

REVIEW**ANTIPSORIATIC THERAPY: DISCOVERING NEW HORIZONS****Pritee Gupta*, Akash Saini**

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Submitted on: 05.05.17; Revised on: 01.09.17; Accepted on: 04.09.17**ABSTRACT**

Psoriasis is inflammatory skin disorder, which is chronic and an autoimmune disease and affect the life of approximately 2% of the world population. There are various topical treatments which has been used such as topical steroids, dithranoletc andall shows very low efficacy, poor solubility andhas low aesthetic and cosmetic appeal, ultimately results in low patient compliance on the other hand systemic therapiesproduces significant side effects. Successive progress in the development of new drug delivery system such as colloidal drug delivery systems has led to effective and safe treatment of psoriasis. Colloidal carriers such as vesicular and particulate carriers includes liposome, emulsome, transferosomes, ethosomes, SLNs, microspheres, micelles, dendrimers etc. have gained unique and impotant position in drug delivery system. Several approaches are done for treatment of psoriasis but, rate of success is always a questionwhen conventional system is concerned for the treatment of psoriasis. Present article is an attempt to improve the therapy of psoriasis related to its pathogenesis and offers disease management of this, treatment of psoriasis and the pharmaceutical approach was done for effective and safe drug delivery for the treatment and management of this disease. It will also discuss details about topical drug delivery in general and its challenges in designing effective drug delivery against psoriasis.

KEYWORDS: Psoriasis, Colloidal carriers, challenges, Nanotechnology**Corresponding Author:** Pritee Gupta**E-mail:** gupta.pg.priti@gmail.com**Indian Research Journal of Pharmacy and Science; 14(2017)1119-1138;****Journal Home Page: <https://www.irjps.in>****DOI: 10.21276/irjps.2017.4.3.6**

INTRODUCTION

Psoriasis is inflammatory skin disorder which is a chronic and an autoimmune disease and affects approximately 2% of the world population¹. It basically involves immoderate growth and discrimination of keratinocytes and thus causes distinct, red, scaly plaques which appear on the skin and therefore also known as papulosquamous disorder. It is caused by activation of T lymphocytes in dermis (primarily CD4+ cells) and epidermis and

thus known as immunologically mediated disease². About 80% of people are suffering from psoriasis vulgaris and are treated topically. The conventional topical aid in controlling psoriasis are having several limitations, for which the novel carriers are reported to deceive with safe and long term use³. Novel carrier such as liposome, SLN, emulsomes, NLC, nanoemulsion and ethosomes have brought us closer to achieve the goal for safe and effective treatment of this disease⁴.

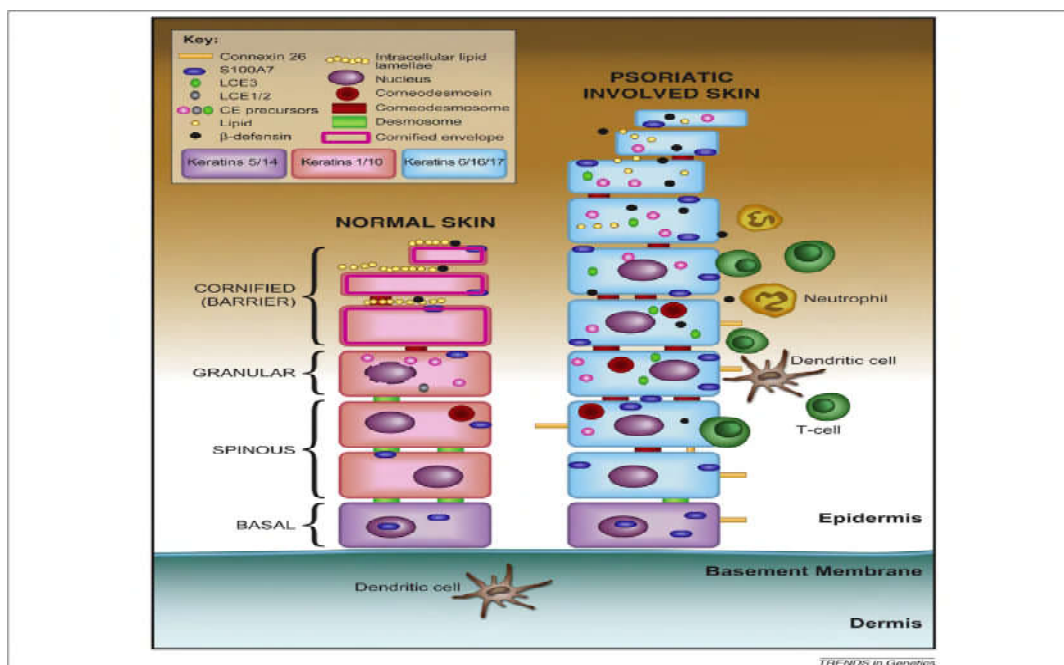


Fig. 1: Difference between healthy and psoriatic skin¹⁰³

EPIDEMIOLOGY

Psoriasis varies considerably among world population. In the United States, approximately 2% of the population is affected with this. High rates of psoriasis have been reported in people of the Faroe Islands where 2.8% of the population is affected⁵. Psoriasis affects almost all the genders equally. A survey on monozygotic twins tells that there is a 70% chance of developing psoriasis in a twin if the index twin has psoriasis. Henseler and Christophers examined a set of 2147 patients and reported that psoriasis is of two types, i.e. type I and type II⁶. Type I is induced at or before the age of 40 years, type II is induced after the age of 40 years. In more than 75% of cases there is

induction of Type I. Type I is more caustic than Type II. Psoriatic disease has a strong association with human leukocyte antigen – Cw6 in patients with early beginning, when compared with later⁷.

PATHOPHYSIOLOGY:

Psoriasis is characterized by expansion and abnormal growth of epidermal keratinocytes. T lymphocytes mainly consist of lymphocyte infiltration and have specific vascular changes in the endothelium of the microvasculature of the dermis and thus include limited neoangiogenesis, dilation of capillaries and high endothelial venule formation in the endothelium. All this causes visible redness in psoriatic skin⁸.

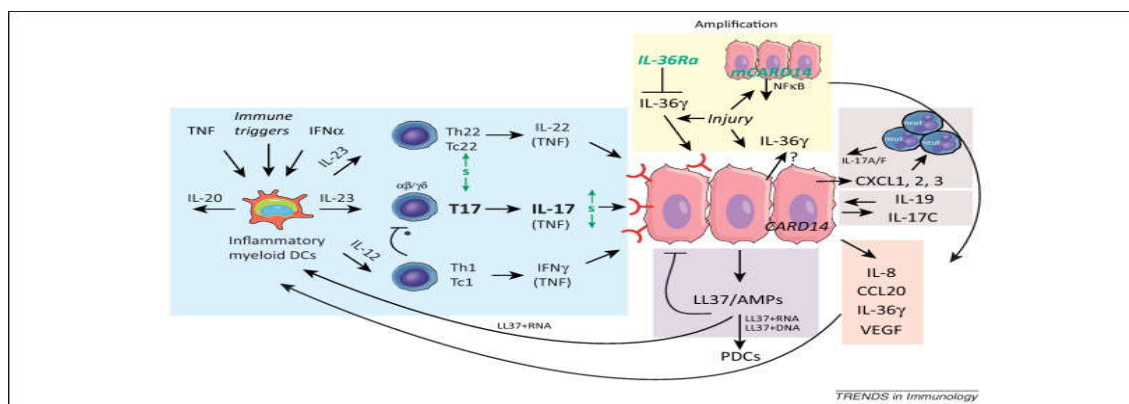


Fig. 2: Pathophysiology of psoriasis¹⁰⁴

Antigen which is present on the major histocompatibility complex (MHC I or II) are recognized by specific T-cell present on receptor or by the APC. An activated T cell expands and enters in blood circulation through interaction between LFA-1 and ICAM-1, and expel through diapedesis in the endothelium at site of inflammation in the skin⁹. After this, the T-cells transmit in the immunologic process through the secretion of pro-inflammatory (type 1 or Th1) cytokines, which

include interleukin (IL)-1, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ. These secretion results in the formation of Th2 cytokine including IL-4, IL-10 and IL-11¹⁰. Each cytokine down regulates the other's responses. The final results of this is the formation of the psoriatic plaque through proliferation of keratinocytes, and thus there is increase in the activity and migration of other inflammatory cells and vascular changes¹¹.

Table. 1: Types Of Psoriasis^{12 13}:

SL.NO	TYPES	FEATURES	SITE EFFECTED
1	PLAQUE	This is the most common form of psoriasis. hair loss is permanent, and occur when excessive traction is applied to scale of hair.	Extensor surfaces (elbows and knees) most common distribution. Lower back, scalp, and nails (frequently effected)
2	GUTTATE	Small salmon pink papules usually with a fine scale are characteristics features.	Mostly occur on trunk and proximal extremities.
3	ERYTHRODERMA	Total involvement of the skin take place by active psoriasis. It can be precipitated by infection, low calcium withdrawal of oral corticosteroids and certain medication including lithium, antimalarial and IL – 2	redness and inflammation on the skin
4	FLEXURAL (INVERSE)	It is erythematous, and not usually scaly and has different skin lesion.	Trunks and limbs. Also effecting the flexures perineal and axillary folds.
5	PUSTULAR	Generalized form is also known as Zumbusch's psoriasis. Due to formation of pustules and scaling redness of skin takes place.	hands and feet are the site which is effected



Fig. 3: Types of psoriasis ¹⁰⁵

TREATMENT OF PSORIASIS:

Currently there are various treatment approved across world which include photo chemo therapy, topical therapy drugs like Cyclosporin, dithranol etc, systemic treatment like methotrexate and oral retinoid therapy¹⁴.

Approval of Systemic therapies, like hydroxyurea etc across the countries for the treatment of psoriasis is very low. Moderate to severe psoriasis treatment is often initiated by photo chemo therapy. Combinational treatment such as (topical, phototherapy and systemic) is very common, and although plays an empirical role. In some places methotrexate is often prescribed only when no

other drug is effective; however, in other countries methotrexate is used as a first-line systemic treatment for severe psoriasis. In many other countries when there is concurrent acute psoriatic arthritis, methotrexate is used as first-line systemic treatment. In Italy, the most commonly used systemic therapy for psoriasis is cyclosporin, when there is resistant to classical therapies methotrexate is usually reserved for treatment. However in some countries Physicians used to combine cyclosporin with methotrexate. Retinoids seem to be the last choice in several European countries and are usually not used in combination, as monotherapy appears to have high efficacy for chronic plaque psoriasis¹⁵

Table. 2: Treatments of Psoriasis

Sl. No	Categories	Drugs Used
1.	Topical Therapies	<ul style="list-style-type: none"> ❖ Vitamin D derivatives ❖ Coal tar preparations ❖ Topical steroids ❖ Dithranol ❖ Vitamin A derivatives
2.	Phototherapy	<ul style="list-style-type: none"> ❖ Psoralens With UVA
3.	Systemic Treatment	<ul style="list-style-type: none"> ❖ Methotrexate ❖ Cyclosporin ❖ Acitretin ❖ Hydroxycarbamide

4.	Biological	<ul style="list-style-type: none"> ❖ Etanercept ❖ Infliximab ❖ Adalimumab ❖ Alefacept ❖ Efalizumab
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COMMON DRUGS USED MAINLY FOR PSORIASIS TREATMENT^{16 17 18 19 20 21};

There are various commonly used drugs for treatment of moderate and severe psoriasis. There are various topical agents which are usually used for mild psoriasis, sometimes they are combined with phototherapy. Sometimes combinations of topical and systemic therapy are used to treat moderate and severe psoriasis. When the effects of topical agents or phototherapy are not effective, systemic agents are added and should be considered. To treat severe

psoriasis biological agents are used and are usually used when patients fail to respond to conventional systemic treatment and life of patient is seriously affected. Topical corticosteroids and vitamin D3 analogs are the mainly used for treatment of mild psoriasis. Ultraviolet B (UVB) therapy is widely used for moderate to severe psoriasis. However in severe cases Acitretin, cyclosporin A (CsA), and other immunosuppressive agents are used. Etanercept and infliximab have also been successfully used in patients with severe psoriasis.

Table. 3: Common Drugs Used Mainly For Psoriasis Treatment^{16 17 18 19 20 21}

S.No	Drugs	Features	Mechanism Of Action	Adverse Effect
1	Dithranol	It is most effective topical therapy in psoriasis. The oxidation products have very low or no effect on psoriasis.	It accumulates in mitochondria where it interacts with the energy which is supply to the cell, through oxidation of dithranol free radicals are released and reduce DNA replication and slows the excessive rate of cell division that occurs in psoriatic plaques.	1. Stains the skin and permanently stains clothing fabrics. 2. Burning sensation and irritation.
2	Methotrexate	Methotrexate (MTX) is first line drug used systemically in psoriasis.	Inhibits dihydrofolatereductase(Fplic acid required for the de novo synthesis of of the nucleoside thymidine requires for DNA synthesis.	Anemia, neutropenia, bruising nausea and vomiting, dermatitis headache and alopecia.
3	Tacrolimus	It is effective and well-tolerated immunosuppressant, and plays important role in the treatment of chronic plaque-psoriasis	Topically inflammation is suppressed and is effective.It binds withimmunophilin FKBP12 and creating a new complexand thus reduces peptidyl- prolylisomerase activity. This complex inhibit calcineurin thus inhibits T-lymphocytesignal transduction and IL-2 transcription.	1.Cancer risk

4	Psoralen	Psoralen is applied topically or taken orally to sensitize the skin, followed by UVA exposure.	The psoralens molecule intercalates between DNA base pairs but also has effect on the cell membrane.	Nausea most common, skin cancer, basal cell carcinoma
5	Cyclosporin-A	Cyclosporin A (CsA) shows their action both through oral as well as topical route. It is having very high molecular weight (more than 500 Da) and limited cutaneous permeation.	mitochondria pore opening is prevented thus inhibiting release of cytochrome c a potent apoptotic stimulation factor	Hyperplasia, ulcers, fever, vomiting diarrhea, high blood pressure, pancreatitis etc
6	VITAMIN D ANALOGS	Calcipotriol, maxacalcitol, tacalcitol, and calcitriol are Vitamin D3 analogues and shows their role in the treatment of mild-to-moderate plaque psoriasis	They bind with VDR receptor. VDR modulates the T cell gene transcription of cell differentiation and cell proliferation related genes.	Local irritation, managed by combining vitamin D3 analogues with topical corticosteroid.
7	Coal Tar	it is valuable, safe, and inexpensive treatment of people with psoriasis. Coal concentration between 0.5 to 5% are safe and effective for psoriasis	Normalizes epidermal growth and reduce scaling	It causes mild burning or skin irritation it also stains clothing and skin.
8	Retinoids	These are widely used drug in the topical treatment of acne, photo-aged skin, psoriasis and other skin disorders. In various types of psoriasis efficacy of aromatic retinoid is marked by the more rapid response for the pustular variety.	Shows modulating and normalizing effect on the proliferation and differentiation of the epidermis. In dermal cell components immunomodulating effects on have also seen.	

CURRENT THERAPY IN PSORIASIS:

Understanding of the pathophysiology of psoriasis has changed from that of keratinocytes disease to a T-cell-mediated disease now usually considered as a systemic chronic inflammatory disease which plays important role for the immunology system and has

changes the treatment mode over the years. Non-selective treatments such as corticosteroids, Hydroxycarbamide, and acitretin, was started first then moving on to more selective treatments such as cyclosporine and at last the highly selective biological therapies are used²². For the management of moderate-to-severe psoriasis tumour necrosis factor

(TNF)- α inhibitors are introduced and changed the understanding of pathophysiology of psoriasis. Inhibition of the binding of lymphocyte function-associated antigen-3 (LFA-3) to CD2 (e.g. with alefacept) or via blocking of the CD11a chain of LFA-1 and inhibition of cell adhesion (e.g. with efalizumab)²³ are the another method of treating psoriasis which targets T cells.

Various biological products are used for psoriatic treatment which modifies the pro inflammatory cytokine levels and increase the expression of specific CYP enzymes as well as the exposure of CYP enzyme substrates, which is considered psoriasis disease-drug-drug interactions (disease-DDI)²⁴. But the major disadvantages of using biological products are that they are costly and repeated injections are also require and some patients experience tacaphylaxis²⁵. For the treatment of plaque psoriasis new biologics and small molecules are briefly discussed in the below section.

1. IL-12/23 inhibitor: They are heterodimeric pleiotropic cytokines each consisting of 2 subunits and are named according to their size²⁶. The production of IL12 are through macrophages and B cells and shows to have multiple effects on T cells and natural killer (NK) cells, whereas for differentiation of Th17 lymphocyte IL-23 is essential. Drugs that inhibits IL-12/23 are discussed below:

a. Briakinumab: They are human monoclonal antibody and inhibits IL-12/23 which targets the common p40 subunit of IL-12 and IL-23. it was found that 82% patients treated with briakinumab achieved a 75% reduction in their baseline Psoriasis Area Severity Index score at week 24 in a Phase III clinical trial and compared with 40% methotrexate treated patients.²⁷ Serious infections, non-melanoma skin cancers and cardiovascular events Some adverse effects which were reported, suggesting that their is need for surveyance with wider use of briakinumab²⁸. Overall, it is demonstrated that for psoriatic effective treatment briakinumab is highly effective and suggests that continued vigilance be used in evaluating the safety profile of this drug.

b. Ustekinumab: They are also human monoclonal antibody which inhibits IL-12/23. It is approved over the world for the treatment of moderate-to-severe plaque psoriasis. These are anticytokinins.²⁹

2. IL-17 inhibitors: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F all are the members of the IL-17 family. All members of this family have a protein structure which is similar with 4 highly conserved cysteine residues and also have similarity with other known cytokines³⁰. In psoriasis pathogenesis it is a key "driver" pro-inflammatory cytokine³¹. It can activate hyperproliferation of keratinocytes and produces antimicrobial peptides, such as cytokines, and chemokines, which, in turn, activate other immune cells leading to development of psoriasis inflammation³¹. Some inhibitors of IL-17 are discussed below.

a. Secukinumab :

It is a human monoclonal antibody IgG1 κ that binds and neutralises with IL-17A. A 12 weeks study reported that treatment of patients with subcutaneous secukinumab resulted in response rates higher as compared with placebo.

b. Ixekizumab:

It is a IgG4 human monoclonal antibody which neutralises IL-17A. After 12 weeks, it is reported that the percentage of patients with moderate-to-severe psoriasis who had a PASI75 or PASI90 was increases in the groups receiving subcutaneous ixekizumab³³.

c. Brodalumab:

It acts as an antagonist to the receptor subunit of IL-17A, IL-17F, and IL-17A/F heterodimer ligands and works in a slightly different way like other IL-17 inhibitors³⁴.

3. Anti-tumour necrosis factor agents:

Certolizumabpegol a new TNF blocker has been introduced and inhibits TNF- α . They are conjugated

with polyethylene glycol. Like other anti-TNF monoclonal antibodies they lacks a fragment crystallizable portion and, consequently, does not induce antibody-dependent cytotoxicity.³⁵ These drugs binds with soluble and membrane-bound TNF-

α , and blocks crucial events associated with psoriatic inflammation³⁶.

4. Small molecules:

For psoriasis treatment various small molecules are introduced, which includes phosphodiesterase (PDE) inhibitors, JAK inhibitors, and A3 adenosine receptor (A3AR) agonists. They are as follows:

a. Phosphodiesterase inhibitors:

The breakdown of 3'-5'-cyclic adenosine monophosphate (cAMP) to AMP is catalyzed by this enzyme. Increase in concentration of cAMP in addition with inhibition PDE-4 reduces the production of pro-inflammatory mediators which are involved in psoriasis inflammation, such as TNF- α and IL-23, and increase the production of anti-inflammatory mediators, such as IL-10³⁷. There are various small molecules which act as a PDE-4 blocker. Apremilast is one of these and was approved by the FDA for treatment of psoriatic arthritis. Intestinal intolerance, a well-known adverse event with PDE-4 inhibitors, was reported³⁸.

b. Janus kinase inhibitors (JAK):

It is protein tyrosine kinases (TYKs) enzymes that are essential for the beginning of activated signalling pathways of cytokine. These enzymes act as activators of transcription (STAT) proteins and also help in

activation of the signal transducer and phosphorylation of protein. These enzymes are of 4 types: JAK1, JAK2, JAK3, and TYK2. JAKs are intracytoplasmic portions of cytokine receptors. Tofacitinib acts as an inhibitor of the JAK1 and JAK3 signalling pathway. It is approved for the treatment of rheumatoid arthritis but not by the European regulatory agencies because of low efficacy and safety³⁹.

❖ Tofacitinib :

Tofacitinib was generally well-tolerated but some side-effects were reported. The most frequently reported AEs were infections (nasopharyngitis, sinusitis, upper respiratory tract infection)⁴⁰.

❖ Ruxolitinib:

Used for myeloproliferative disorders and are used in systemic treatment. It acts as an inhibitor of JAK1 and JAK2. Recently, topical formulations of ruxolitinib have been developed for psoriatic therapy⁴¹.

A3 adenosine receptor agonists:

These are G protein-coupled receptors and are involved in a variety of intracellular signalling pathways and physiological functions. Adenosine acts as a natural ligand of A3AR receptors. These are highly found in peripheral blood mononuclear cells isolated from patients with psoriasis^{42,43}.

NANOTECHNOLOGY BASED APPROACHES FOR EFFICIENT DRUG DELIVERY:

During psoriasis treatment it was found to be unsatisfied or moderately satisfied with their current treatment. It is because of ineffective delivery of drugs and undesirable skin irritation due to topical treatments is the main reason for lack of patient compliance⁴⁴.

Through the development of nanotechnology we can achieve a continuous delivery of drugs to a target and are site specific and act as a predictable and reproducible kinetics over an extended period of time in the circulation. The development of this concept includes minimization of drug-related side effects due to controlled therapeutic blood levels, patient compliance due to reduced dose frequency. Various novel vesicular drug delivery systems have been introduced for various routes of administration, to achieve site specific and sustained drug delivery⁴⁵. If the drugs are targeted to its specific site of action it seems to improve the amount of drug which further helps in low toxicity and also improves the therapeutic index. This delivery system also shows reduction in systemic side effects to a great extent⁴⁶. These systems offer various advantages over conventional delivery systems such as reduction in drug degradation and drug loss, high bioavailability, prevention through harmful toxic effects, versatility and flexibility in nature, better patient compliance⁴⁷.

There are various types of nanotechnology based approaches for efficient drug delivery in psoriasis

treatment and classified into various groups.

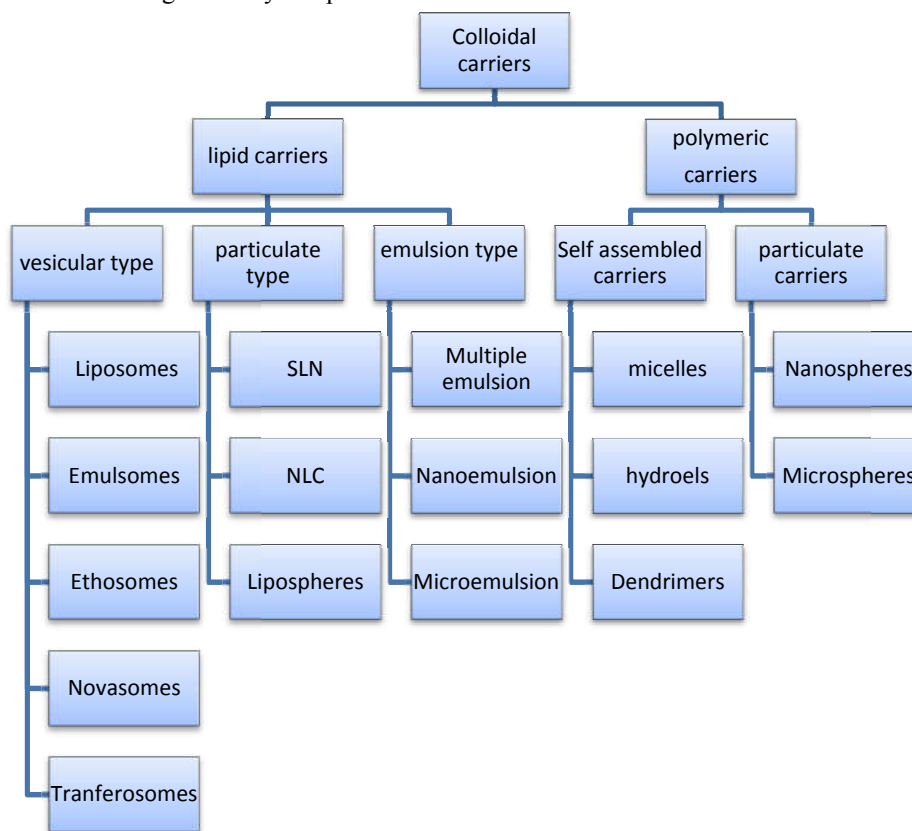


Fig. 4: Nanotechnology based Approach

LIPID CARRIERS:

- I. Vesicular type
- ii. Particulate types
- iii. Emulsion types

1. Vesicular type: Drugs are delivered through various routes of administration, number of vesicular drug delivery systems have been developed to achieve site specific and controlled & sustained drug delivery. These systems are used to increase therapeutic index, high solubility and stability and degradation of drug molecules⁵⁰. There are various types of vesicular carriers which are used for effective delivery and targeting of drug molecules.

a. Liposomes: These are microscopic structures consisting of lipid bilayer with aqueous inner core. They have various advantages and are superior to conventional dosage forms. Phospholipids are one of the major components in this and thus play a promising role in drug delivery of lipophilic drugs⁵¹.

Pathomthat, S et al 2012 reported that the liposomes in which methotrexate is entrapped help to enhance the skin permeability characterized by the higher concentration and MTX are accumulated in the epidermis and dermis layers of skin. The increased permeability of MTX-entrapped liposomes was because of the deformable characteristic of oleic acid and act as a skin penetration enhancer of⁵².

Saraswat, A et al. 2007 reported that 0.5% dithranol loaded liposomal gel is effective in plaque psoriasis and has no adverse effects. It is coupled with low

fabric and has easy washability, dithranol loaded liposomal gel has much more potential to be acceptable by the patients and physicians than currently available formulations⁵³.

b. Ethosomes

These are lipid vesicles which are soft and malleable in nature and are composed of phospholipids, alcohol in high concentration 20 to 45% and water. They work by the mechanism of permeation through skin due to high deformability. This carrier provide effective delivery of lipophilic, hydrophilic as well as amphiphilic drug⁵⁴.

Rakesh R. et al. 2011 reported that they improve the penetration of drugs through the skin barrier and thereby increase the efficacy. The ethosomes are versatile in nature and are effective for transdermal as well as topical drug delivery of few drugs such as minoxidil, testosterone, etc. Delivery of some antigens such as Hepatitis B surface antigen and DNA through ethosomes helps in transcutaneous immunization and gene therapy. Several phytochemicals and herbal extracts have been successfully delivered with the help of ethosomes and have various advantages over conventional drug delivery systems.⁵⁵

c. Emulsome:

Emulsomes are vesicular type of drug delivery system. They have the characteristics of both liposomes and emulsion. Emulsomes are one of delivery system which is formulated in absence of ionic or non ionic, non natural synthetic surfactant or cosurfactant. Due to high lecithin content they are stable in nature. Their hydrophobic core are surrounded and stabilized by one or more layers of phospholipids molecule⁵⁶.

Gupta S et al. 2007 reported that Amphotericin B loaded emulsomes (both plain and O-palmitoylmannan (OPM) coated) shows better antileishmanial activity. Their study confirms that the efficacy of Amphotericin B is increased if the drug is coated with OPM grafted emulsome form⁵⁷.

Raza K et al 2012 reported dithranol loaded emulsomes have high skin permeation flux as well as

high skin retention. An improved antipsoriatic activity and practically devoid of any skin irritation has been reported. The dithranol loaded emulsomes enhanced the pharmacodynamic activity, and also made the drug available in the skin. Thus, this carrier system improves the duration as well as the onset of action of dithranol. Their systematic study helps in developing "optimized" nano colloidal formulations for topical. The lipids (namely Compritol and phospholipid) showed considerable influence on emulsomal features and thus improves entrapment efficiency, particle size, skin permeation and retention⁵⁸.

d. Novasome :

These are micro vesicle which are formed from phospholipids which are biocompatible in nature and are amphiphilic in nature. These drug delivery systems are effective in nature for a variety of drugs. There is no incompatibility problem with this carrier due to incorporation of incompatible drugs between the bilayers. There is increase in the efficacy and efficiency with this for the treatment

with almost no side effects. They are natural and do not cause any kind of cytotoxicity. Novasomes can be formulated to the desired release action and absorption level. It is one of the most effective method to treat skin disorders.

Agarwal et al. 2013 reported that novasomes helps to increase the stability of product, extended shelf life from weeks to sometimes years, prevention of oxidation and emulsification, and permits isolating antagonistic ingredients within the formulation until use. The control release of active ingredients through heat, pressure and/or time also enables through novasomes.⁵⁹

2. Particulate carrier: In this system there is either dispersion of drug in lipid matrix or dissolved in lipid matrix. Thus due to this they prevent rapid drug release and allow controlled and sustained release of drug. There is high drug loading and stability is increased. These carriers provide the effective and safe drug delivery in various skin disorders including psoriasis. Various particulate lipid based colloidal

carriers that have found application in antipsoriatic drug delivery⁶⁰. They are as follow

a. Solid lipid nanoparticle: These are novel carriers used for delivery of drug at a specific target. It is composed of triglycerides or other glyceride and waxes which are solid in nature.

Sonawane R et al reported that Betamethasone dipropionate and calcipotriol loaded solid lipid nanoparticles distribution of drugs to epidermal and dermal region of skin was observed which is essential for safe and effective anti-psoriatic therapy. Draize patch test and TEWL demonstrated negligible skin irritation and better skin tolerability of SLNs. The in vitro HaCaT cell line study demonstrated that SLNs delayed the abrupt growth of keratinocytes, while in vivo mouse tail model showed that SLNs gel significantly decreased the epidermal thickness and increased melanocyte count in comparison to commercial Daivobet ointment⁶¹.

b. Nanostructured lipid carrier: NLC are modern or new generation type of solid lipid nanoparticles. These are prepared when solid lipids are mixed with incompatible lipids leading to a lipid matrix. NLC are used in various types of skin diseases such as psoriasis, eczema etc and generally used for topical delivery drug⁶².

Shinde. G. et al. 2013 reported about nanostructured lipid carrier (NLC) loaded gel for psoriasis and reported optimized NLCBG batch enhanced the permeation, sustained the drug release and enhanced the drug release at the site of action. The optimized NLCBG was compared with marketed preparation for skin permeation and skin retention study which concludes that optimized formulation better result than marketed preparation. Skin irritation study was also shown that no irritation on skin and show prolong release up to 24 hr⁶³.

Agrawal.Y.et al.2010. reported that its use enhanced the therapeutic response and topical treatment of psoriasis, Acitretin loaded NLC gel were observed and concluded they have low adverse effects during therapy, have better patient compliance. Thus, Acitretin loaded NLC gel considered as a

supplementary to oral therapy, particularly in last stage of psoriatic treatment.⁶⁴

3. Emulsion based carrier: These are emulsion based carriers in which dispersion of two or more immiscible liquid are involved which are further stabilized by surfactant or co surfactant.

a. Micro emulsion: These are thermodynamically stable emulsion. These are biphasic in nature and dispersions of two immiscible liquids which are stabilized by an interfacial film of surfactant molecules in conjunction with a co-surfactant take place. These are of 2 types oil-in water (O/W) or water-in-oil (W/O) and having size range from 5 to 100 nm. These carriers have been reported to improve the oral bioavailability of drugs.⁶⁵

Shende, G. et al. 2014⁶⁶ reported that Anthralinmicroemulsion gel using Karanj oil for treatment of psoriasis with an objective of improving solubility of the Anthralin. From the results of the present research work it can be concluded that Anthralinmicroemulsion gel containing carbopol 940 as gelling agent prepared with karanj oil can provide a basis for successful design of topical delivery of Anthralin in psoriasis treatment⁶⁶.

b. Nano emulsion: These carriers are thermodynamically stable and transparent systems of oil, water, surfactant and co-surfactant with a droplet size ranging from 20– 200 nm. It is a promising tool for drug delivery due to their stability, ease of preparation, and having high solubility of drug molecules.⁶⁷

Ali,M et al. 2012 reported that the nanoemulsion was stable system and are practically non-irritating in nature in the organotypic HET-CAM model. An optimized formulation was used to confirm the non-irritation nature by histopathological study using rat

skin. An optimized formulation was taken to see the anti inflammatory activity and it was carried out by carragennen induced paw edema. Thus it serves as an alternative and effective treatment for skin diseases such as atopic dermatitis and psoriasis⁶⁸.

Polymer based carrier:

Carriers made up of Polymeric plays a very important role in drug delivery system for controlled and sustained release of therapeutic agents. They contain natural or synthetic polymer as an important excipients where encapsulation of drug moiety within micro- or nanosystems are within the polymers⁶⁹. Various classes of polymeric colloidal carriers used in the therapy of psoriasis are discussed below:

1. Self assembled carriers: Carriers are having a complex structure which involves non-covalent interactions formed by spontaneous arrangement of molecular units. At interfaces amphiphilic molecules assemble themselves in the presence of specific solvents. They keep their hydrophobic regions isolated from contact with polar solvents⁷⁰.

a. Dendrimers: Dendrimers are made up of polymeric materials. They have high degree of surface functionality and versatility due to their typically symmetrical shape around the core and adopts a spherical three dimensional structure⁷¹. Dendrimers consist of three structural components ; (a) An initiator core (b) Interior layers composed of repeating units, radically attached to the interior core (c) Exterior attached to the outermost interior generations.

Agrawal, U. et al. 2013 reported that in controlled and targeted drug delivery hyperbranched

polypropylene imine (PPI) dendrimer plays a very important role because of their mono-dispersity, high-density of functional group at peripheral, having precise shape and size, surface chemistries. Improves the topical bioavailability of the molecules in a controlled manner. The flux of dithranol has increased and shows to be very effective across the skin of rat. The dithranol loaded dendrimer helps in targeting drug to the epidermal and dermal sites within the skin, thus creates new approach for controlled and sustained delivery, for the treatment of psoriasis. The PPI loaded into dendrimers enhanced drug retention time in the skin and reductions in skin irritation take place⁷².

b. Micelles: Colloidal systems consist of amphiphilic group their assemblance take place above the critical micelle concentration (CMC) to form a specific core. Polymeric micelles, consist of block copolymer containing amphiphilic group with different lipophilic and hydrophilic properties⁷³.

Maria, L. et al 2014 reported that a stable 0.1% TAC (tacrolimus) formulation using MPEG-dihex PLA (methoxy-poly(ethylene glycol)-poly-(hexyl substituted lactides) micelles was successfully developed and characterized. Experiments demonstrated that the 0.1% micelle formulation significantly increased the cutaneous bioavailability of TAC as compared to Protopic (0.1% w/w). The biodistribution study showed that after application for 12 h, micelles increased TAC delivery into the stratum corneum and viable epidermis. Given that immune cells, responsible for the inflammatory response in psoriatic lesions, are located in this latter layer and the dermis, the results suggested that the micelle formulation might be able to increase clinical efficacy without increased risk of systemic exposure. This study suggests that micelles are innovative, safe biomaterial based nano carriers that enable targeted cutaneous delivery of TAC. Further studies will be performed to optimize the ease of application of the micelle formulation and to test efficacy in vivo, first in a psoriatic skin model and then in patients⁷⁴.

c. Hydrogels: Multicomponent systems consisting of a three-dimensional network of polymer chains and water that fills the space between macromolecules. It can be synthesized in a number of chemical ways which includes like polymerization and parallel cross-linking of multifunctional monomers, synthesis of polymer molecules having reactive groups and their subsequent cross-linking are also involved, various cross-linking agents are also used by reacting polymers with this^{75,76}.

Sah, K. A et al. 2011 methoxsalen entrapped in Microemulsion-based hydrogel serves as effective promoters for the local effect in the skin. The accumulation of methoxsalen in skin enhanced the targeting of the drug without any systemic side effects. It is better vehicle for topical delivery of drug than conventional⁷⁷.

Particulate carrier: These are polymer based matrix system in which either dispersion of drug takes place or dissolution of drug take place. The drug release take place through diffusion, swelling, or erosion controlled.

a. Nanospheres: Drug entrapment in nanospheres through dispersion in the polymer matrix. Biodegradable or non-biodegradable polymers are used. For controlled or site specific delivery of drugs biodegradable polymer are significantly used as drug delivery systems. Uniform dispersion of drug in the polymer matrix takes place.⁷⁸

Brian, E K. et al. 2012 reported that Paclitaxel loaded tyroSpheres are non toxic in nature and provide greatly enhanced solubility. It controls the hyperproliferation of keratinocytes therefore Paclitaxel loaded tyro Spheres helps in bringing the system back into equilibrium. Low dose frequency of Paclitaxel and deposition of Paclitaxel into the epidermis takes place and thus have low side effects associated with systemic exposure⁷⁹.

b. Microspheres: These are polymeric based matrix systems with size ranging in micron normally 1 μm to 1000 μm . It provides controlled and sustained release and reduction in the dosing frequency which improves therapeutic effect and patient compliance.⁸⁰

Ulya, B. et al 2011. It is a novel drug delivery for the safe and effective delivery of drugs including antipsoriatic drugs. Clobetasol propionate-loaded PLGA microspheres were successfully prepared as a topical delivery using o/w emulsion using solvent evaporation method for psoriasis treatment. The drug permeability is increased by using emulgels. The clobetasol propionate loaded PLGA microspheres significantly reduce the drug release from the emulgel. There is reduction in the topical and systemic side effects of the drug and the efficiency and efficacy of treatment is increased due to prolonged release of clobetasol propionate from the emulgel containing PLGA microspheres⁸¹

3.) Capsular carriers: These are reservoir based system in which the drug is restricted to a reservoir or present within a core which is enclosed within polymeric membrane. Inside the cavity the active

substance is present in liquid or solid form or as a molecular dispersion. Capsules utilized as drug delivery carriers can mask the tastes and have controlled release properties.⁸²

a. Nanocapsules: These are nanoparticles in nature, consists of one or more active materials in core and a shell known as protective matrix in which the therapeutic substance may be encapsulate. They have protective coating, usually pyrophoric in nature and easily oxidized. Provides sustained release, increase drug selectivity and effectiveness, improved drug bioavailability and reduction in drug toxicity⁸³.

Oriq and group developed tretinoin-loaded nanocapsules. There is increase drug stability in nanocapsule as reported by photodegradation studies. These systems improved half life of tretinoin nanocapsule suspensions as compared to tretinoin methanolic solution. Thus, nanocapsules act as a promising carrier for tretinoin in treatment of psoriasis.⁸⁴

b. Microcapsules: It is drug delivery system in which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material, ranging in size from 1 to 5,000 microns. Through this technique taste masking of bitter drugs is improved, provides controlled release and sustained action dosage forms, incompatible materials get separated, protection of drug from moisture and light.⁸⁵

4.) Nanogel: Avasatthi, V. et al reported that MTX-NLC gel showed the gradual release with more effective eradication of psoriatic manifestations when topically applied. The findings of this formulation pave the way for treatment of psoriasis with the topical colloidal formulation of MTX. However, significance of MTX-NLC gel may only be established, when evaluated clinically.

CHALLENGES IN PSORIATIC TREATMENT

There are several therapeutic agents but stills treatment of psoriasis remains a challenging task due to non-appropriateness of an ideal drug molecule. The major challenges in the psoriasis treatment are elaborated below⁸⁷:

1. Delivery of anti-psoriatic drugs due to Lack of efficient carrier.

Antipsoriatic drug delivery has inherent side effects of drug molecules or their incorporation in the conventional vehicles is improper. There are lots of variation in the physicochemical characteristics of the carrier and of the active molecules used and thus causes variation in absorption of drug and efficacy of drug⁸⁸. To overcome the problems associated with conventional vehicles Novel colloidal delivery carriers can be used. The advantages of novel colloidal carriers are protection of entrapped drugs against detrimental external and internal factors, therapeutic drug levels is maintained by controlled drug release for a longer period of time, specific sites of action by passive or active targeting thus ensuring different interaction pathways with target cells away from sites of their toxicity leading to improvement of the drug therapeutic efficacy and effective internalization⁸⁹.

2. Inappropriate animal model

Inappropriate animal model is another challenge in the development of an ideal drug and delivery carrier for the psoriasis treatment which would purely mimic histological and immunophenotypic characteristics of psoriasis as this disease usually occurs only in humans. Although numerous immunological and genetic animal models have been developed, but none of these models demonstrate all the characteristics of psoriasis with associated limitations. There are some exhaustive reviews available exclusively on animal models of psoriasis⁹⁰. Principally three major animal models are used like spontaneous mutation models, Xenotransplantation model and transgenic model⁹¹.

FUTURE CONCEPTS

The concept of general and non-specific immunosuppressant as a first-line therapy for psoriasis should be revised in the light of modalities targeting single cytokines or intracellular key proteins implicated in psoriasis pathogenesis. To improve our understanding of disease pathogenesis and of common pathways in psoriasis, psoriatic arthritis or rheumatoid arthritis there is some new modalities that helped us⁹². In the field of

dermatology a number of new therapies are approached and clinical practice is done. For psoriatic arthritis ustekinumab was the first anti-cytokine biologic used exclusively by dermatologists.

Safety and efficacy of directly neutralizing IL-23, without affecting IL-12 and Th1 responses was considered, which was necessary to control tumors and viral infections. For therapy of patients with psoriasis the targeting of IL-23a, with p40, is currently under investigation. This experience is important for IL-23/Th17 and IL-12/Th1 responses in psoriasis and can destroy an old dogma concerning the relevance of Th1 cells in this disease⁹⁴. Approaches primarily used in dermatology are by neutralizing IL-17 or blocking IL-17R. The autoimmune disease psoriasis can be treated by neutralizing the cytokines and its efficacy of antibodies against TNF, IL-17 or IL-23 demonstrate clearly that secreted by Th17 cells, neutrophils and mast cells or by inhibiting the cytokine-mediated activation of these cell populations. Biologics are used for neutralizing Th17 cytokines and prevents extension of Th17^{95 96}. For the treatment of psoriasis neutralization of Th17-associated cytokine IL-22, which affects keratinocytes is very effective. Alternatively, reduction in the inflammation by administering cytokines takes place, and prevents Th17 and/or Th1 responses. Administration of IL-4 improved psoriasis inflammation and induction of Th2 responses in a phase 1/2 trial take place^{97 98}.

In clinical practice of psoriasis oral compounds play an important role. For patients with multiple sclerosis the use of DMF has a new therapeutic approach. Apremilast, increase safety profile and its efficacy and extend the list of oral compounds in psoriasis. A promising approach for systemic or even topical treatment of psoriasis is by directly targeting cytokine receptor signaling pathways with JAK inhibitors^{99 100}. In many countries we are in the unique position where psoriatic patient has established eight different systemic therapies. To extend our therapeutic spectrum there are at least four upcoming biologics and three oral compounds. We have to understand the mechanisms in non-responders, and those with a loss of response, in order to provide lifelong protection from psoriasis and psoriatic arthritis. Also, the

advantages and safety issues of combination therapies still have to be studied in more detail. The development of further effective and safe anti-psoriatic therapeutics is not yet complete^{101 102}.

CONCLUSION

Psoriasis is one of the major chronic skin inflammatory and autoimmune diseases that hinders modern society and being associated with high morbidity factors and still remains incurable. Successful management of psoriasis can be reached by an excessive number of therapeutic agents. Every treatment strategy has multiple and wide-ranging adverse effects. However, conventional pharmacotherapies insufficient for effective treatment of psoriasis; they have several limitations, and have low efficacy. Novel carriers such as liposomes, ethosomes, and lipid nanoparticles etc have been able to carry the majority of antipsoriatic agents and have improved therapeutic potential. Nanomedicines act as drug carrier provide enhanced therapeutic efficacy with lesser toxicity, dose reduction, drug localization

and drug at specific site. However, most of the studies lacks clinical outcome in psoriasis thus required the research directed toward the clinical study to establish the fate of nanoparticles as prospective antipsoriatic nanomedicines.

ACKNOWLEDGEMENT

This research was partially supported by Dr. H.S. Gour University, Sagar, M.P. 470003, India. We thank our Teachers who provided insight and expertise that greatly assisted the research, although they may not agree with all of the interpretations/conclusions of this paper.

We would also like to show our gratitude to the Punjab University for sharing their pearls of wisdom with us during the course of this review, and we thank reviewers for their so-called insights. We are also immensely grateful to our seniors for their comments on an earlier version of the manuscript, although any errors are our own and should not tarnish the reputations of these esteemed persons.

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CONFLICT OF INTEREST REPORTED: NIL ;

SOURCE OF FUNDING: NONE REPORTED

