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A recent review on Nanoemulsion as a topical delivery system of antipsoriatic drugs

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ABSTRACT

Psoriasis and psoriatic arthritis are a chronic skin disease of autoimmune system that is identified as patches of abnormal skin, affecting 2-5% of the world's population. Psoriasis is an incurable lifetime disease which can be controlled and relieved through medication. Various approaches have been explored to treat the disease. Treatment of psoriasis includes topical therapy, systemic therapy and phototherapy. Topical therapy is the main psoriasis treatment. However, the conventional topical treatment such as gel and cream have low efficiency to poor cosmetic and aesthetic appeal leading to poor patient compliance or adherence. Nanoemulsions are transparent or translucent dispersions, having the droplet size less than 100 nm with ultra-low interfacial tension, large o/w interfacial areas and long term physical stability recently, much attention has been paid to the application of Nano emulsion as drug delivery system. A small droplet size would enhance the drug delivery and penetration of a drug through the psoriasis skin layer. A good selection of oils and surfactants would enhance the transdermal treatment efficacy in psoriatic patient.

Keywords: Nano emulsion topical drug delivery, psoriatic treatment

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INTRODUCTION

Psoriasis is one of the skin diseases, affecting 2–5% of the world's population. Psoriasis is a skin autoimmune disorder, resulting in an excessive growth and aberrant differentiation of keratinocytes. This disease could develop at any age, but it usually occurs before the age of 40, and is quite uncommon in children. Psoriasis is not life threatening, but it is a debilitating chronic illness with pronounced physical, psychological and social implications. In addition, approximately 5–8% of patients with psoriasis developed psoriatic arthritis, which causes much pain and further reduced mobility.[1]

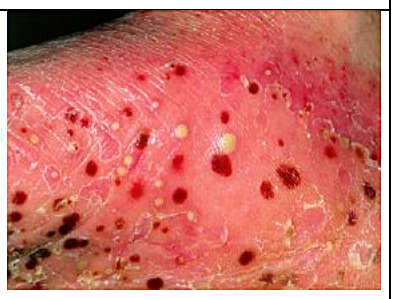
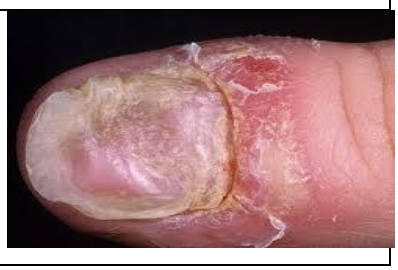
Psoriasis is a T-cell-mediated autoimmune inflammatory skin disease that manifests in such symptoms as skin-surface inflammation, epidermal proliferation, hyperkeratosis, angiogenesis, and abnormal keratinization.[27]as for psoriatic skin, the mitotic activity of basal keratinocytes is 50-fold compared to normal skin activity. Therefore, keratinocytes of psoriatic skin have only 3–5 days to be removed from the basal layer to the cornified layer (28–30 days for normal skin). This limited period, accompanied by rapid differentiation activity, causes the dead skin to be accumulated on the skin's surface, resulting in a thick and dry skin surface. More simply, psoriasis presents as thick patches of red, dry, and itchy skin. Treatments can only help to reduce and relieve the problems, not cure them. The current standard treatment for managing psoriasis includes topical therapy as first-line treatment for mild disease, followed by phototherapy and systemic (or oral) therapy for more severe disease.[28]

In addition, approximately 5–8% of patients with psoriasis developed psoriatic arthritis, which causes much pain and further reduced mobility.[1] They also experience extreme itching of the skin, which leads to scaly, painful and disgorging lesions. Typical skin lesions affected by psoriasis can be observed clearly and the coverage area is well defined. When the coverage area of the affected body surface is more than 20%, the condition is categorized as a severe case.[2] The area involved is not limited to any specific part of the body as the disease could be found a sminor spots which are distributed over the entire skin.[3] Visible psoriasis conditions with very thick and red patches may give an impact on the psychosocial lives of patients, especially to their social interactions.[4] Overall, patients with psoriasis oven describe the feelings of self-consciousness, helplessness, embarrassment, anger and frustration,[5,6] which would eventually lead to low self-esteem, lack of self-

condensed, poor self-image and generally lower sense of well-being.[7] Recently, psoriasis was found to be associated with many diseases such as independent risk factor for diabetes and cardiovascular diseases, including hypertension and hypercholesterolemia. [8,9] The relation between psoriasis with cardio metabolic disorder such as hypertension, obesity and chronic kidney disease was reported[10] and has been confirmed through investigation in pediatric patients.[11] For example, a study was found that the obesity in children with psoriasis tobe 1.7 times higher in frequency when compared with the children without psoriasis.[12]

This disease has different types: psoriasis vulgar is, guttate psoriasis, erythrodermic psoriasis, pustular psoriasis and nail psoriasis. The first type is the most common form of psoriasis, which is characterized by red, scaly and raised plaques. Classic psoriasis vulgaris mainly infects specific areas such as elbows, knees and the scalp. It can also remain localized or become generalized over time and the plaques may differ in size [29,30]. Treatment of psoriasis depends on many factors such as the extent of the disease, its influence on patient's life, and the life perception of patient's illness [30].

Table 1: Classification of Psoriasis[45]

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.	
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.	

1. AVAILABLE FORM OF ANTIPSORIATIC DRUGS AND POTENTIAL LIMITATION IN THE TREATMENT OF PSORIASIS. [42]

In this section, we review a few conventional and wide available treatments of psoriasis from topical, systemic and photo or radiation therapies.

1.1. Topical therapy

Topical therapy is the main psoriasis treatment with more than50% of patients using it as compared to the other therapy.[16]Antipsoriatic drugs for dermal use are commercially available generally in the form of gels, shampoos, creams, ointments or lotions. In plaque psoriasis cases ,the most prescribed topical medication is from the corticosteroid family such as hydrocortisone, betamethasone, dexamethasone, etc. Even though many methods have been offered to deliver corticosteroids, a major problem of using this range of drugs is their side effects, which include cutaneous atrophy, development of striae, formation of telangiectasia and perioral dermatitis on the face.[17] Moreover, although using topical corticosteroid is highly effective initially, it leads to the development of tachyphylaxis problem which is a rapidly diminishing response to successive doses of a drug, rendering it less effective with prolonged use.[18] Besides, this type of steroidal drug would cause decolourisation and thinning of the skin

followed by easy bruising even with a minimum shear.[19] Thus, it is not suitable for face and also for children.

1.2. Systemic therapy

Systemic therapy includes methotrexate, cyclosporine and antibody therapy. Methotrexate is the oldest therapy and one of the most effective treatments. However, it gives a short term side effect of bone marrow toxicity which could lead to death.[20] Another side effect includes nausea, aphthous stomatitis and development of megaloblastic anaemia.[18] Besides, the use of methotrexate should be prescribed with caution in the presence other patient's conditions including obesity, diabetes and heavy alcohol intake because of the increase risk of liver fbrosis.[21]

1.3. Phototherapy

Photo or light therapy also includes radiation therapy using usually ultraviolet source.[22] The combination of ultraviolet B (UVB) with topical treatment such as tar or emollient is still been used in current medication of psoriasis. Broadband UVB is reported to be one of the safest treatments for psoriasis. However, it needs to be done at least three times per week for several months to see the result.[22] Narrowband UVB is more effective than the broadband UVB phototherapy.[23] PUVA is another treatment of phototherapy which involves the use of psoralen and ultraviolet A. A light-sensitive drug, psoralen absorbs long wavelength ultraviolet (UVA) light. Psoralens are either taken orally or applied topically where the infected area of patient's skin will be immersed in water containing 8-methoxypsoralen capsules, which is followed exposing this area with the UVA light.[24,25] Despite its effectiveness to clear the symptoms the affected area, it is associated with the development of skin squamous cell carcinomas leading to the development of a skin cancer in the thin, ?at squamous cells.[18] Even though PUVA and UVB seem to be effective towards psoriasis disease, but the impracticality of its application has been the main issue for many patients.[26]

2. CHALLENGES IN TOPICAL TREATMENT OF PSORIASIS[42]

Stratum corneum is the main barrier in the percutaneous absorption of topically applied drugs. The successful performance of these systems for drug delivery completely depends on their capability to penetrate through several barriers of the skin, drug release and their stability in the nanoscale size. However, for the topical treatment of psoriasis using drug delivery system, there still remain two major challenges. Firstly, the lack of efficient carrier for delivery of anti-psoriatic drugs where efficient delivery of antipsoriatic drug depends on variety of physicochemical characteristics of the carrier and the active moiety used,[14] leading to variation in drug absorption and the drug efficacy. Secondly, appropriate animal model with completely psoriatic condition is lacking for in vitro and in vivo studies.

(1) Psoriatic lesions can have both significantly thickened and thinned epidermis. Different morphology of the skin could increase the diversity in drug absorption, hence increase challenges in formulation development

(2) Most patients with psoriasis feel that the current therapy is either not effective or not aggressive enough. Therefore, to develop a new therapy which can be once a day

Application and shows quick response is another challenge.

(3) Effective management of psoriasis o?en requires combining therapy to achieve optimal response while minimizing side effects. Therefore, any new topical therapy should have the appropriate safety and efficacy when used in combination with another topical medication, for example systemic therapy and/ or phototherapy.

(4) New topical formulations must have appropriate cosmetic elegance such as ease of use, no potential staining on clothing, bedding, etc., upon the application of rapid absorption and less greasy in order to improve patient's adherence to therapy.

(5) The formulations which can be used in many areas of the body including the hair-bearing sites are preferred by patients with plaque psoriasis.

(6) For the various types of therapy and the presence of generic products on the market, the competitive costs of any new drugs is the most important in influuencing the choices of the product.[13,15]

3. NANOEMULSIONS: NOVEL COLLOIDAL DRUG DELIVERY SYSTEM FOR PSORIASIS[42]

An emulsion is a dispersed system containing at least two immiscible liquid phases. In order to ensure stability, an emulsion must contain a suitable emulsifying agent aside from the dispersed phase and dispersion medium[1, 2.] There are two basic forms of emulsion. The first is the oil-in water(O/W) emulsion in which oil droplet are dispersed and encapsulated within the watercolumn[3].The second is the water-in-oil (W/O) emulsion in which droplet of water is dispersed and encapsulated within the oil. An o/w emulsion is formed when a small amount of an appropriate surfactant is mechanically agitated with the oil in water. this results in a two phase dispersion where one phase exists as droplets coated by surfactant that is dispersed throughout the continuous, other phase.[4] These emulsion are milky or turbid in appearance due to the fact that the droplet size range from 0.1 to 1 micron in diameter. As a general rule, the types of surfactant used in the system determine which phase is continuous. If the surfactant is hydrophilic, then oil will be emulsified in droplets throughout a continuous water phase. The opposite is true for more lipophilic surfactants. In w/o water phase emulsified in droplets that are dispersed throughout a continuous oil phase in this case[5,6]

Nanoemulsions are transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and co-surfactant molecules having a droplet size of less than 1000 nm. Nanoemulsion, is a multiphase colloidal dispersion, is generally identified by its stability and clarity. Apply high shear generally obtained by micro fluid or ultrasonic approach generally used to reduce the droplet size to nanoscale. Various works are done to correlate the different transdermal drug release from various delivery systems. [4]

4. NANOEMULSION IN TOPICAL APPLICATION[43]

Nanoemulsion is a novel drug delivery system alternative to increase drug delivery and increasing efficacy of poorly soluble drugs, by increasing its absorption through the skin, better retention time of drug in the target area and prevent the side effects [31]. The benefits of nanoemulsion with globules in nano-scale size of an emulsion does not relay on the emulsion physical properties itself [32], yet encounter the bioavailability of therapeutic drugs in whole. Apparently, there have been researches on the bioavailability of lacidipine via transdermal route was 3.5 times higher than that of oral route which believed to be due to avoidance of first-pass metabolism [33]. In nanoemulsion, the small size of particles, the more quantity of drug is able to be incorporated in nano globules, which subsequently increases

the thermodynamics towards the skin. One of the studies consequently narrates the implications of Nile red (NR) dye loaded in lecithin nanoemulsion was able to penetrate the skin 9.9-fold greater than the NR-loaded general emulsion [34]. Besides that, ethyl oleate and propylene glycol, ingredients used and it act as permeation enhancers [35].

The greatest difficulty upon transdermal drug delivery refers to barrier properties of stratum corneum a 10 µm to 20 µm thick tissue layers with great composed structured lipid/protein matrix [36]. On recent study, of demal delivery lipophilic flurbiprofen in nanoemulsion proves and an increase in efficacy by 4.4 times compared to oral administration [37]. Hence, the nanoemulsion is a spontaneous easy emulsifying method which provides more advantages over other carrier such as polymeric nanoparticle and liposomes, including low cost preparation procedure, high hydrophilic and lipophilic drug loading system to enhance the longer shelf live upon preserving the therapeutic agents [37].

5. ADVANTAGES AND DISADVANTAGES [44, 38]

5.1. Advantages

a) Increase the rate absorption.

b) Eliminates variability in absorption.

c) Helps solubilize lipophilic drug.

d) Provides aqueous dosage form for water insoluble drugs.

e) Increases bioavailability.

f) Various routes like topical, oral and intravenous can be used to deliver the product.

g) Rapid and efficient penetration of the drug moiety.

h) Helpful in taste masking.

i) Provides protection from hydrolysis and oxidation as drug in oil phase in O/W Nanoemulsion is not exposed to attack by water and air.

j) Liquid dosage form increases patient compliance.

k) Less amount of energy requirement.

l) Nanoemulsions are thermodynamically stable system and the stability allows selfemulsion of the system.

5.2. Disadvantages

a) Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.

b) Limited solubilizing capacity for high-melting substances.

c) The surfactant must be nontoxic for using pharmaceutical applications.

d) Nanoemulsion stability is influenced by environmental parameters such as temperature pH. **7.**

6. COMPONENTS IN THE TOPICAL NANOEMULSION FORMULATIONS FOR ANTIPSORIATIC DRUGS [45]

6.1 Oil Phase

Selection of oil phase such as saturated and unsaturated 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, perfluro chemicals, pine nut oil, safflower oil, sesame oil, soybean oil, squalene, sunflower oil, wheat germ 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 [40].

6.2 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 [41].

6.3 Co-surfactant

Cosurfactants are generally used to modify the curvature and fluidity of the interfacial film, 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) [40].

6.4 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 [39].

7. METHODS OF PREPARATION OF NANOEMULSION [45]

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.

7.1 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[40].

7.2 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.

7.3 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.

7.4 Phase inversion temperature technique[41, 42]

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.

7.5 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. [40]

7.6 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 [39,41].

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