in 1.5 – 3% of population worldwide (Cox *et al.*, 2010b).
- Of patients, 75% present with symptoms of psoriasis before age 45yrs.
- Although once in a while life-threatening, psoriasis has an adverse physical and emotional effect on quality of life (Fisher, 2004).
- Prevalence rates are to a great degree high in aboriginal tribes in Australia, Africa, south America, and other developing areas of the world.
- In 2009 review investigation of 30,078 youngsters in India, scabies was observed to be the second most regular skin infection in all age gatherings of kids, and the third most normal skin disease newborn children.

1.5 ETIOLOGY OF PSORIASIS

1.5.1 Genetics

Around 33% of individuals suffering from psoriasis report a family history of this illness. Studies recommend that in indistinguishable twins if one of them has the disorder there is 70% possibility of other to develop psoriasis and for non-indistinguishable twins the hazard is around 20%. These discoveries demonstrates that both a genetic susceptibility and a natural reaction were responsible in creating

psoriasis (Krueger and Ellis, 2005). Nine loci have been recognized by Classic genome-wide linkage analysis on various chromosomes related with psoriasis. They are called psoriasis susceptibility 1 through 9 (PSORS1 through PSORS9). Certain transformations of those genes are regularly found in psoriasis (Colombo *et al.*, 2014b). Some different genes that are modified in psoriasis have been recognized by Genome-wide association. Some of these genes are additionally engaged with other immune system diseases and some of them express inflammatory proteins, which influence cells in the immune system.(Colombo *et al.*, 2014b).

About 35%–50% of psoriasis heritability are because of PSORS1, (Smith and Barker, 2006b). It controls genes that influence the immune system or encode skin proteins in the real histocompatibility complex (MHC) PSORS1 is situated on chromosome 6, which controls essential immune functions. HLA-C variation HLA-Cw6, these are the genes in the PSORS1 locus related with psoriasis (Prieto-Pérez *et al.*, 2013) which encodes a MHC class I protein. Immune system has two noteworthy genes interleukin-12 subunit beta (IL12B) on chromosome 5q are under scrutiny, which communicates interleukin-12B; and IL23R on chromosome 1p, which expresses the interleukin-23 receptor, and is capable in T cell separation. Both Interleukin-23 receptor and IL12B have been unequivocally connected with psoriasis (Prieto-Pérez *et al.*, 2013). T cells are associated with the inflammatory process in psoriasis(Colombo *et al.*, 2014b).

1.5.2 Medications

Beta blockers (Jain, Sima, 2012), lithium, antimalarial medications (Jain, Sima, 2012), non-steroidal anti-inflammatory drugs (Jain, Sima, 2012), terbinafine, calcium channel blockers, captopril, glyburide, granulocyte colony-stimulating factor (Jain, Sima, 2012), interleukins, interferons (Jain, Sima, 2012), lipid-lowering drugs (James, W. D. *et al.*, 2015), and paradoxically TNF inhibitors such as infliximab or adalimumab (Guerra and Gisbert, 2013a) etc. causes drug induced psoriasis.

1.5.3 Lifestyle

Chronic infections, changes in season and atmosphere and stress are responsible for worsening of disease (Prieto-Pérez *et al.*, 2013). Different elements incorporate scratching psoriasis skin sores, skin dryness, high temp water, intemperate liquor utilization, cigarette smoking, and obesity (Prieto-Pérez *et al.*, 2013; Richard *et al.*, 2013a).

1.5.4 Oxidative pressure

Expanded urinary loss of albumin and take-up of albumin is likewise expanded by liver as a result of this concentration of albumin is diminished and additionally zinc concentration is diminished because of that there is further lessening in superoxide dismutase which builds the oxidative pressure which causes psoriasis Figure 1.3.

1.6 TYPES OF PSORIASIS

There are five fundamental kinds of psoriasis: Plaque, Guttate, Pustular, Inverse, and Erythrodermic (Menter *et al.*, 2008). 90% of the cases are of Plaque psoriasis, which is also called psoriasis vulgaris. It normally gives red patches covered with white scales on top. Back of the lower arms, shins, around the paunch catch, and the scalp are the most affected zones of the body in plaque psoriasis. Guttate psoriasis has drop formed sores (Menter *et al.*, 2008).Pustular psoriasis presents with little non-irresistible discharge filled blisters (Jain, Sima, 2012). Red patches in skin folds are formed in Inverse psoriasis (Menter *et al.*, 2008). Erythrodermic psoriasis happens when the rash turns out to be exceptionally broad, and can create from any of alternate kinds.

Fingernails and toenails are influenced in a many people sooner or later in time. Changes in nail shading or pits in the nails may be incorporated in this case. Psoriasis is generally thought to be a genetic disease which is activated by natural elements.

There are 5 kinds of psoriasis which is spoken to in Table no. 1.2. (Naldi and Gambini, 2007).

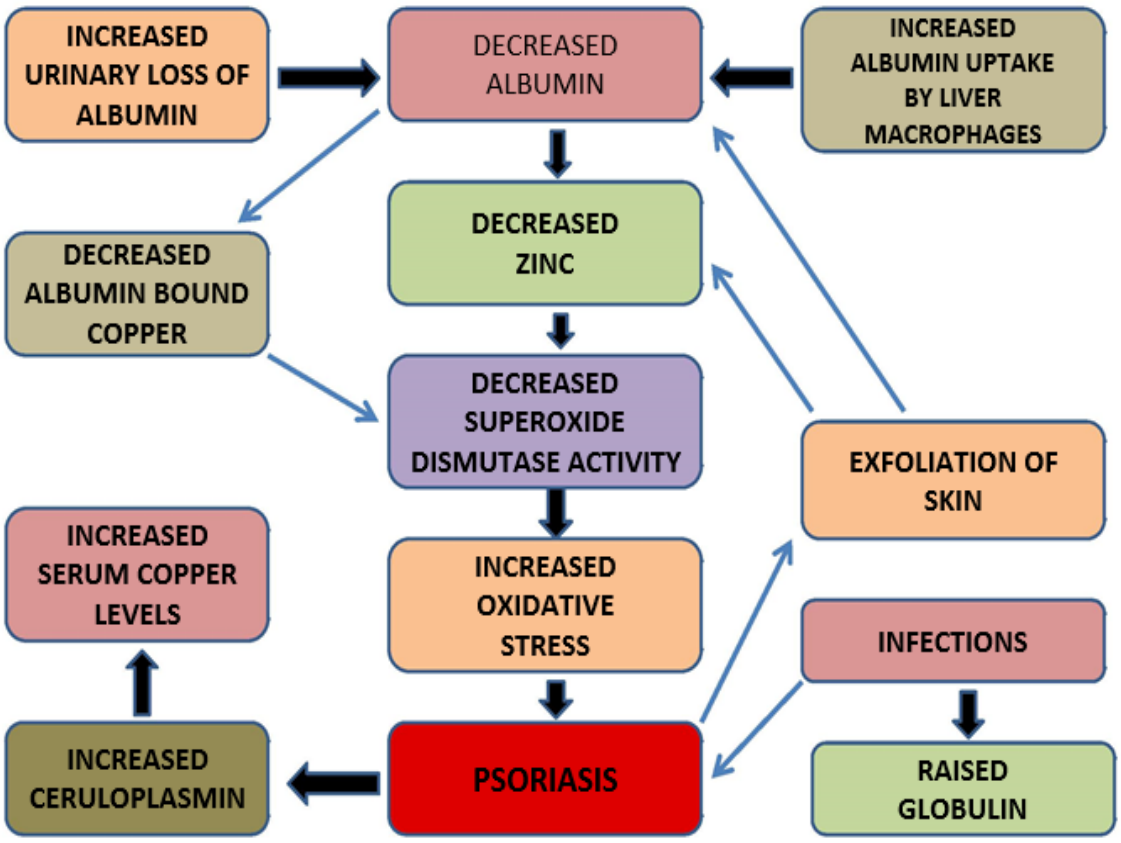
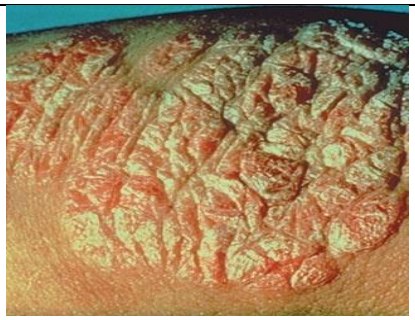
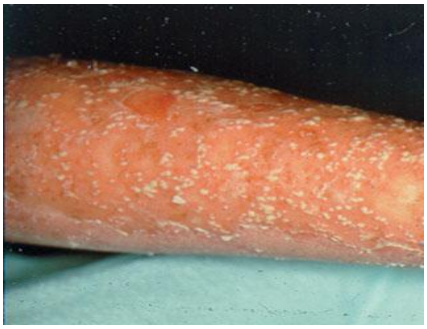
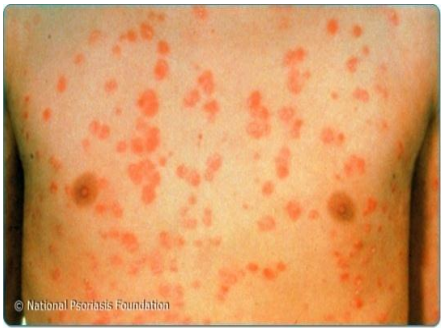
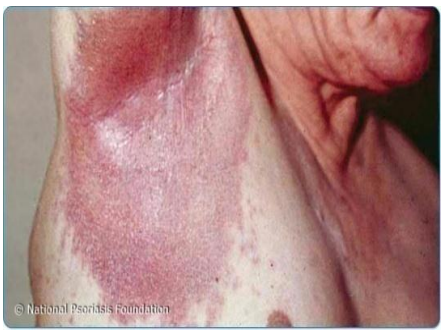
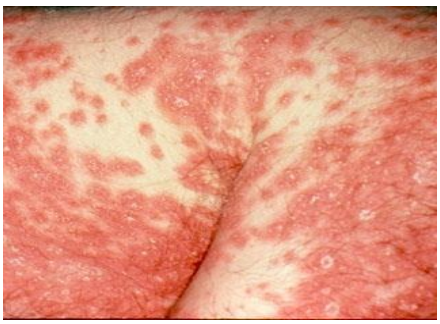


Figure: 1.3 Etiology of Psoriasis

Table 1.2 Classification of types of psoriasis and their features

TYPES	FEATURES	FIGURE
Plaque	Plaque psoriasis is the most common form of the disease it appeared as raised, red patches covered with a silvery white buildup of dead skin cells or	

	scale. These patches or plaques most often appear on the scalp, knees, and elbows and lower back. They are often itchy and painful, and they can crack and bleed.	
Pustular	It is primarily seen in adults. It may be localized to certain areas of the body, e.g. hands and feet. Can be generalized, covering most of the body. It tends to go in a cycle as reddening of the skin followed by formation of pustules and scaling.	
Guttate	Appears as small, red, separate spots on the skin. Lesions usually appear on the trunk and limbs and commonly number in the hundreds. Sometimes lesions form on the scalp, face and ears. They are not usually as thick as the lesions that characterize plaque psoriasis. This form can precede or co-exist with other forms of psoriasis, such as plaque.	

Inverse	Inverse psoriasis shows up as very red lesions in body folds, such as behind the knee, under the arm. It may appear smooth and shiny. Many people have another type of psoriasis elsewhere on the body at the same time.	
Erythrodermic	It is the least common type of psoriasis and may occur once or more during a lifetime in 1 to 2 percent of people who develop psoriasis. It generally appears on people who have unstable plaque psoriasis. This means the lesions are not clearly defined. Widespread, fiery redness and exfoliation of the skin characterize this form. Severe itching and pain often accompany it.	

1.7 CONVENTIONAL TREATMENT

On the level of severity there are conventional treatments for psoriasis. Mild psoriasis treatment includes calcipotriene (a vitamin D3 analog), topical corticosteroids, tars, anthralin, tazarotene (a retinoid), and phototherapy. Scalp psoriasis generally treated

with salicylic acid shampoos. Drugs which are used for treatment of psoriasis are specified in Table no. 1.3. For treatment of psoriasis narrow-band UVB is less powerful yet it is more secure than psoralen in addition to bright A (PUVA), which increases the risk of skin cancer. Exposure of sun is another type of phototherapy. Development of T-helper 2 (Th2) immune responses were indirectly altered as an impact of UV exposure as it diminishes antigen presenting cells (Chen *et al.*, 2013a).

Oral retinoids, methotrexate, cyclosporine, and natural operators are utilized for foundational treatment of psoriasis that has critical effect on other real frameworks. Two types of contraception must be utilized by female patients and after treatment they should not, they must not become pregnant for less than 3 years but rather there are some unfavorable impacts, for example, mucocutaneous impacts, alopecia, hoisted triglycerides and hepatitis. Frequent monitoring of blood counts, urinalysis, and comprehensive metabolic profiles are required in the treatment with acitretin. Ways to deal reduce acitretin toxicity are alternating use, maintenance dose is reduced to each third day, blend treatment with PUVA or topical calcipotriene is additionally an alternative, low-fat eating regimen, and fish oil supplementation, exercise and liquoravoidan.Methotrexate (MTX) causes deficiency of active folic corrosive as it represses dihydrofolate reductase and it additionally incites adenosine A1,which is a potent anti-inflammatory agonist (Swanson *et al.*, 2007). The most widely recognized and genuine antagonistic impacts of MTX are liver fibrosis and myelosuppression. While myelosuppression does not typically happen, patients utilizing MTX much of the time report side effects of cerebral pain, exhaustion, and queasiness. Folate supplementation diminishes the frequency of hepatotoxicity, megaloblastic frailty, and gastrointestinal narrow mindedness (Fiorentino, 2007).

Table 1.3 List of topical novel drug delivery systems for psoriasis

Drug		**Anthralin**	Acitretin	Alefacept	Calcipotriene	Calcipotriene and Betamethasone Dipropionate	Clobetasol Propinate	Cyclosporine	Desonide
Generic Name		Anthralin	Acitretin	Alefacept	Calcipotriene	Calcipotriene and Betamethasone Dipropionate	Clobetasol Propinate	Cyclosporine	Desonide
Trade Name(s):	**India**	Psorisome Psoriatec	Acrotac10 (mg) Aceret (25mg)		Heximar, Psotriol		Clop-AS Tigerderm -5 (5mg)	Sandimmun Neoral, Sandimmun Neoral (50mg)	Desowen Desowen (Skin) (10mg)
	Int.	Dritho-Scalp, Zithronal RR,	Neotigason, Soriatane	Amevive	Dovonex.	Taclonex	Clobevate, Clobex	Gengraf, Neoral, Sandimmune	Desowen, Tridesilon
Contraindications		Contraindicated in patients with acute psoriatic eruptions or history of hypersensitivity.	Contraindicated in patients with liver, kidney impairment, during pregnancy (before the	Contraindicated in patients with HIV, and hypersensitivity.	Hypersensitivity.	Contraindicated in patients with pustular psoriasis, poor calcium metabolism and hypersensitivity.	Hypersensitivity	Hypersensitivity	Hypersensitivity

		start, during and at least 2-3 yr after cessation of therapy), lactation, increased level of lipids in blood.						
Pregnancy Category	**A B C D X**	**A B C D X**	**A B C D X**	**A B C D X**	**A B C D X**	**A B C D X**	**A B C D X**	**A B C D X**
Indications	Adult: Topical- As 0.1% ointment/paste: Apply for a few hr before washing off once daily. Apply to skin or scalp for 20 to 60 minutes once a day, then washed or shampooed off. Apply for	Adult: PO- The recommended dose is 25 to 50 mg per day, given as a single dose with the main meal.	The recommended dose is 15 mg given once weekly as an intramuscular injection.	Adult: Topical-As 0.005% cream/ointment: Apply 1-2 times/day. Max: 100 g per week.	Topical- Adults- Apply once daily for up to 4 weeks.	Apply a thin layer to the affected skin area twice daily, rub gently.	Adult- PO- The recommended initial dose range is 10 to 15mg/kg/day. Maintenance: 2 to 6mg/kg/day	t should be applied on the affected areas as a thin layer two or three times daily depending on the severity of the condition

	a few hours before washing off once daily. In some cases, it is applied at night and allowed to remain on the affected areas overnight, then washed off the next morning or before the next application.							
Precautions	Caution should be exercised in patients with history of inflamed psoriatic eruptions	Avoid blood donation during therapy or at least 1-3 years after stopping therapy. It may make	It should not be used in children. Avoid live vaccination while taking this medication.	Caution needed for pregnant and breastfeeding women, and people with hypersensiti	For external use only; avoid contact with eyes, mouth and vagina. Monitor serum calcium level regularly while using this	For external use only; avoid contact with your eyes, mouth, or nose. It should not be used in children less than 18 years old.	This medication may reduce platelet counts; avoid injury or bruising. ♦ Avoid eating	avoid contact with eyes, nose and mouth. Avoid excess dosage.

		your skin sensitive to light, so avoid sunlight.		vity. Avoid using this medication on your face.	medication. Caution should be exercised in patients with history of skin scar, increased level of blood calcium, skin infection, during pregnancy and breastfeeding.		Grapefruit or drinking Grapefruit juice while taking this medication	
Side Effects	**Local** - Irritation and staining of treated areas.	Heart attack, Headache, shakiness, sleeplessness	Dizziness, increased cough, muscle pain, nausea	Burning, itching and skin irritation	**Central Nervous System** - Headache. **Skin** - Itching, psoriasis and scaly rash. **ENT** - Throat inflammation.	Infection/irritation, itching and cracking	Kidney dysfunction, tremor and high blood pressure, Cramps	Stinging, burning, irritation, skin inflammation
Storage Conditions	Store it at room temperature. Keep away from heat and light. Keep	Store between 15° and 25°C (59° and 77°F) in an airtight	Store it in refrigerator (2-8°C). Safety Labeling Changes	Store it at controlled room temperature (15° C - 25° C).	Store it at room temperature	Store it at room temperature	Store it at room temperature (25°C), and in an airtight container.	Store between 15° and 30° C

	container tightly closed.	container. Protect from light. Avoid exposure to high temperatures and humidity after the bottle is opened. Keep away from children.	Approved By FDA				Safety Labeling Changes Approved By FDA	

For those cases which are not controlled with PUVA, acitretin, or MTX, Cyclosporine, a powerful and poisonous medication, is utilized yet in patients with abnormal renal function, ineffectively controlled hypertension, hepatic dysfunction, it is contraindicated.

Biological agents block T-cell initiation and TNF, drugs like Amevive® meddles with T-cell actuation and reductions circling CD 45 RO+ T cells. During treatment with this operator CD4 cells must be observed week by week. Efalizumab (Raptiva®) is a humanized antibody to CD11 that interferes with T-cell moving into excited tissues and counteracts T-cell activation.

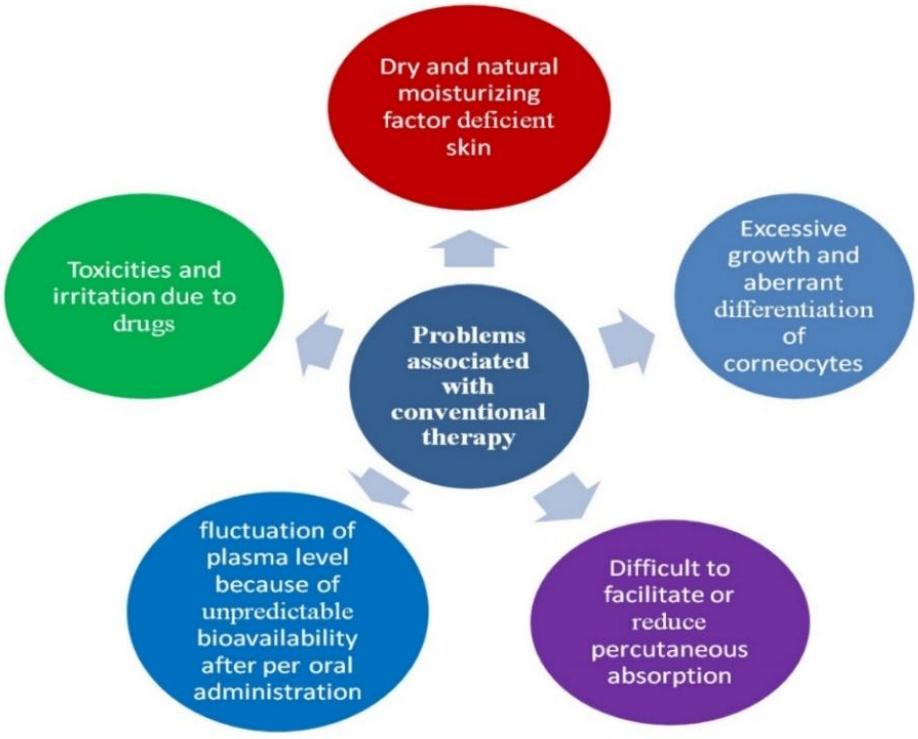


Figure: 1.4 Problems associated with conventional therapy

While it is rapidly effective, but rebound may occur there are numerous conceivable dangers of TNF-blockers incorporate repeat of hepatotoxicity, inactive tuberculosis, lymphoma, and congestive heart disappointment. Difficulties that stay

with biologics for psoriasis are Poor understanding the real system in psoriasis and psoriatic joint pain, Poor understanding reactions of various patient to treatment, Predicting clinical reaction before treatment, developing oral, inhaled, and topical details is additionally a major challenge, Determining whether treatment changes long haul results. Connection of transdermal ways to deal with regular treatment based on benefits and bad marks is appeared in Table no.1.4.

Their futures may convey stem-cell therapy and gene-based treatments that specifically repress particular genes which are responsible of psoriasis. Nonetheless, the unfavorable impacts and lethality with traditional medications of psoriasis can be overcome by compelling common medicines that can be utilized as options. Figure.1.4 portrays the issues related with conventional therapy.

Table:1.4. Correlation of transdermal approaches to conventional treatment on the basis of merits and demerits.

TRANSDERMAL APPROACHES		**CONVENTIONAL TREATMENT**	
Merits	**Demerits**	**Merits**	**Demerits**
Reduction in dosing frequency leads to improved patient compliance	High cost of formulation	low cost formulation	Increasing dosing frequency leads to poor patient compliance
Eliminates peak-valley Fluctuations	Required skilled worker for preparation of these formulations	There is no need skilled workers	Fluctuations in peak and valley plasma concentration
Reduction in Gastrointestinal (GI) irritation and other dose-related side effects	Stability problems are seen in some cases like liposome	Provide better Stability	Due to the first pass metabolism in liver, GI irritation is more pronounced
Provides sustained release for longer period of time	The main limitation in transdermal patch approach that it causes skin irritation or skin infection due to the	No such problems occur conventional treatment	Frequent dosing required

	high frequency applied through iontophoresis		
Prevent degradation of drugs,	_	_	Degradation of drugs can occur
Selective targeting of the drug to the site of action leads to lesser side effects.	_	_	Conventional therapy provides no targetability in tissues and organs
High solubilization capacity for hydrophilic and lipophilic drugs,	_	_	Solubilization problem of drugs.
Increase the permeability through skin.	_	_	Difficult in permeate through skin

1.8 CHALLENGES IN TOPICAL DELIVERY OF DRUGS IN PSORIATIC SKIN

Amid the most recent decades, for transdermal medication conveyance numerous inorganic and colloidal particles, for example, nanospheres, nanocapsules, nanostructured lipid carriers, and so on have been investigated. For the effective utilization of these frameworks for medicate conveyance totally relies upon their capacity to penetrates through a few barriers, controlled release of their substance and their stability in the nanosize. Distinctive medication conveyance frameworks, for example, liposomes, nanoparticle, dendrimers and strong lipid nanoparticles, were created to conquer physicochemical constraints of medications, for example, poor solubility, low penetrability, high molecular weight, short half-life, reactions and systemic toxicity etc. As indicated by the examinations detailed as of recently, stratum corneum (sc) is not a passive layer, yet an "active-wall," which restricts the entrance of molecules. It permits entering almost every one of the materials to some degree however no molecules can completely go through this layer. The intercellular lipids are the real courses of entrance over the SC (Morganti *et al.*, 2001a) there is list of

topical novel drug delivery systems for psoriasis mentioned in Table 1.5 . Hydration condition of stratum corneum is the most important factors in determining the rate of percutaneous absorption of a given solute. For the water concentration gradient the level of hydration is a reason among dermis and the surface of the skin and additionally the capacity of the stratum corneum to "bind" with water(Hadgraft, 1996).Conveyance of solutes through the skin is related with various troubles as appeared in fall in the levels of ceramides and "Rigidization" of psoriatic skin has been ascribed to an ascent in the levels of cholesterol(Wertz *et al.*, 1989). Aside from this, normal moisturizing factors (NMFs) like water are relatively missing in the psoriatic skin. Because of numerous viewpoints, focusing on the psoriatic tissues utilizing topical course represents a major test.

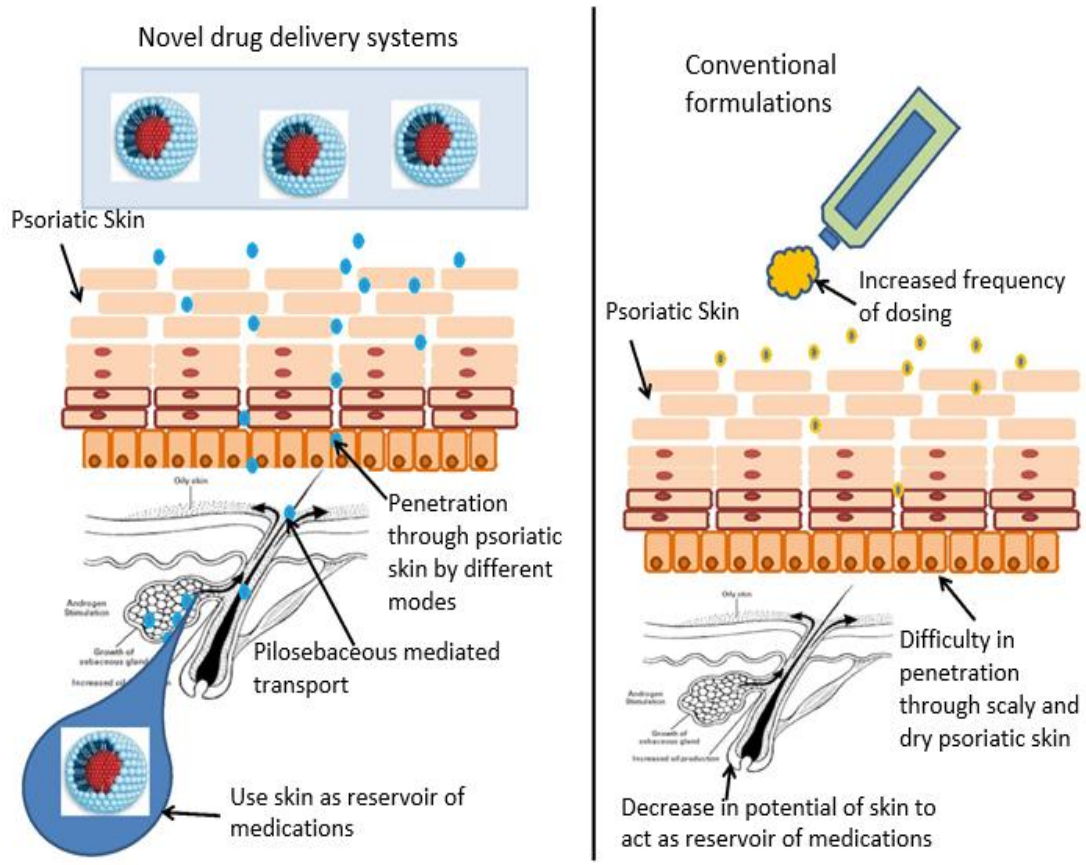


Figure. 1.5 Advantage of novel carrier over conventional system

There are a few topical therapeutic agents which are existing for the treatment of psoriasis. Be that as it may, none of them can be seen as a perfect drug molecule. This may either be because of their natural symptoms or their in-fitting entanglement in the ordinary framework. Due to distinction in the physicochemical attributes of the carrier and the active compounds, the degree of medication absorption through skin may vary, and in this manner, there might be an adjustment in the medication proficiency. Subsequently, the carriers which depend on logical methodologies can alter the physicochemical properties of the medications and can diminish the power and occurrence of symptoms related with these active moieties (Staidle *et al.*, 2011). The advantage of novel carrier over conventional system is shown in Figure1.5.

Major Challenges in care of topical drug delivery

- There are variety in percutaneous retention on account of site, age, and diseased condition
- Dry and common moisturizing factor deficient skin
- Toxicities and irritation because of medications
- Bioequivalence criteria
- Difficult to encourage or decrease percutaneous retention because of deficient understanding of technologies
- Potential of skin to go about as reservoir of medications

Table 1.5 List of topical novel drug delivery systems for psoriasis.

AntiPsoriatic Drug	Novel Drug Delivery Systems	Reference
Hydrocortisone	Liposome-gel	(Kim, M.-K. *et al.*, 1998)
Tacrolimus	Ethosomes in gel	(Li *et al.*, 2012)
Hydrocortisone	Drug β-Cyclodextrine complexes into SLNs	(Cavalli *et al.*, 1999)
Fluocinolone acetonide	Cyclodextrin inclusion complexincorporated in	(Varshosaz *et al.*, 2012)

	multivesicular Liposomes	
Methoxsalen	Chitosan coated microemulsion	(Behera *et al.*, 2010)
Betamethasone	PLGA/PLA nanoparticles (plus zinc)	(Ishihara *et al.*, 2005)
Betamethasone	PLGA (poly(D,L-lactic-co-glycolic acid)) nanoparticles	(Özcan *et al.*, 2013)
Ciclosporine Dexamethasone	PLGA nanoparticles	(Jain, Sanyog *et al.*, 2011) (Gómez-Gaete *et al.*, 2007)
Clobetasol-17-Propionate	PLGA microspheres	(Badıllı *et al.*, 2011)
Dexamethasone	Poly(ε-caprolactone) (PCL) Nanocapsule	(Friedrich *et al.*, 2008)
Hydrocortisone	PCL nanoparticles	(Rosado *et al.*, 2013)
Ciclosporine	Polymeric micelle (PEG-dihex PLA deblock copolymer)	(Lapteva, Mondon, *et al.*, 2014)
Methotrexate	Poly(NIPAM-co-BA) nanogel	(Singka *et al.*, 2010)
Tacrolimus	Methoxy-poly(ethylene glycol)-dihexyl substituted polylactide (MPEG- dihexPLA) deblock copolymer micelle	(Lapteva, Santer, *et al.*, 2014)
Anthocyanin complex Dithranol Methotrexate	Niosome	(Priprem *et al.*, 2015) (Brülls and Rasmuson, 2002) (Abdelbary and AbouGhaly, 2015)
Betamethasone Clobetasol-17-Propionate	Lecithin/chitosan nanoparticles	(Özcan *et al.*, 2013) (Şenyiğit *et al.*, 2010)
Tacalcitol Clobetasol-17-	Liposome	(Körbel *et al.*, 2001; Rao and Murthy, 2000)

propionate Dithranol Tacrolimus Tretinoin Triamcinolone		(Kumar *et al.*, 2015; Özcan *et al.*, 2013) (Crozier, 1968; Yu and Liao, 1996)
Calcipotriol	Pegylated liposomes	(Knudsen *et al.*, 2012)
Dexamethasone Hydrocortisone Triamcinolone	Transferosome	(Cevc, Gregor and Blume, 2004) (Fesq *et al.*, 2003)
Cyclosporine	Flexible vesicles and conventional vesicles	(Guo *et al.*, 2000)
Methotrexate	Deformable liposomes	(Srisuk *et al.*, 2012; Trotta *et al.*, 2004)
Ciclosporine Methotrexate Psoralen Tacrolimus Tretinoin Tretinoin	Ethosome	(Dubey *et al.*, 2007; Li *et al.*, 2012; Raza, Singh, *et al.*, 2013; Verma and Fahr, 2004; Zhang, Y.-T. *et al.*, 2014)
Acitretin	Nanostructured lipid carriers (NLCs)-hydrogel	(Silva *et al.*, 2012)
Betamethasone Ciclosporine Clobetasol-17-propionate Dithranol Methoxsalen. Mometasone furoate Prednicarbate Psoralen Tretinoin Triamcinolone	SLNs (Solid lipid nanoparticles)	(Kim, S. T. *et al.*, 2009; Zhang, J. and Smith, 2011) (Kalariya *et al.*, 2005) (Gambhire *et al.*, 2011) (Battaglia *et al.*, 2012) (Madan *et al.*, 2014; Schlupp *et al.*, 2011) (Fang, J.-Y. *et al.*, 2008) (Pradhan *et al.*, 2016) (Sonawane *et al.*, 2014)
Betamethasone dipropionate and calcipotriol Halobetasol	SLN-hydrogel	(Bikkad *et al.*, 2014) (Wang *et al.*, 2012) (Lin *et al.*, 2010)

Tacrolimus		
Calcipotriol and methotrexate Clobetasol-17-propionate Fluocinolone acetonide Methotrexate Methoxsalen Psoralen Tacrolimus Tretinoin	NLCs	(Pinto *et al.*, 2014; Pradhan *et al.*, 2015) (Nam, S.-H. *et al.*, 2011) (Baboota *et al.*, 2011) (Marepally *et al.*, 2014) (Sonawane *et al.*, 2014) (Raza *et al.*, 2011)
Betamethasone dipropionate and salicylic acid Methoxsalen	Microemulsions in hydrogel	(Baroli *et al.*, 2000)
Dithranol Methoxsalen Tacrolimus	Microemulsion	(Sah *et al.*, 2011) (Shinde *et al.*, 2013) (Wohlrab *et al.*, 2012)
Methoxsalen	Nanoemulsion	(de Carvalho Vicentini *et al.*, 2013)
Cyclosporine A Tacrolimus	Liquid crystalline nanoparticles	(Thapa and Yoo, 2014) (Petrilli *et al.*, 2016)

1.9 CLOBETASOL PROPIONATE

Clobetasol propionate is a very potent topical corticosteroid class compound. Topical steroids are used in addition to moisturisers for treating inflammatory skin conditions such as eczema and dermatitis. Owing to its anti-inflammatory, antipruritic and immunemodulating properties, clobetasol propionate is used to treat psoriasis (Decroix et al. 2004). Clobetasol propionate induces phospholipase A2 inhibitory proteins, thereby controlling the release of the inflammatory precursor arachidonic acid from membrane phospholipids by phospholipase A2 (Sch€afer-Korting et al. 2005). It was also found that if clobetasol propionate (CP) was incorporated in the nanoemulsion it shows significant increase in their anti-inflammatory activity. It was

reported that CP-loaded nanoemulsion significantly increased NTPDase (Nucleoside triphosphate diphosphohydrolases) activity in lymphocytes. This membrane protein is responsible for the hydrolysis of extracellular ATP (Adenosine triphosphate) which is responsible for cell proliferation, differentiation and inflammatory processes (Alam et al. 2013). For topical formulations use of conventional excipients could serve the purpose only to a limited extent of absorption, penetration, and retention through psoriatic barrier cells (Katare et al. 2010). With the discovery of newer chemicals like squalene biocompatible and biodegradable materials like phospholipids and novel drug delivery technologies like deformable liposomes, SNLs, liposomes, nanostructured lipid carriers (NLCs), microemulsions and nanoemulsions, etc. have the possibility to improve the efficiency and safety of the topical products to a great extent and also improve the absorption, penetration and retention in skin (Katare et al. 2010). It was found that the addition of corticosteroid and a keratolytic agent such as salicylic acid in nanocarrier would result in enhancement and sustaining of corticosteroid delivery rate leading to better anti-psoriatic activity. Clinical use of corticosteroid is restricted to some extent due to its poor permeability across the skin. So to increase its permeation across the skin, nanocarriers were prepared and characterised (Baboota et al. 2011).

1.9.1 Primary characteristics

It is of Synthetic origin and belongs to Steroid. It belongs to Glucocorticoid agonist pharmacological group on the basis of mechanism of action and also classified in Dermatological Products and Corticosteroid Topical pharmacological group. The Molecular Weight of Clobetasol Propionate is 467.00. Its pKa is not ionizable. Figure1.6

1.9.2 Pharmacokinetics

Metabolism is reported negligible, hepatic. Renal Excretion accounts for only and its half life is ranges from 2-3 hrs.

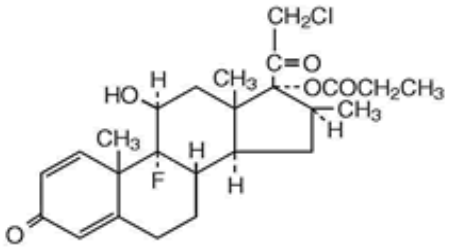


Figure 1.6 Structure of clobetasol propionate

IUPAC: (11 - β,16β) - 21 - Chloro - 9 - fluoro - 11 - hydroxy - 16 - methyl - 17 - (1 - oxopropoxy) - pregna - 1,4 - diene - 3,20 - dione
Molecular Formula: $C_{25}H_{32}ClFO_5$

1.9.3 Mechanism of action

Clobetasol propionate appears to induce phospholipase A2 inhibitory proteins, thereby controlling the release of the inflammatory precursor arachidonic acid from membrane phospholipids by phospholipase A2 as shown in Figure 1.7.

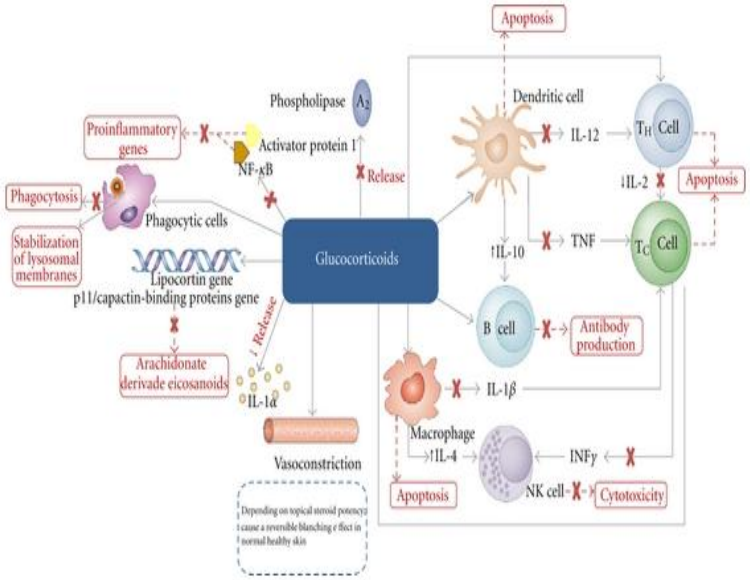


Figure 1.7 Mechanism of action of glucocorticoids (clobetasol propionate)

1.10 REQUIREMENT FOR NOVEL CARRIERS

For safe and effective therapy, the advancement of new medications has been the basic practice however improvement of new medication alone isn't sufficient to guarantee advancement and achievement in drug treatment, since purposes behind the failure of treatment were poor medication solubility, because of poor absorption there is lacking medication fixation, fast digestion and disposal, sedate dissemination to different tissues combined with high drug toxicity, and there were variance in level of plasma in view of flighty bioavailability of drug after per oral administration, including the impact of food on plasma levels (Mehnert and Mäder, 2001). Every one of these variables influence the conveyance of the medication inside the body, as there is obvious deviation from the coveted site of activity, i.e., the target site. A promising technique to defeat these issues are utilized, for example, as per the particular need of the treatment an appropriate medication bearer framework ought to be created to accomplish controlled and confined conveyance of the active medications. This is the modification(s) in physicochemical properties of the particles, which prompt enhanced medication conveyance toward the coveted destinations. Further, it additionally enhances the accessibility of the medications at the particular receptor site and aides in upgrading drug−receptor association mediation of specialized composition and design of the carrier systems. The novel transporters have been utilized through every one of the courses of organization. However, the topical course has been a standout amongst other courses for treatment of dermatological issue all the more adequately. Figure1.8 demonstrates the carrier systems for topical and transdermal drug delivery.

These novel transporter frameworks are distinctive in their composition and constructs including their exterior and interior design when compared to conventional systems such as ointments and creams, colloidal carriers have accomplished consideration amid the ongoing years. These nanosystems incorporate nanoparticles, liposomes, ethosomes, nanoemulsions, microemulsions, nanosuspensions, micelles

and soluble polymer-drug conjugates.

Drug molecules get entrapped inside the inner areas of these carrier systems. Relationship of medications with bearers is regularly noncovalent, in view on combined strength of weak binding forces. With the invention of new technologies many newer carrier systems are developing and the demand of targeted delivery like ethosomes, emulsomes, resealed erythrosomes, magnetic nanoparticles, and bilosome additionally expanding.

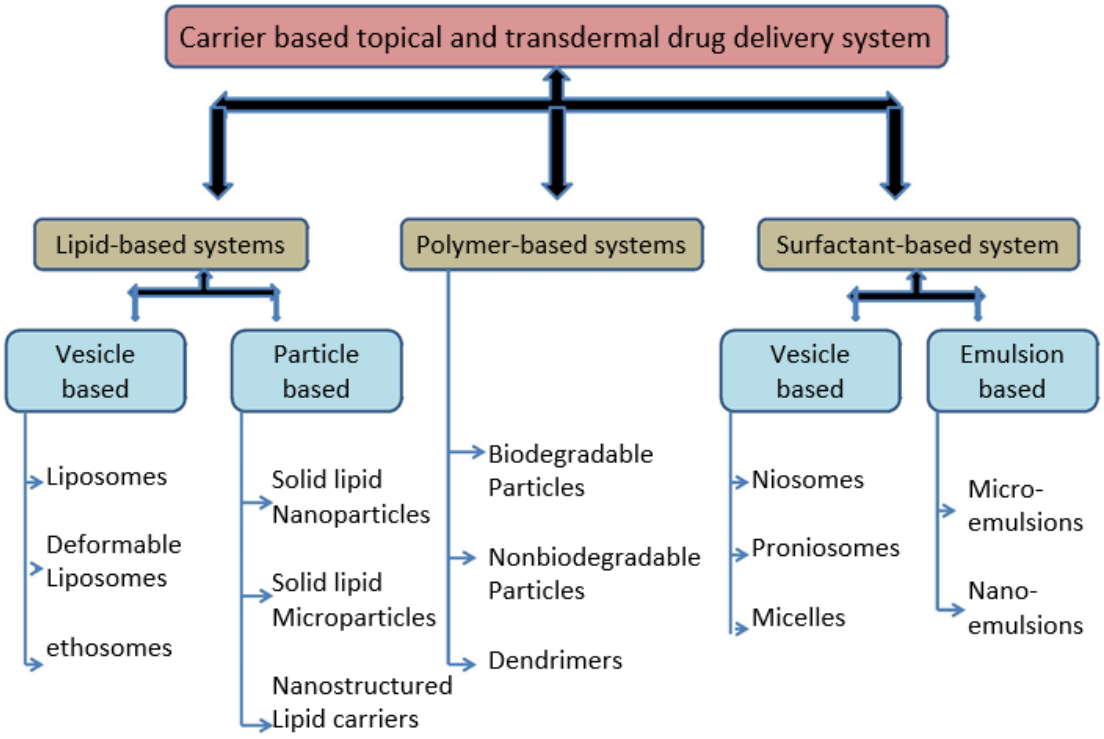


Figure. 1.8 Different carrier systems for topical and transdermal drug delivery

1.11 MECHANISM OF UPTAKE OF NOVEL CARRIERS

In the free drug mechanism after releasing from the carriers the drug permeates through skin (Ganesan *et al.*, 1984). In the penetration enhancing mechanism, after the carrier systems were applied, there were changes in the ultra-structures of the intercellular lipids were seen proposing an expansion in penetration efficiency (Kato

et al., 1987). During the time spent adsorption or combination, the vesicles may adsorb or fuse to the stratum corneum lipid grid, increasing drug portioning into the skin with progressive exchange of medication straightforwardly from vesicles to skin. In entire vesicular skin penetration mechanism, for instance customary liposomes can't enter the human skin yet ultradeformable liposomes have been accounted for to penetrate the skin intact and dive deep in stratum corneum (Masini *et al.*, 1993). The transfollicular conveyance from liposomes was improved simply after it was joined with iontophoresis method (Han *et al.*, 2004). Ethanol may furnish the vesicles with delicate adaptable attributes which enable them to penetrate effortlessly into more profound layers of the skin. The ethosome vesicles can penetrate through the penetrate stratum corneum. The medication is released in the more profound layers of the skin and its transdermal retention could be the consequence of combination of ethosomes with skin lipids and medication release at various points (Elsayed *et al.*, 2007) and different routes of delivery are intercellular penetration and transport through pilosebaceous glands which is appeared in Figure 1.9.

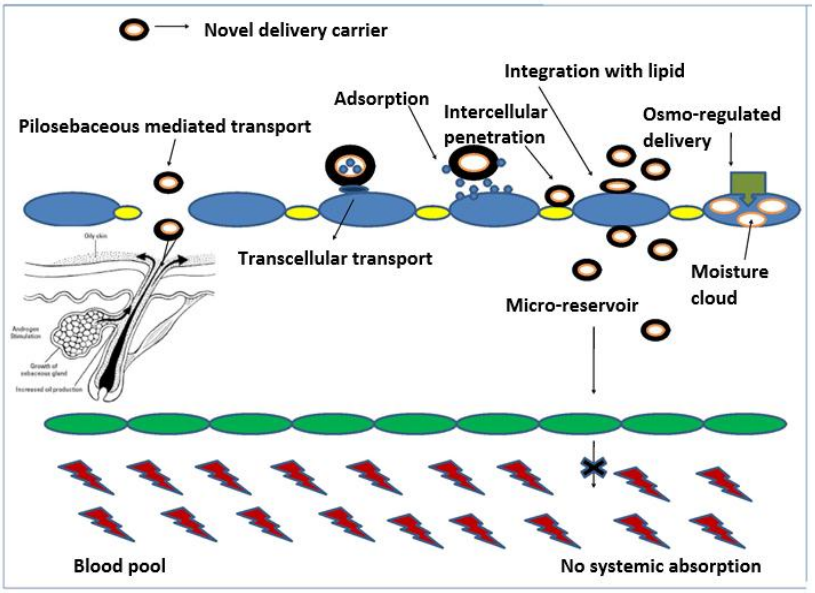


Figure 1.9 Mechanism of uptake of novel carriers through topical route

1.11.1 Significance of Novel drug delivery systems used in treatment psoriasis

- Increased penetration through psoriatic skin
- Delivery toward the desired sites
- Providing protection to the drug molecules
- Systems Biocompatibility
- Passive focusing on
- Variety of medications can be loaded
- Modification in physicochemical properties
- Minimizes dosage of drug

1.12 NANOEMULSION

At the point when the estimation of an emulsion globule comes to around 20 to 500 nm then Figure 1.10 Nanoemulsions are obtained they oppose the physical disturbance caused by gravitational partition, flocculation and blend on account of their littler droplet size. The droplet's Brownian movement is sufficient to beat the gravitational detachment drive as a result of this nanoemulsion likewise keeps away from the creaming procedure. Size of nanoemulsions can likewise demonstrate their impact on a few properties, for example, as particle stability, color, appearance, texture, rheology and shelf life**.** Nanoemulsions are outstanding for their capacity to protect drug from instability issues, increment skin penetration, and their prolonged activity on the skin (Solans *et al.*, 2005). The medication as well as, the kind of emulsion and the oil phase all are critical concerns when endeavoring to optimize topical drug permeation this is finished by formulating methyl 5-aminolevulinic corrosive (mALA) and 5-aminolevulinic corrosive (ALA) at equimolar fixations in o/w and w/o nanoemulsions for delivery to the skin (Zhang, Y. *et al.*, 2011). As compared to the aqueous control the consistency of drug flux was enhanced by the

emulsions. Also, of α-terpineol, which is a penetration enhancer, and a part of the oil phase does not further expand drug permeation via the skin. Khandavilli and group formulated a nanoemulsion (NE) to accomplish infiltration of paclitaxel more profound into the skin layers while it expands the skin retention (Khandavilli and Panchagnula, 2007). Upon dermal application, the medication was predominantly limited in more profound skin layers, with negligible systemic escape. Bernardi planned rice bran oil nanoemulsions and evaluated it for its irritation potential and saturating activity on ordinary and infected skin types volunteers (Bernardi *et al.*, 2011). It has been discovered that It has been with regard to marketed product optimized dithranol-loaded emulsomes showed improved antipsoriatic activity on a mouse-tail model (Raza, Katare, *et al.*, 2013). The selected composition also, improves the medication penetration and greater skin retention. When compared to the marketed product the detailing was observed to be genuinely stable, non-irritant and biocompatible.

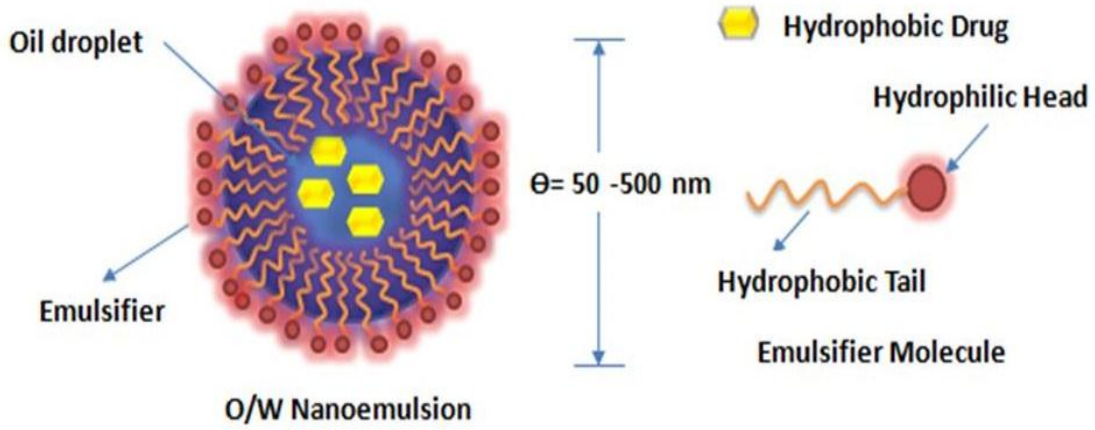


Figure 1.10 Structure of nanoemulsion.

1.13 NANOSTRUCTURED LIPID CARRIER

Nanostructured lipid transporters (NLCs) are the latest generation of Solid lipid nanoparticles (SLNs) demonstrates enhanced properties of adjustment of the release profile, , drug loading, and stable drug incorporation during storage. NLCs are set up

by blending solid lipids with spatially incompatible lipids leads to the formation of special structure lipid matrix. NLCs give more space to medicate settlement since it is a mixture of a liquid and solid lipid which don't make consummate crystalline structure with numerous imperfections. Cases of solid lipids incorporate triglycerides (tristearin, trimyristine and so on), waxes (carnauba, cetylpalmitate), fatty acids (stearic corrosive, palmitic acid), while fluid lipids contain medium chain oleic acid, triglycerides, isopropyl myristate. Their topical applications on skin were additionally affirmed effectively. NLC systems are a promising carrier for the topical conveyance of antipsoriatic drugs by upgraded skin pervasion, negligible skin irritation, and the compatibility of the drugs (Müller *et al.*, 2007). Calcipotriol and methotrexate has joined for effective conveyance of the medications in nanostructured lipid bearers for topical delivery (Lin *et al.*, 2010). It has been explored that the penetration rate of these NLCs through the skin of a bald mouse which was more prominent than a commercial dermal ointment containing tacrolimus (Nam, S. H. *et al.*, 2011).

Therefore, present work is proposed to develop a clobetasol propionate loaded nanostructured gel formulation for the treatment of psoriasis to overcome the barriers of stratum corneum. The formulation has the additional advantages over the conventional ointment which are as follows:

1. Better permeation and penetration across skin barriers.
2. It forms a depot under skin which shows better local actions because of squalene present in nanostructured lipid carrier as liquid lipid which shows higher affinity of the system towards pilosebaceous gland.
3. It circumvents the associated systemic toxicity.
4. Due to depot formulation, it releases the drug steadily and slowly for a long time.
5. The drug is protected from metabolic degradation due to encapsulation in carrier system.

1.13.1 Salient Features of Nanostructured Lipid Carrier (NLC)

- Because they are formed from natural phospholipids, they are biocompatible and biodegradable, comparable to liposomes. They have a high entrapment efficiency (almost 90% in the case of lipophilic drugs) and preserve the encapsulated drug from metabolic degradation. They serve as a store, slowly and gradually releasing their contents (Cevc, G and Blume, 1992; Cevc, Gregor *et al.*, 1997).
- They can be employed for both systemic and topical medication delivery. Easy to scale up because the technique is straightforward and does not necessitate the use of pharmaceutically undesirable chemicals.
- They can be utilised for both low and high molecular weight medications.
- they can be applied non-occlusively, where they pass through the stratum corneum's multi-layered lipid matrix as a result of hydration or a transepidermal gradient (Hsu and Armstrong, 2014).

1.13.2 Type of NLCs

NLCs differ from SLNs in the following ways: higher loading capacity for particular medications, less water in the dispersion, and the ability to avoid or limit drug expulsion during storage. However, no substantial difference in biotoxicity has been documented between SLNs and NLCs. The structure of NLCs has been given in three different ways, as seen in Figure 1.11.

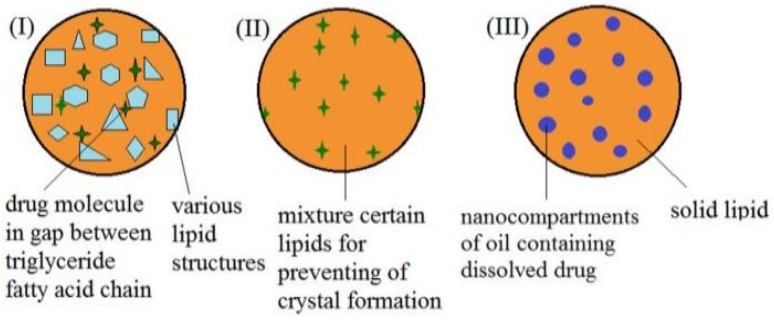


Figure 1.11 Types of NLCs

The first is the imperfect kind, which consists of a mixture of solid and liquid fats (oil) in diverse lipid forms. Specific crystallisation circumstances result in a highly disordered product. Imperfect lipid matrix structure creates a space between triglyceride fatty acid chains in crystal, allowing medicines to enter the matrix more easily. The second class is the formless type (non-crystalline matrix), which is a type of NLC that lacks a crystalline structure and hence hinders loaded drug evacuation, and is also known as the amorphous type. Crystals occur upon cooling in this form, and particular lipids mixtures must be utilised to prevent this. Multiple type is the third class; in this class, medication solubility in liquid lipid is greater than in solid lipid, preventing solid lipid breakdown. NLCs in this form are similar to w/o/w emulsions(Naseri *et al.*, 2015). Figure 1.11 depicts a diagrammatic representation of many forms of NLCs.

1.13.3 Method of preparation of nanostructured lipid carrier (NLCs)

LNPs (Lipid nanoparticles) can be produced in a variety of ways. High pressure homogenization at elevated or low temperatures (including hot and cold homogenization), solvent emulsification, evaporation or diffusion, supercritical fluid supercritical fluid extraction of emulsions (SFEE), ultrasonication or high speed homogenization, and spray drying are all common methods for preparing NLCs (Patel, D. *et al.*, 2012).

- **High pressure homogenization (HPH)**

HPH technology has established itself as a reliable and effective method for producing lipid nanoparticles. This method for large-scale synthesis of LNPs can also be used, unlike previous techniques. There were two types of homogenization methods developed: hot and cold. In both methods, the medicinal ingredient is dissolved or disseminated in melted lipid prior to HPH. The fluid in the homogenizer is moved by high pressure (100–2000 bar). The average particle size is submicron. Homogenization has various advantages, including large-scale production, the

absence of organic solvent, increased product stability, and improved drug loading, but it is difficult to apply due to high pressure and temperature conditions (Yuan *et al.*, 2007).

- **Hot homogenization**

Homogenization occurs at temperatures over the lipid's melting point in this process. By mixing, drug-loaded lipid melt is dispersed in a hot aqueous surfactants phase (isothermal) and pre-emulsions are formed. Particle size decreases mostly due to lower viscosity at high temperatures. There are three major issues with hot homogenization. The first is drug degradation that is temperature dependent, the second is drug penetration into the aqueous phase during homogenization, and the third is the complexity of the nanoemulsion crystallisation stage, which leads to numerous modifications and/or supercooled melts(Naseri *et al.*, 2015).

- **Cold homogenization**

The medication is dissolved in the lipid melt and then rapidly cooled with liquid nitrogen or dry ice, similar to the hot homogenization process. Milling produces nanoparticles with a diameter of 50-100 nm that disperse in a cool surfactant phase to generate a pre-suspension. PHP is carried out at room temperature, which causes the nanoparticles to break down into SLNs. To address the issues with the hot homogenization approach, the cold homogenization technique has been expanded. (Naseri *et al.*, 2015).

- **Solvent emulsification /evaporation**

The lipid is dissolved in a water-insoluble organic solvent in this procedure. After that, a surfactant-containing emulsion in an aqueous phase is created. Evaporation under lower pressure is used to remove the solvent from the emulsion. Evaporation causes nanoparticles to disperse in the aqueous phase (using lipid precipitation process in the aqueous phase). This method, unlike cold homogenization, will not be subjected to heat stress, however the organic solvent utilised in this process is a

drawback. The size of the particles varies depending on the solid lipid and surfactant used. (Naseri *et al.*, 2015).

- **Spray drying**

This technology is an alternative to the lyophilization method for producing pharmaceuticals from aqueous SLN dispersion. Spray drying, rather than lyophilization, is a more cost-effective method for producing lipids, but it is not widely employed. Because of the high temperatures and shear forces applied, particle aggregation occurs. Lipids with a melting point greater than 70 °C have been found to be appropriate for spray drying in prior research. (Naseri *et al.*, 2015).

- **Ultrasonication or high-speed homogenization**

Ultrasonication or high-shear homogenization is one of the procedures for producing LNPs. This phase disperses the aqueous phase, which contains a lot of surfactants, and the lipid phase. The high surfactant content will be viewed as a disadvantage. Another drawback of this approach is that it does not produce a tight particle size distribution, which leads to storage instability.

1.14 DEFORMABLE LIPOSOMES

Liposomes being the most successful drug delivery carriers it is widely used as carrier in pharmaceutical and cosmetic industries. Liposomes can entrap both lipophilic and compounds and facilitate their targeted delivery, it also helps to entrap unstable compounds for eg. antioxidants, antimicrobials, and bioactive elements and avoid their decomposition. The drugs entrapped inside the liposomes are protected from degradation and oxidation during blood circulation. This phospholipid barrier remains undamaged and protect the drug until delivered to the exact target. (Hofheinz *et al* 2005). Liposomes are concentric bilayered vesicles in which an aqueous volume is altogether enclosed by a membranous lipid bilayer for the most part made out of manufactured or characteristic phospholipids. In liposomal system phospholipids are

significant part these phospholipids incorporate with skin lipids and keep up hydration condition and enhance sedate entrance and localization in the skin layers. liposomes are considered as better conventional preparations for topical treatment (Moghimi and Patel, 1993);(Cevc, Gregor, 1996);(Schmid and Korting, 1996). Liposomes as medication bearers indicate great remedial impact with fewer side effects. It has been accounted for that encapsulation of retenoids in liposomal carriers, for example, vitamin A acid or tretinoin indicates reduced local irritation (Trapasso *et al.*, 2009). Reports have proposed that when tacrolimus was embodied in liposomal carriers in topical formulation it has upgraded its entrance through skin. Reports with different models proposed that Liposomal tacrolimus will be less toxic at that point free tacrolimus when they are entered in the circulatory system. So, the patients who require higher concentrations of ointment to large areas of skin can use liposomal tacrolimus instead of free (Patel, S. *et al.*, 2010). Tamoxifen stacked liposome have created and characterized for topical treatment and revealed better skin permeation of Tamoxifen and retention in the skin (Bhatia *et al.*, 2004). Entrance of calcipotriol into the stratum corneum is influenced by the size of the liposomes, smaller unilamellar vesicles of liposomes demonstrates improved medication infiltration when contrasted with large multilamellar vesicles. This additionally demonstrates the liposomes can migrate into the stratum corneum as intact vesicles at some extent (Srisuk *et al.*, 2012). The methotrexate loaded deformable liposomes showed enhanced permeability when contrasted with the conventional liposomes and this was a result of versatile attributes of the oleic acid containing in deformable liposomes, oleic acid likewise indicates skin penetration enhancer. Conceivable advantages of joining methotrexate and menthol in a vesicular gel base for enhancing the medication dispersion, accessibility and patient tolerability was examined (Nagle *et al.*, 2011). By utilizing the rat tail model antipsoriatic effectiveness of the formulations tested *in vivo*, demonstrated that the vesicular gel having menthol prompted greatest medication maintenance in the skin. The *in vivo* studies about additionally decided the adequacy

of the formulation in inducing a normal pattern of variation in the rat tail skin that at first showed parakeratosis, which is also characteristic of psoriatic epidermis. Major drawback associated with this formulation was its poor colloidal stability.

1.14.1 Mechanism of Penetration of Deformable liposomes

Natural "transdermal osmotic gradients," i.e. another much more significant gradient is available over the skin, are the cause of this high flux rate. The skin penetration barrier creates an osmotic gradient that inhibits water loss through the skin and maintains a water activity differential between the living epidermis (75 percent water content) and the virtually entirely dry stratum corneum near the skin surface (15 percent water content) (Cevc et al., 1996). Systematically, the mechanism of deformable liposome penetration can be divided into three categories:

- The interaction of hydrophilic lipid residues with proximal water causes polar lipids to attract water molecules, causing hydration, and lipid vesicles to migrate to areas with higher water concentrations. The difference in water content between the stratum and epidermis of the skin creates a transdermal osmotic gradient, which allows deformable liposomes to penetrate the skin.

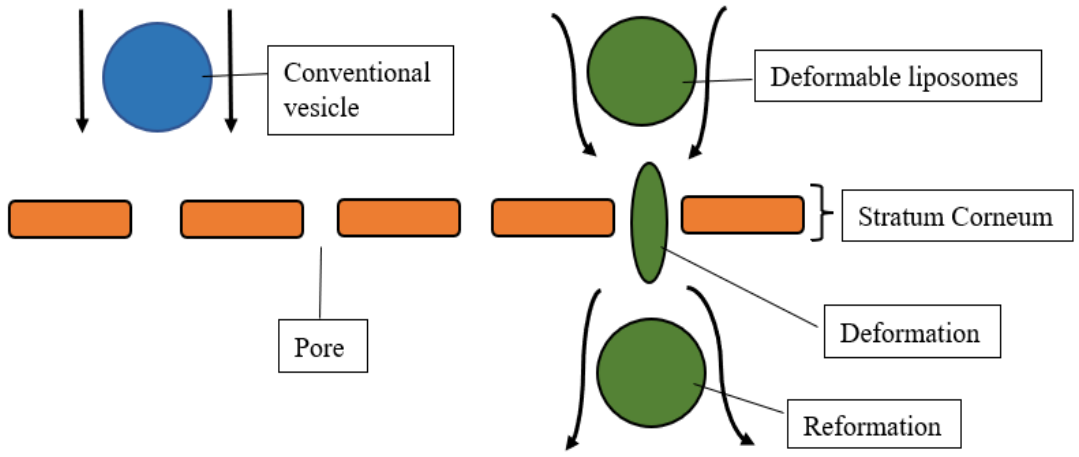


Figure 1.12 Schematic diagram of the two micro-routes of penetration

- By enforcing their own path, deformable liposomes cause hydration, which widens the hydrophilic pores of the skin, allowing for a slow release of medication that binds to the targeted organ (Figure 1.12).

- Deformable liposomes operate as penetration enhancers by disrupting intercellular lipids in the stratum, thereby widening skin pores and facilitating molecular interaction and system penetration across the skin. The 'transdermal osmotic gradient' that forms across skin in the case of deformable liposomes is higher than that of other vesicular systems, according to studies. As a result, they have a higher penetration rate than other vesicular systems (Gompper et al.,1995).

1.15 NANO GEL

Gillian S. Leslie Singka et al. have created nano gels for the topical delivery of MTX differs from 100 nm to 1 μm in size. The swelling nature of the colloidal particles in numerous solvents was one reason for the wide utilization of this conveyance. The monomers utilized in nanogels were having imperative significance in volume phase transition depending upon different improvements, for example, temperature, dissolvable compose and ionic quality. Styrene, divinyl benzene, methyl methacrylate and so forth could be utilized for the creation of nanogels. The most broadly utilized monomer is NIPAM (N-isopropylacrylamide) since it could fall at low temperature (32-34°C). So in that review, the nanogel was set up with co-polymer of NIPAM and non-ionic monomer butacrylate The nanogel could experience de-swelling and the removal of MTX was affected by change in temperature amid entrance through skin. The joining of immersed Na2CO3 could upgrade MTX motion from nanogel and by the utilization of NIPAM monomers, the biosynthesis of PEG2 could be lessened which was known to be an irritation mediator.

1.15.1 Advantages of using nano gel as a Drug Delivery System

By using w/o/w emulsions, hydrophobic medicines can be easily integrated into gels.

Solubility acts as a barrier because of those most hydrophobic drugs cannot be incorporated directly into gel bases, and problems develop during drug release. Emulgel aids in the integration of hydrophobic medicines into the oil phase, followed by the dispersion of oily globules in an aqueous phase, resulting in an o/w emulsion. This emulsion can also be added to a gel base. It's possible that this will provide better drug stability and release than merely integrating medicines into a gel foundation. Singh and colleagues (Singh et al., 2014).

Increased stability

Other transdermal preparations, in comparison to emulgels, are less stable. Creams display phase inversion or breaking, while ointment indicates rancidity due to the oily base, just like powders.

Greater capacity for loading

Other innovative techniques, such as niosomes and liposomes, are nanoscale and may leak due to vesicular features, resulting in lower trapping efficiency. Gels, on the other hand, have a higher loading capacity due to their extensive network.

Possibility of production and cheap preparatory costs

The preparation of emulgels is made up of simple and short procedures, which makes production more feasible. Emulgel manufacture does not necessitate the use of specialist equipment. Furthermore, the materials employed are readily available and inexpensive. As a result, the cost of producing emulgels is reduced.

No intensive sonication

Intensive sonication is needed in the production of vesicular molecules which may result in leakage and drug degradation. As no sonication is needed in the case of

emulgels, so these problems are not seen.

Controlled release

Emulgels can be used to extend the effect of drugs having shorter half life.

Patient compliance

They are easy to apply.

1.16 RESEARCH ENVISAGED

Psoriasis vulgaris is an autoimmune disease caused by inappropriate activation of the cellular immune system. Psoriasis is a psychosocially debilitating disorder that affects 1 to 3% of the population worldwide (Afifi *et al.*, 2005). It involves in excessive growth and deviant differentiation of keratinocytes (Lowes *et al.*, 2007). There is an increase in proliferation of epidermis with dilation of dermal capillaries, infiltration of inflammatory cells in skin layers (dermis, epidermis), and localized infiltration into skin layers. It leads to localized skin deregulation that plays a major role in the development of scaly erythematous plaques (Lowes *et al.*, 2007). Other symptoms are swelling of the skin, pain, itching and skin flaking (Mazzotta *et al.*, 2007).

Sebaceous glands are small oil (sebum) producing glands that are attached to hair follicles. These glands are not evenly distributed all over the skin but are more prevalent on the face, scalp, chest and neck. As our present study is on Plaque psoriasis which is most often found on the scalp, the lower back, the face, the palms and soles of feet these areas are sebaceous gland rich areas(www.psoriasis.org). About 10 percent or more of body-surface area is covered in chronic plaque psoriasis (Ellis and Krueger, 2001).

Clobetasol propionate is a very potent topical corticosteroid class compound. Topical steroids are used in addition to moisturizers for treating inflammatory skin conditions such as eczema and dermatitis. Owing to its anti-inflammatory, antipruritic and immune-modulating properties, clobetasol propionate is used to treat psoriasis

(Decroix *et al.*, 2004). Clobetasol propionate induces phospholipase A2 inhibitory proteins, thereby controlling the release of the inflammatory precursor arachidonic acid from membrane phospholipids by phospholipase A2 (Schäfer-Korting *et al.*, 2005). It was also found that if clobetasol propionate (CP) was incorporated in the nanoemulsion it shows significant increase in their anti-inflammatory activity. It was reported that CP-loaded nanoemulsion significantly increased NTPDase (Nucleoside triphosphate diphosphohydrolases) activity in lymphocytes. This membrane protein is responsible for the hydrolysis of extracellular ATP (Adenosine triphosphate) which is responsible for cell proliferation, differentiation and inflammatory processes (Alam *et al.*, 2013).

For topical formulations use of conventional excipients could serve the purpose only to a limited extent of absorption, penetration, and retention through psoriatic barrier cells (Katare *et al.*, 2010). With the discovery of newer chemicals like squalene biocompatible and biodegradable materials like phospholipids and novel drug delivery technologies like deformable liposomes, SNLs, liposomes, nanostructured lipid carriers (NLCs), microemulsions and nanoemulsions *etc*. have the possibility to improve the efficiency and safety of the topical products to a great extent and also improve the absorption, penetration and retention in skin (Katare *et al.*, 2010). It was found that the addition of corticosteroid and a keratolytic agent such as salicylic acid in nanocarrier would result in enhancement and sustaining of corticosteroid delivery rate leading to better anti-psoriatic activity. Clinical use of corticosteroid is restricted to some extent due to its poor permeability across the skin. So to increase its permeation across the skin, nanocarriers were prepared and characterised(Baboota *et al.*, 2011).

Sebum is secreted from sebaceous glands and is composed of three components (Huang *et al.*, 2009) that are Squalene (12- 15%) one of the major ingredient of sebum (Pappas, 2009)along with it there are some glycerides and wax esters. Psoriatic skin has 30% fewer sebaceous gland and hair follicles as compared to

normal skin. Due to the loss of sebum in psoriatic skin these sebaceous glands and hair follicles get closed or inactivated (Fang *et al.*, 2014). Therefore, by incorporating squalene in novel carriers could help restore the lipid content of sebum. In the lipid milieu of the skin, lipid carriers become readily available and create a drug depot. NLCs (nanostructured lipid carriers) have proven to be quite useful in enhancing the topical usefulness of medicines. NLCs have a better capacity to fuse with sebum in the follicles due to the presence of both solid and liquid lipids (Aljuffali *et al.*, 2014). Because of their greater ability to control drug release and entrap medication inside the lipid environment, NLCs are far more favourable than solid lipid nanocarriers or liposomes. It's conceivable because the solid lipid's flawed structure allows for a larger surface area and more space for drugs dissolved in liquid lipids. As a result, NLCs have a greater drug loading capacity (Ghasemiyeh and Mohammadi-Samani, 2018). A hydrous environment should be maintained over the desired region of skin in order to ensure increased partitioning of lipid carriers to the stratum cornium. At the same time, a semisolid consistency is essential to avoid quick content drainage and to extend the stay period. As a result, moisturization of the desired location of action is also an important factor to consider. As a result, a viscous hydro-gel with a moisturising effect would be the best choice.

The aim of this study is to develop a squalene integrated of clobetasol propionate loaded nanocarriers and evaluate its potential in the plaque psoriatic animal model. These nanosystem due to presence of squalene would increase lipid content and because we are using hydrogels it will improve moisture content of the skin.

In this research work it is hypothesized that these systems will improve drug deposition in the skin as sebum derived lipids are used which shows affinity towards sebaceous gland, these Nano-systems may enhance clobetasol propionate penetration through the barrier layer of the psoriatic skin because of their flexible nature and deposition in sebaceous glands. This may indicate a minimized absorption into

systemic circulation as shown in Figure 1.13.

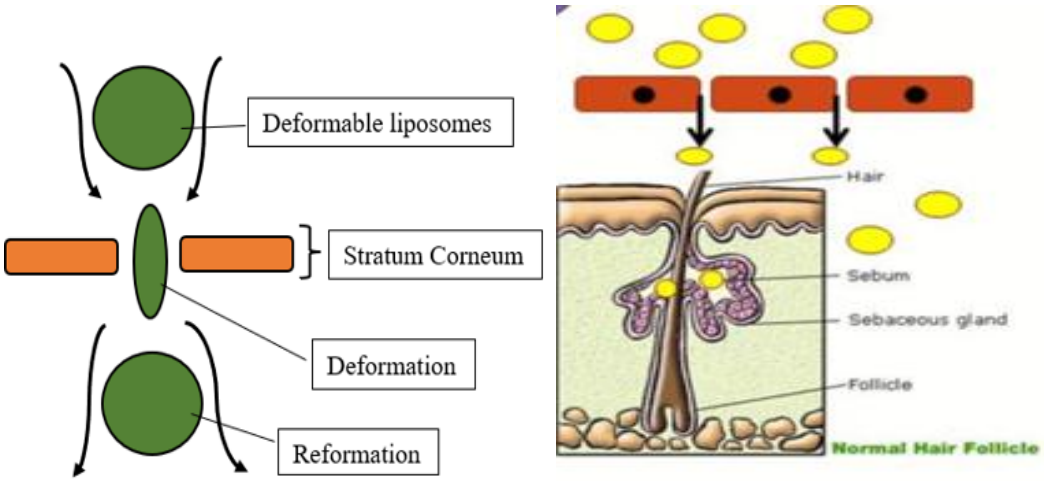


Figure 1.13 Diagrammatic representation showing research envisaged

1.17 RESEARCH OBJECTIVES

The main aim of the current study was to design, develop and evaluate some novel drug delivery systems containing antipsoriatic agent (Clobetasol Propionate).

Objective 1. To increase the therapeutic effectiveness of antipsoriatic drug.

Objective 2. To increase permeation through psoriatic barrier cells.

Objective 3. To utilize sebaceous glands as a depot for sustained release of the drug.

Objective 4. To minimize absorption in systemic circulation hence side effects are minimized.

1.18 PLAN OF WORK

1. **Extensive Literature Survey**

2. **Preformulation studies of bioactive (Clobetasol propionate)**
   - Identification studies using UV Spectroscopy and HPLC studies
   - Melting point analysis and Purity studies using FTIR Spectrum and DSC

- Partition Coefficient analysis
- Solubility studies
- DSC

3. Development of the analytical method for the determination of Clobetasol propionate using HPLC.

4. Preparation, optimization and characterization of (Nanoemulsion, NlCs, Deformable liposomes)

- Optimization (Lipid ratio, Surfactant ratio, Particle size, Zeta potential, Homogenization speed and time, Sonication time, Entrapment efficiency, Percentage drug loading)
- Characterization
    - Particle shape and size
    - Entrapment efficiency
    - Surface charge and charge density
    - *In-vitro* drug release study
    - Percentage drug loading
    - Differential scanning calorimetry (DSC) study

5. Formulation studies (Carbopol gel)

- *In-vitro* skin permeation studies
- Viscosity studies
- Release profile
- Spreadability

6. **Physical stability studies**

7. ***Ex-vivo*** **studies**

- Skin permeation and retention studie

8. ***In-vivo*** **efficacy studies (antipsoriatic activity) using IMQ-induced psoriatic model in Swiss Albino Mice**

- Skin irritation test
- Histopathology
- Pharmacokinetic studies

9. **Statistical Analysis**

10. **Thesis Compilation, the publication of research outcomes, and thesis submission.**