Available online on 15.10.2018 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

TOPICAL DELIVERY OF NANOEMULSION FOR ANTIPSORIATIC DRUGS

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ABSTRACT

Psoriasis is an autoimmune disorder of the skin characterized by relapsing episodes of inflammatory lesions and hyperkeratotic plaques with worldwide occurrence of around 2–5%. Psoriasis is a disease known to be caused by multitude of both genetic and environmental factors such as trauma, drugs, infection, alcohol, smoking and stress but its accurate origin is still not known. Further, available treatment options are associated with both inappropriate cosmetic appearance and related toxicities leading to poor patient compliance in long term use. Nanotechnology based drug delivery system has immense potential to enhance the bioavailability and effectiveness of drugs in their dosage forms, especially lipophilic drugs. Lipid based carrier system can overcome the lipid imbalance and normal moisturizing factors. Nanoemulsions, as one of a new carrier apparently have the prospective to conquer numerous problems related with topical antipsoriatic therapy. This delivery system could perhaps offer a good alternative in topical psoriasis treatment. Not only on how nanoemulsions prepared, but it depends on the active ingredients used and the selection of oil could as well enhance the efficiency of topical treatment towards psoriasis. A good combination of both active and suitable oils would result a better treatment and better effect.

Keywords: Topical nanoemulsion, Antipsoriatic therapy, Critical quality attributes.

Article Info: Received 23 July, 2018; Review Completed 11 Sep 2018; Accepted 13 Sep 2018; Available online 15 Oct 2018

Cite this article as:

Khurana B, Arora D, Narang RK, Topical delivery of nanoemulsion for antipsoriatic drugs, Journal of Drug Delivery and Therapeutics. 2018; 8(5-s):1-11 **DOI:** http://dx.doi.org/10.22270/jddt.v8i5-s.1914

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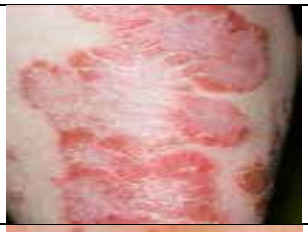
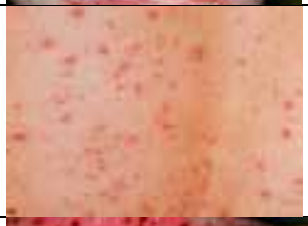
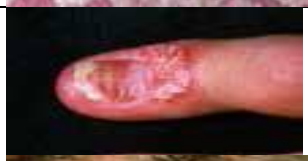
1. INTRODUCTION OF PSORIASIS

Psoriasis is an autoimmune disorder of the skin characterized by relapsing episodes of inflammatory lesions and hyperkeratotic plaques with worldwide occurrence of around 2–5% The psoriasis can be classified on the basis of extent of inflammatory process, localization of rash, severity of the patient condition, and other clinical traits into chronic plaque, guttate, pustular, erythroderma, Scalp, nail, facial, flexural psoriasis and Psoriatic arthritis as shown in table 1. Amongst these, chronic plaque psoriasis (CPP) represents major occurrence proportion with equivalent likelihood in both sexes and early onset before the age of 40 years. [1]

Table 1: Classification of Psoriasis

Plaque psoriasis	Most people have plaque psoriasis. This looks like patches of pink or red skin covered with silvery white scales (sometimes called plaques). The silvery white scales are dead skin cells. The patches are slightly raised from the surface of the skin.	
Guttate psoriasis	This looks like lots of small red scaly patches dotted across your skin. These patches can cover quite a large area of your skin.	
Pustular psoriasis	This can be a severe type of psoriasis where lots of small blisters appear on your skin. It needs emergency medical attention.	
Erythrodermic psoriasis	This is a rare and severe type of psoriasis. Most or all of the skin on your body becomes red and inflamed. It needs emergency medical attention.	
Scalp, nail, facial and flexural psoriasis	Psoriasis can be more difficult to treat on some parts of the body. Flexural psoriasis happens in skin folds, armpits, under the breast, between buttocks and in the groin area where it can affect the genitals.	 

2. PATHOGENESIS OF PSORIASIS

Psoriasis is a disease known to be caused by multitude of both genetic and environmental factors such as trauma, drugs, infection, alcohol, smoking and stress but its accurate origin is still not known. It negatively produces both physical and psychological impacts on patients' health and quality of life involving social disgrace, state of agony, distress, and physical disability. This strained situation drives the patients to contemplate suicide amounting to around 30% cases. Unlike normal skin, pathological progression of psoriasis is supposed to rely on multitude of coherent events involving the activation of circulating immune cells and their secreted signaling molecules like cytokines, chemokines and growth factors. These all events further progress to mark hyperkeratosis, congealing of epidermis and neovascularization of circulating immune cells and their secreted signaling molecules as shown in figure 1. Cytokines play an important role in progression of psoriasis. Major cytokines include tumor necrosis factor alpha (TNF-α), Interleukin-23 (IL-23) and IL-17 which aids in the production of other proinflammatory cytokines and psoriasis lesions formation [1]. Several of these pro-inflammatory cytokines e.g. TNFα, IL-12 and IL-23 rely on nuclear factor kappa B (NF-κB) as a downstream mediator of their effects on a transcriptional level. Accordingly, increased levels of activated NF-κB are found in psoriasis skin compared with healthy skin.

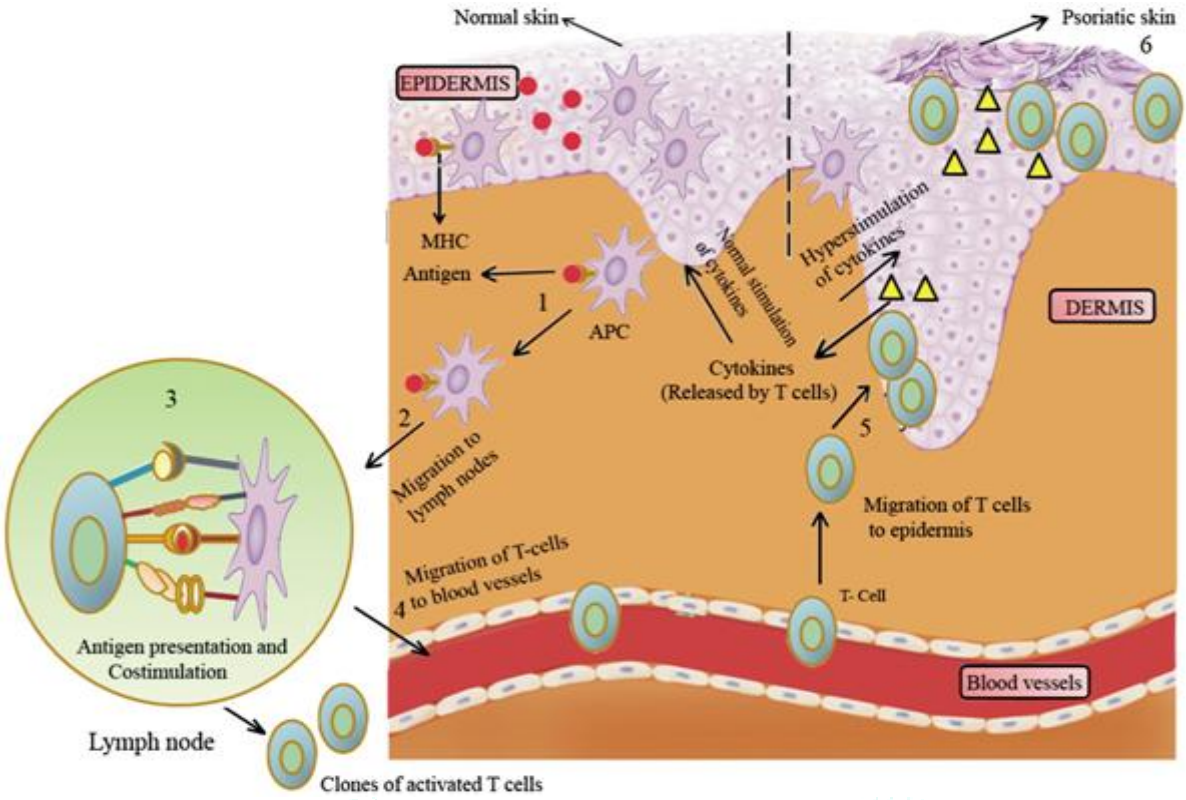


Figure 1: Different Events in the Pathogenesis of Psoriasis

3. AVAILABLE TREATMENT STRATEGIES FOR PSORIASIS

Generally, treatment choices for psoriasis involve three main modes namely topical therapy, phototherapy and systemic therapy. For psoriasis treatment topical therapies are considered first. Phototherapy is suggested in case of non-effectiveness of topical therapy or relentlessness of the psoriasis condition, which is followed by systemic medications as shown in table 2 [2].

Among the currently available treatments, none of the treatment for psoriasis is found to be safe, effective and able to completely cure the disease. Further, available treatment options are related with both inappropriate cosmetic appearance and related toxicities leading to poor patient compliance in long term use. Phototherapy and systemic agents exhibit numerous ill effects such as hepatotoxicity, renal toxicity, hypertension, hyperlipidemia and skin cancer. Moreover the currently available treatments based on conventional formulation for psoriasis are associated with problems like increased dosing frequency, increased side effects and decreased safety profile for long term use. Among the currently available treatments, none of the treatment for psoriasis is found to be safe, effective and able to completely cure the disease. Further, available treatment options are associated with both inappropriate cosmetic appearance and related toxicities leading to poor patient compliance in long term use. Therefore improvement of a perfect therapy for psoriasis is a great confront. The lack of effective and safe treatment for psoriasis has created needs to develop and implement novel approach with a view to make the therapy more useful and acceptable [3, 4]. To overcome the drawbacks of conventional dosage forms, formulation development is aimed to design drug cargo exhibiting ease of administration, reduced dosing frequency, and sustained release for improved therapeutic benefit to psoriatic patients.

Table 2: Available treatment strategies for psoriasis

Type of Therapy	Class	Drugs in Class
Topical	Tars	Tar
	Antracens	Dithranol
	Psoralens	Trioxysalen – Methoxsalen
	Others	Fumaric acid – vitamin D (Calcipotriol, Tacalcitol, Calcitriol) – Tazarotene
Phototherapy		Artificial or natural light sources
Systemic	Psoralen	Methoxsalen – Bergapten- Trioxysalen
	Retinoids	Etretinate – Acitretin

4. NEED OF TOPICAL NANOTECHNOLOGICAL BASED DRUG DELIVERY SYSTEM

Nanotechnology based drug delivery system has immense potential to enhance the bioavailability and effectiveness of drugs in their dosage forms, especially lipophillic drugs. For the effective treatment of cutaneous originated disorders such as Psoriasis, the drug should ideally be confined to the surface or within the site of application without appreciable systemic drug absorption. Thus, the site of application forms the target of topical drug delivery systems. Although topical drug delivery offers certain advantages over systemic delivery for selected drugs and conditions, the resistance against drug transport across skin barrier remains a major challenge to efficient drug delivery by this route. There is also potential of skin irritation or contact dermatitis arising from one or more components in the topical formulation. In some cases poor permeability of some drugs through the skin leads to poor pharmacological response. Possibility of allergic reactions and degradation of drug by the enzymes present in epidermis may create problems. Rigidization of psoriatic skin has been attributed to a rise in the levels of cholesterol and fall in the levels of ceramides. Apart from this, normal moisturizing factors (NMFs) like water are almost absent in the psoriatic skin of a patient. As a result of these factors, targeting drug molecule in a vehicle to the psoriatic tissues using topical route poses a big challenge. Lipid based carrier system can overcome the lipid imbalance and normal moisturizing factors. The most widely used drug delivery systems include lipid based nanoparticles i.e. nanoemulsions, solid lipid nanoparticles, lipid nanocapsules, nanosuspension, liposomes, liquid crystalline nanoparticles, lipid-drug conjugates) or polymer based nanocarriers (polymeric nanoparticles, polymeric micelles, polymer-drug conjugates) as shown in table 3 [3].

Table 3: List of topical novel drug delivery systems for psoriasis

Novel Drug Delivery Systems	Anti-Psoriatic Drug	Ref
Liposome-gel	Hydrocortisone	4
Transfersome in gel	Tacrolimus	5
Drug β-Cyclodextrine complexes into SLNs	Hydrocortisone	6
Cyclodextrin inclusion complex incorporated in multivesicular liposomes	Fluocinolone acetonide	7
Chitosan coated microemulsion	Methoxsalen	8
PLGA/PLA nanoparticles (plus zinc)	Betamethasone	9
PLGA (poly(D,L-lactic-co-glycolic acid)) nanoparticles	Betamethasone	10
PLGA nanoparticles	Ciclosporine Dexamethasone	11 13
PLGA microspheres	Clobetasol-17-propionate	12
Poly(ε-caprolactone) (PCL) nanocapsule	Dexamethasone	14
PCL nanoparticles	Hydrocortisone	15
Polymeric micelle (PEG-dihexPLA diblock copolymer)	Ciclosporine	16
Poly(NIPAM-co-BA) nanogel	Methotrexate	17
Methoxy-poly(ethylene glycol)-dihexyl substituted polylactide (MPEG-dihexPLA) diblock copolymer micelle	Tacrolimus	18
Niosome	Anthocyanin complex Dithranol Methotrexate	19 20 21
Lecithin/chitosan nanoparticles	Betamethasone Clobetasol-17-propionate	10 22
Liposome	Tacalcitol Clobetasol-17-propionate Dithranol Tacrolimus Tretinoin Triamcinolone	23 24 21 25 10 26 27
Pegylated liposomes	Calcipotriol	28
Transferosome	Dexamethasone Hydrocortisone Triamcinolone	29 30
Flexible vesicles and conventional vesicles	Cyclosporine	31
Deformable liposomes	Methotrexate	32, 33

Ethosome	Ciclosporine Methotrexate Psoralen Tacrolimus Tretinoin Tretinoin	34 35 36 37 26
SLNs (Solid lipid nanoparticles)	Betamethasone Ciclosporine Clobetasol-17-propionate Dithranol Methoxsalen. Mometasone furoate Prednicarbate Psoralen Tretinoin Triamcinolone	38 39 40 41 42 43 26 44 45 46 47
SLN-hydrogel	Betamethasone dipropionate and calcipotriol Halobetasol Tacrolimus	48 49 50
Nanostructured lipid carriers (NLCs)-hydrogel	Acitretin	51
NLCs	Calcipotriol and methotrexate Clobetasol-17-propionate Fluocinolone acetonide Methotrexate Methoxsalen Psoralen Tacrolimus Tretinoin	52 53 54 55 62 47 56 26
Microemulsions in hydrogel	Betamethasone dipropionate and salicylic acid	57
Microemulsion	Dithranol Methoxsalen Tacrolimus	58 59 60
Nanoemulsion	Methoxsalen	61
Microemulsions in hydrogel	Methoxsalen	5
Liquid crystalline nanoparticles	Cyclosporine A Tacrolimus	64 65

5. NANOEMULSIONS AS TOPICAL DELIVERY FOR ANTIPSORIATIC DRUGS

Nanoemulsions are emulsions with droplet size on the order of 100 nm. A typical nanoemulsion contains oil, water and an emulsifier. Nanoemulsions can be rendered into several dosage forms, like liquids, creams, sprays, gels, aerosol, and foams; and can be administered by equally varying routes like topical, oral, intravenous, intranasal, pulmonary and ocular. They possess higher solubilization capacity than simple micellar dispersions, greater kinetic stability than coarse emulsions and have found use in cosmetic industry [66].

5.1. Advantages of Nanoemulsion

Their long-term physical stability is a direct consequence of small droplet size, which impairs conventional destabilization phenomena like creaming, sedimentation and coalescence. When administered topically, miniscale size of droplets in nanoemulsion and their capability to solubilize very hydrophobic drugs provides a pathway to drastically increase rate of drug dissolution and subsequently expected systemic bioavailability through trancellular route as shown in figure 2. Drug release from nanoemulsion involves partitioning of it from oil into surfactant layer and then into aqueous phase, thus avoids occlusive effects [67].

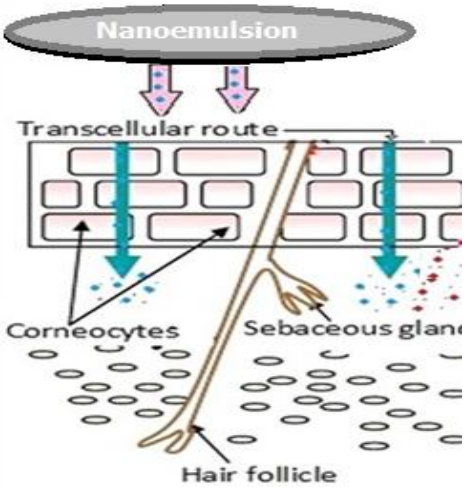


Figure 2: Mechanism of absorption of Nanoemulsion

6. METHODS OF PREPARATION OF NANOEMULSION

There are basically two methods of preparation of nanoemulsion as shown in figure 3. High energy emulsification methods generate highly disrupting forces that break down the oil and water phases, causing them to intersperse and form nanometer-sized droplets. Whereas low energy emulsification methods include heat, stirring and phase inversion [68].

6.1 High Pressure Homogenization

This is highly efficient method of preparation of nanoemulsion in which forcefully introduction of oil and water along with surfactants, cosurfactants are passed through a small orifice at high pressure. At first, emulsion is formed with large volume fraction of dispersed phase, which may be diluted later on. Excess amount of surfactants are added to avoid coalescence[73, 80].

6.2 Microfluidisation

In this method water and oil are introduced through small orifice by pressure pump from opposite direction into mixing area, where they mixed with other high shear and converted into small droplets which in turn used to prepared nanoemulsion [58].

6.3 Sonication

It is widely used method in which probe sonicator is placed in the mixture oil and water with surfactants, cosurfactants to give mechanical force by which dispersion is converted into small sized droplets [61].

6.4 Phase inversion temperature technique

In this technique at room temperature oil, water and surfactants are mixed and then temperature is increased, then surfactant mixed in the oily phase. Due to change in temperature phase inversion prevents coalescence and produce stable nanoemulsions [59].

6.5 Solvent displacement method

In this method nanoemulsions can be prepared by pouring the organic phase containing oil dissolved in a solvent into aqueous phase having surfactants at room temperature. The preparation of nanoemulsion occurs by diffusion of organic solvent, evaporated by vacuum. Small sized droplets of nanoemulsion can be prepared by taking appropriate ratio of solvent to oil. [73]

6.6 Spontaneous emulsification

In the solution of oil and surfactant water is added at constant temperature and mixed lightly to produce o/w nanoemulsions. The preparation of nanoemulsion depends on surfactant structure, its concentration, interfacial tension, interfacial and bulk viscosity, phase transition region [68, 74, 75].

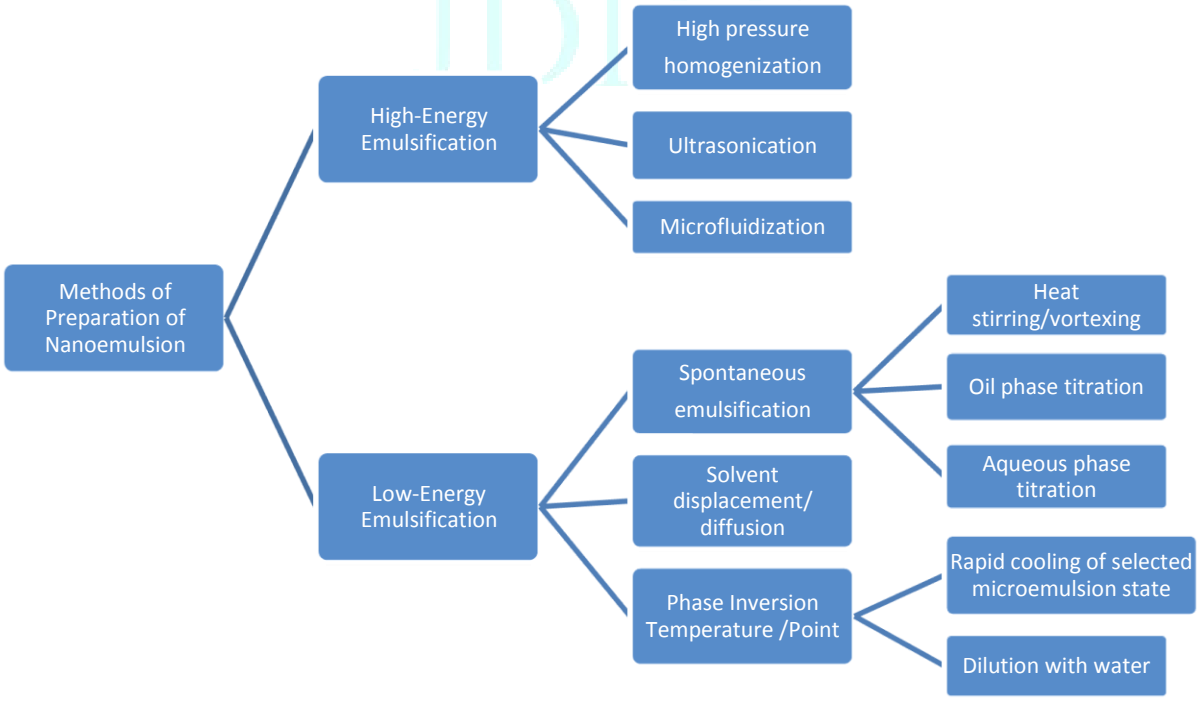


Figure 3: Methods of Preparation Nanoemulsion

7. COMPONENTS IN THE TOPICAL NANOEMULSION FORMULATIONS FOR ANTIPSORIATIC DRUGS

7.1 Oil Phase

Selection of oil phase such as saturated and unsatuated fatty acids/fatty acid esters like castor oil, coconut oil, corn oil, cottonseed oil, evening primrose oil, fish oil, jojoba oil, lard oil, linseed oil, mineral oil, olive oil, peanut oil, PEG-vegetable oil, perflurochemicals, pine nut oil, safflower oil, sesame oil, soybean oil, squalene, sunflower oil, wheatgerm oil can be done. Oil phase helps in penetration of drugs. Mostly antipsoriatic drugs are lipophilic and have a log P value of 3, which makes it suitable for being encapsulated in emulsion. Sometimes combination of oils is used to encapsulate antipsoriatic drugs [73].

7.2 Surfactant

Selection of surfactant is used to decrease the interfacial tension and makes a stable emulsions having requisite particle size, but which also ensure minimal skin irritancy there are basically four types of surfactants i.e. nonionic, zwitterionic cationic, anionic.. Commonly used surfactants include Tween®, Cremophor®, Transcutol® P, Plurol Oleique®, Plurol Isostearique® and Labrasol® , Lecithin, Organogels [75].

7.3 Co-surfactant

Cosurfactants are generally used to modify the curvature and fluidity of the interfacial fillm, leading to the decrease of interfacial tension. Cosurfactants are short and medium chain alcohols and polyglyceryl derivatives, including ethanol, isopropanol, isopropyl myristate and propylene glycol (PG) [73].

7.4 Other Excipients

Antioxidants (a-tocopherol, ascorbic acid) Tonicity modifiers (glycerol, sorbitol, xylitol) pH adjustment agents (NaOH or HCl) Preservatives, aqueous phase (sodium chloride and buffer salts) and penetration enhancers, Viscosity enhancing agents (e.g., Carbopol®, Aerosil®, gelatin) are incorporated to reduce the fluidity and generate the desired final consistency of the product [69].

8. CHARACTERIZATION OF NANOEMULSION

8.1. Drug-excipients compatibility studies: Excipients are determined by Fourier Transform Infrared Spectroscopy (FTIR) and UV Spectrophotometry studies can be used for the determination of physicochemical compatibility and interactions between the drug and excipients. Drug-excipient interactions recommended that 1:1 ratio of drug and excipient maximizes the possibility of interaction and helps in easier detection of incompatibilities [61].

8.2. Globule size distribution & polydispersity index: The mean globule size of the nanoemulsion can be determined by Photon Correlation Spectroscopy (PCS) using a Zeta sizer. This analytical results reveals the mean diameter of the particle at 25 °C, and at an angle of 90 degree (n=10). The PCS analysis yields a mean diameter (z-average) as a light intensity-weighed size of bulk population and the polydispersity index as a measurement for the width of a globule size distribution [60].

8.3. Zeta potential: The electrophoretic mobility can be obtained by a Laser Doppler Anemometer connected with the zeta sizer instrument. Dilute suitable amount of sample (50-100µL) with 5mL of water (0.45µm) and inject in the electrophoretic cell of the instrument where a potential set at ±150mV. The zeta potential values can be calculated by the instrument software using Smoluchosky equation [61].

8.4. Morphology by transmission electron microscopic (TEM): TEM helps to visualize the inherent matrix of individual globule and its shape. A drop of the suitably diluted sample was placed on to a holey carbon coated copper grid and left for 10 minutes. Then kept grid inverted and apply a drop of phosphotungstic acid (PTA) to the grid for 10s. Remove excess of PTA by absorbing on a filter paper and analyze the grid at particular magnification [5].

8.5. pH: The pH of the formulation can be measured in a pH meter [58].

8.6. Viscosity: The viscosity of the nanoemulgel can be determined by a Brookfield viscometer which rotates for 10min at 100 maximum rotations per minute with spindle [57].

8.7. Drug content: The amount of drug present in the nanoemulgel can be determined by dissolving 5g of nanoemulgel in 25ml of phosphate buffer solution at pH 7.4 by sonication. After sonication filter the solution, then filtrate dilute suitably and the take absorbance at 273nm in UV-Visible spectrophotometer finally calculate the percentage of drug content [56].

8.8. Spreadability: Spreadability test can be performed by measuring the spreading diameter of the nanoemulgel between two glass slides. Weigh about 0.5g of sample and place at the centre (within a circle) of the glass plate, over which place a second glass plate and press between the two slides and measure the spreadability of the gel in cm after 5 minutes [60].

8.9. Pseudo Ternary Phase Diagrams: It is characterized by a range of physical properties that are important determinants of their structure, drug release and stability. Pseudo ternary phase diagrams are often constructed to indicate the boundaries of the different phases as a function of the composition of the aqueous, oil and surfactant/cosurfactant components. Mixtures of the oil, surfactant and cosurfactant at certain weight ratios at ambient temperature (25 ºC) are dilute with the aqueous solution under moderate agitation. After equilibrium, the combinations of the three components that give rise to clear emulsions, shown by visual inspection or polarised light microscopy, are mapped on the phase diagram as shown in figure 4 [60].

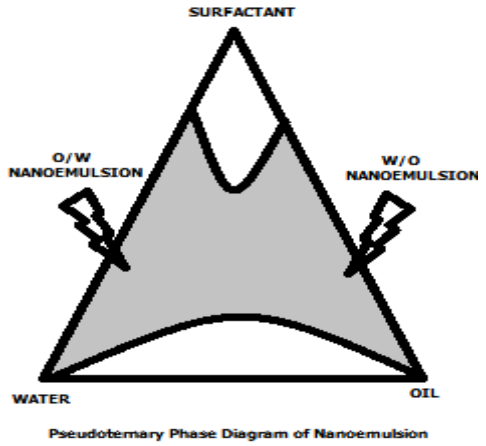


Figure 4: Phase diagram for formulation of nanoemulsion

8.10. In-Vitro release In-vitro release studies can be carried out by using dialysis membrane bag method. The dialysis membrane is conditioned by soaking in phosphate buffer 7.4 for 8 hours. Take drug loaded nanoemulgel of about 3mL in the dialysis membrane and immerse in 200mL of phosphate buffer solution (pH 7.4). Withdraw sample of 5mL from the dissolution setup at regular intervals for 8 hours and replace an equal volume of phosphate buffer (pH 7.4) to maintain a sink condition. Analyze samples by using UV spectrophotometer at 290nm and calculate the amount of drug release and compare with the marketed conventional dosage form [70-71].

9. STABILITY OF NANOEMULSIONS

Emulsion stability is dependent on role of surfactants, its composition and the drop size distribution. Major instability is due to coalescence in which there is fusion of droplets by breaking the film between the two globules which in turn increase the size of nanoemulsion as shown in figure 5. It can be preventing by adding a sufficient amount of surfactant while preparing nanoemulsions. Another one is Ostwald ripening in which emulsions get destabilized with the passage of time due to molecular diffusion and change in droplet size of nanoemulsion. There is mass transfer occurs form dispersed phase to continuous phase [72].

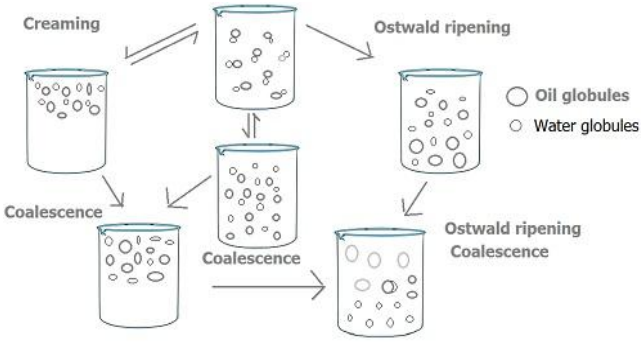


Figure 5: Physicochemical mechanisms cause instability

10. VARIOUS ANTIPSORIATIC DRUGS LOADED IN NANOEMULSION

Already extensive research has been done on nanoemulsion loaded antipsoriatic drugs as shown and discussed in table 4.

Table 4: Various antipsoriatic drugs loaded in nanoemulsion

Antipsoriatic Drug	Method of Preparation	Ingredients used in Nanoemulsion	Ref
Aceclofenac and capsaicin	Solvent evaporation method and high-pressure homogenization method.	Polyvinyl alcohol ,dichloromethane, tween 80, sodium tripolyphosphate, polyethylene glycol	73
Turmeric oil	Emulsification method	Tween 20, tween 80, lecithin, labrasol, isopropyl alcohol	74
Clobitasol propionate and calcipotriol	Emulsification method	Capmul MCM C8 EP, Cremophor RH 40 and Labrafil 1944 CS	75
Betamethasone dipropionate	Spontaneous Emulsification method	Babchi oil, eucalyptus Oil, tween 20 and ethanol	76
Betamethasone dipropionate and salicylic acid	Aqueous phase titration method	Oleic acid, sefsol, tween 20, isopropyl alcohol	77
Clobetasol propionate	Aqueous phase titration method	Eucalyptus oil, tween 20, ethanol, and distilled water	78
Betamethasone valerate	Aqueous phase titration method	Sefsol, tween 20, transcutol p	79
Cyclosporine	High-shear homogenizer	Nutmeg oil, virgin coconut oil, tween 80,xanthan gum	80

11. CONCLUSION

Though development has been made in understanding the mechanism of action of psoriasis and in make out efficient treatments, the exploration for the best treatment approach for psoriasis still remains a major confront. Many topical cures are available for the treatment of psoriasis, but there is a lack of consistency of approach which is acceptable for moderate to severe psoriasis. Psoriasis is a lasting disease in which the patients have to take long term medication treatment. In addition, there is still no available delivery system for psoriasis which is safe, effective, patient's compliance and affordable to completely cure the disease. Lipid based carrier system can overcome the lipid imbalance and normal moisturizing factors. Nanoemulsions, as one of a new carrier apparently have the prospective to conquer numerous problems related with topical antipsoriatic therapy. This delivery system could perhaps offer a good alternative in topical psoriasis treatment. Not only on how nanoemulsions prepared, but it depends on the active ingredients used and the selection of oil could as well enhance the efficiency of topical treatment towards psoriasis. A good combination of both active and suitable oils would result a better treatment and better effect. Nanoemulsion are the best suited nano delivery systems to encapsulate and deliver poorly water soluble drugs successfully due to their inherited properties. Nanoemulsions offer enhanced solubilization capacity for poorly soluble drugs, increased drug loading, and in turn lead to a higher bioavailability of the formulated therapeutic moiety.

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