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Nanoemulsion as a Topical Delivery System of Antipsoriatic Drugs

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Abstract

Psoriasis is one of the most common skin disease, affecting 2–5% of the world's population. It is a skin autoimmune disorder, resulting in an excessive growth and aberrant differentiation of keratinocytes. Psoriasis is an incurable lifetime disease which can only 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 first line treatment and it is the most practical medication method for psoriasis patients. However, the conventional topical treatments such as gel and cream have low efficiency, poor cosmetic and aesthetic appeal, leading to poor patient compliance or adherence, while systemic and photo therapy produce significant adverse side effects. Nanoemulsion is defined as an emulsion system consisting of oil, surfactant, and water with an isotropic, transparent (or translucent) appearance. The emulsion droplet size is defined to be less than 200 nm. Nonetheless, if the emulsion has low surfactant content and is kinetically stable, the size of less than 500 nm can be accepted as nanoemulsion. A small droplets size would enhance the delivery and penetration of drug through the psoriasis skin layer. There has been a growing interest in using nanoemulsions in topical applications, due to their high stability and optically transparent or translucent, make them good and very dermatologically attractive. A good selection of oils and surfactants would enhance the transdermal treatment efficacy. This review highlights the potential of drug-loaded nanoemulsion for the treatment of psoriasis towards achieving better efficacy and eliminating side effects.

1. Introduction

Psoriasis is an inflammatory condition of the skin. This disease could develop at any age, but it usually occurs before the age of 40, and 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 cause much pain and further reduced mobility.[1] They also experience extreme itching of the skin, which leads to scaly, painful and disfiguring 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 as minor 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 often describe the feelings of self-consciousness, helplessness, embarrassment, anger and frustration,[5,6] which would eventually lead to low self-esteem, lack of self-confidence, 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 cardiometabolic disorder such as hypertension, obesity and chronic kidney disease was reported[10] and has been confirmed through investigation in paediatric patients.[11] For example, a study was found that the obesity in children with psoriasis to be 1.7 times higher in frequency when compared with the children without psoriasis.[12]

Although the disease was diagnosed much earlier, a patient with a psoriatic condition was treated since 20 years ago.[13] Topical therapy is the primary treatment for mild to moderate psoriasis and serves as a useful additional support for systemic therapy in severe diseased cases. However, the efficacy and the patient's compliance or adherence to topical therapy in psoriasis has been a major concern. The patient's compliance (or adherence) is referred to the extent to which a patient correctly follows medical advice. Approximately, 70% of psoriasis patients in three extensive surveys were found to be unsatisfied or moderately satisfied with their current treatments,[14] which include topical therapy (e.g. coal tar[15] and dithranol[16,17]), phototherapy (e.g. ultraviolet B (UVB)[18]), and systemic therapy (e.g. retinoid[19]). These well tested and tried methods are far from satisfactory, for example the use of coal tar for topical therapy is not completely safe or fully effective. Available treatment options were reported to have undesirable cosmetic appearance and irritations, leading to patient skipped their doses especially for long term treatment.[20] The ideal therapy for psoriasis is yet to be developed and implemented with an objective of being more useful and acceptable to patient. A promising strategy to overcome these problems includes the development of a suitable drug carrier system to achieve controlled and localized delivery of the active drug according to the specific therapeutic needs.[21]

Nanoemulsion is a colloidal carrier system containing surfactant, water and oil. Its high kinetic stability, low viscosity, and optical transparency make them very useful in many dermatological applications.[22] Nanoemulsions have a very small and uniform-sized droplet, usually less than 200 nm, but if the emulsion has low surfactant content and is kinetically stable, the size of less than 500 nm can be considered as a nanoemulsion.[23,24] Their high kinetic stability prevents them from separation, sedimentation or creaming.[25] These properties

are highly valuable in the pharmaceutical industry due to good stability, enhanced drug solubility and significant effect on topical systems.[26] Nanoemulsions offer various advantages over conventional delivery system such as minimization of drug degradation and drug loss, increase drug bioavailability, increase in the fraction of drug accumulation in the target area, prevent harmful toxic effects, versatility and flexibility in handling drug with better patient's compliance especially for cosmetic reason.[22]

In this review, the conventional formulations for psoriasis treatment are briefly described. Nanoemulsion as a potential colloidal carrier system for psoriasis treatment will be discussed in detail in the next section. This review also covers a brief explanation on the limitations of using other colloidal carriers when compared to nanoemulsions.

2. Pathogenesis of Psoriasis

In general, psoriasis is characterized by four abnormalities: 1. vascular changes where the papillary blood vessels become dilated and tortuous, resulting in redness or erythema, a hallmark of psoriasis; 2. inflammation where polymorphonuclear leukocytes from the dermal vessels enter the epidermis; lesions are also rich in activated $CD4^+$ and $CD8^+$ T cells that release pro-inflammatory cytokines; 3. hyperproliferation of the keratinocytic layer (acanthosis); and 4. an altered epidermal differentiation where corneocytes retain their nuclei in the cornified layer (parakeratosis) and the granular layer is lost[27] (**Fig. 1**).

(Fig.1. Should be placed here)

Different types of psoriasis identified depend on the symptom, namely plaque psoriasis, guttate psoriasis, inverse psoriasis, erythrodermic psoriasis and pustular psoriasis.[28] Unlike normal skin, the evolution of psoriasis usually relies on their multitude of coherent events involving the activation of circulating immune cells and their secreted signalling molecules like cytokines, chemokines and growth factors. These further accelerate hyperkeratosis and neovascularization in psoriatic skin.[29]

3. Challenges In Topical Treatment of Psoriasis

Stratum corneum is the main barrier in the percutaneous absorption of topically applied drugs. During the last decades, colloidal carrier systems such as nanostructure lipid bilayers, solid lipid nanoparticles, etc. have been discovered for topical delivery. 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,[30] 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. Although numerous immunological and genetic animal models have been developed, none of these models demonstrate all the characteristics of psoriasis with associated limitations. For example, a spontaneous mutation model, which characterized as homozygous asebia, flaky skin mice and spontaneous chronic proliferative dermatitis mutation displays few pathological

characteristics similar to psoriasis like hyperkeratosis and scaly formation but lacks the T-cells and neutrophils which do not echo psoriatic lesions.[31]

In addition to these major challenges in the development of delivery system for topical treatment of psoriasis, there are several more specific issues to be addressed concerning antipsoriatic topical products. (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 often 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 influencing the choices of the product.[28,32]

4. Available Form of Antipsoriatic Drugs and Potential Limitation In The Treatment of Psoriasis

In this section, we review a few conventional and wide available treatments of psoriasis from topical, systemic and photo or radiation therapies. We describe the drugs, method of applications, and limitations of the therapies.

4.1 Topical Therapy

Topical therapy is the main psoriasis treatment with more than 50% of patients using it as compared to the other therapy.[33] Antipsoriatic drugs for dermal use are commercially available generally in the form of gels, shampoos, creams, ointments or lotions as summarized as in **Table 1**. 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.[47] 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.[48] Besides, this type of steroidal drug would cause decolourisation and thinning of the skin followed by easy bruising even with a minimum shear.[49] Thus, it is not suitable for face and also for children.

(Table 1: Should be placed here)

Despite the corticosteroid treatment, the use of retinoid as the main active ingredient for topical delivery also has been marketed. Commercially, tazarotene can be found in the form of cream, gel and foam for psoriasis treatment. Tazarotene gel and cream are available at the concentration of 0.05% and 0.1%. However, the use of this retinoid could lead to a local cutaneous irritation.[50,51] As a result, it must be prescribed together with a topical corticosteroid in order to overcome the problem. Another type of active ingredient that is also available for topical application is the group D analogue such as calcipotriene. But when the patients apply a large quantity of the drug, it would lead to hypercalcaemia.[52]

Another example of drug for psoriasis is dithranol or anthralin, which is available commercially in a concentration ranging from 0.1 – 2.0% in a cream or ointment base. It is a synthetic analogue of the araroba tree extract, chrysarobin, which has long been used effectively in combination with UVB phototherapy for treating psoriasis.[53] Dithranol stains skin, clothing, bathtubs and other objects a purple colour, limiting its acceptance by many patients. It can also substantially irritate the skin. Despite this negative feature, dithranol works well to clear psoriasis and is associated with prolonged remission after discontinuation of the medication, ranging from 3.9 to 6.0 months.[54] Another options for topical therapy is by using coal tar. Both dithranol and coal tar treatments would be the least favoured by patients due to their unpleasant odour, product migration and local irritation.[55]

The use of tacrolimus with salicylic acid as penetration enhancer for topical application has been reported.[56] However, this method seems to be not a favourable treatment since it causes a burning and stinging sensations on the applied area. This side effect leads to the peeling of the skin layer causing the patients to stop the treatment. Monoolein also has been used as penetration enhancer to increase the penetration rate of other psoriatic drug such as

cyclosporin to the skin. Unfortunately, this method was found to be not very efficient due to the involvement of skin pretreatment which causes an irreversible change to the nature of skin.[57] Hijamah is a traditional technique where the cup will be put on the body, creating a vacuum suction in it to collect the stagnant blood from the particular area, was found to show a good result in the treatment of psoriasis.[49] However, hijamah need to be performed in aseptic condition by a well-trained Hijamah-physician, and this would be not really practical for psoriasis patients.

4.2 Systemic therapy

Systemic therapy includes methotrexate, ciclosporin 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.[58] Another side effect includes nausea, aphthous stomatitis and development of megaloblastic anaemia.[48] 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 fibrosis.[59]

Clinically, ciclosporin is delivered orally into the patients' body system. Ciclosporin is available in a soft gelatine capsule or oral solution containing emulsion preconcentrates, known as Sandimmune®. However study found that this formulations show bile-dependent absorption and exhibit significant inter- and intra-patient variability. Thus, a new formulation, Neoral®, was developed. Both of these conventional products are targeted to be consumed orally. Various adverse side effects such as nephrotoxicity, cardiotoxicity, hypertension and hepatotoxicity were observed due to the intake of ciclosporin. [60,61] According to Gisondi et

al., ciclosporin can induce or worsen arterial hypertension, increase insulin resistance and interfere with fatty acid metabolism inducing dyslipidemia and hyperuricemia.[62]

Acitretin is another type of oral retinoid for psoriasis treatment. This oral retinoid therapy could cause side effects such as the hair loss of patients, cheilitis (lips cracking), thinning of the nail plates, desquamation of the palms and soles and sticky sensation to the skin. Meanwhile, the chronic usage would lead to calcification of ligaments and tendons. Research found that the systemic therapy would result with more chronic side effects as compared to the topical therapy.

4.3 Phototherapy

Photo or light therapy also includes radiation therapy using usually ultraviolet source.[63] 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.[64] Narrowband UVB is more effective than the broadband UVB phototherapy.[65] 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.[66,67] Despite its effectiveness to clear the symptom to 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, flat

squamous cells.[48] 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.[68]

5. Nanoemulsions: Novel Colloidal Drug Delivery System For Psoriasis

There has been a growing interest in the use of nanoemulsions as a colloidal drug carrier for pharmaceuticals, especially in topical applications. A topical drug delivery system is a system that brings a certain drug into the body through contact with the skin as illustrated in **Fig. 2**. Crossing the skin barrier is a challenge for a topical delivery. Penetration of the active drug can vary depending on the physicochemical features of the delivery system. Besides, selection of a suitable drug delivery system depends on the type of active ingredient, patient preference and anatomical sites illnesses.[69]

(Fig. 2. Should be placed here)

Nanoemulsions with narrow size distributions, offer several advantages for topical delivery with pharmaceutical active ingredients, including controlled droplet size, the ability to efficiently dissolve lipophilic drugs, extended release of lipophilic and hydrophilic drugs[70] as well as it can increase the hydration and viscoelasticity of the skin.[71] Topical drug delivery also offers the advantages of patient's compliance, ease of delivery, avoidance of first-pass metabolism, avoidance of the risks and inconveniences of intravenous therapy[72,73] Because of the droplet size of nanoemulsions are very small, by applying topically it can enhanced the drug permeation as compared to other topical treatment (**Table 2**).

(Table 2: Should be placed here)

Other advantage of topical drug delivery is refer to their efficacy, which the lower daily dose of the drug by continuous drug input avoids fluctuations in drug levels.[80] Topical medication is an alternative to the oral medication and it can be easily removed in case of poisoning. [81,82] Topical medication also suitable for self-medication, which will potentially reduce the cost of treatment.[83] Apart from these advantages, there are several disadvantages of topical drug delivery system including skin irritation or contact dermatitis and poor skin permeation, due to the large hydrophilic molecules specifically in emulsion.[84] In fact, the outer layer of skin (stratum corneum) is the main stronghold against drug penetration to the deeper layers of the skin.[85]

Other alternatives such as liposome, niosome, nanostructured lipid carriers (NLC), ethosomes and solid lipid nanoparticle (SLN) could be used for safe and effective delivery of antipsoriatic drugs.[86] However, these have their limitations as listed in **Table 3**. Novel topical drug delivery systems aim for better therapeutic benefits of existing drugs, as well as safe and effective delivery of new medicines to meet the body's need, particularly for psoriasis patients.[87] Nanoemulsions are well characterized and are a promising topical drug delivery system for patients with psoriasis. Considering the benefits, there have been recent attempts to use nanoemulsions to improve existing topical drug formulations to treat psoriasis. In fact, a number of studies about nanoemulsions as topical delivery of antipsoriatic drugs have been reported. Nanoemulsions have improved topical delivery properties *in vitro*, *in vivo* and in the transdermal permeation of antipsoriatic drugs (e.g. 5-aminolevulinic acid[88] and paclitaxel[89]) over the conventional topical formulations such as liposome[90] and ethosome.[91]

(Table 3: Should be placed here)

Nanoemulsions increase the efficiency of any drugs or other molecules in the droplets to cross biological membranes, including the skin. For example, the topical delivery of betamethasone dipropionate using nanoemulsions has been reported. Shrestha et al. developed a hydrogel-thickened nanoemulsion (HTN) that offers long-term stability, and is a promising formulation for treating psoriasis.[97] Furthermore similar research on other HTN formulation was developed for belcomethasone dipropionate,[98] and was prepared by aqueous phase-titration. As a result, the optimized formulation was characterized by small particle diameter, indicating long-term stability. Moreover, the permeation study indicated that the nanoemulsion gel increased the flux and permeability coefficient as compared to the marketed gel**.**

6. Components In The Topical Nanoemulsion Formulations For Antipsoriatic Drugs

A nanoemulsion contains oil, surfactant and water in specific proportions. The selection of a suitable oil, surfactant and/ or co-surfactant to improve the topical permeation of antipsoriatic drugs is not trivial. It involves several factors, such as the kind of delivery system used, and the nature and concentration of active ingredients and excipients. Besides, the components need to be pharmaceutically acceptable, non-irritating, non-sensitizing to the skin and fall into the generally regarded as safe category (GRAS). Higher solubility of the drug in the oil phase at room temperature is another important criterion, as it would help the nanoemulsion to maintain the drug in its solubilized form even at body temperature.

6.1 Selection of oil phase

Generally, saturated and unsaturated fatty acids/fatty acid esters can be used as effective penetration enhancers for a variety of drugs such as ketoprofen,[99] ibuprofen,[100,101] lornoxicam,[102] piroxicam[103] and chloramphenicol.[104] Fatty acids enhancers with a saturated alkyl chain of C_{10}-C_{12} and a polar head group such as squalene, which is derived from vegetable oil[105-107] and enhancers with an unsaturated C_{18} alkyl chain such as oleic acid[108] and linoleic acid[109,110] can be used as an oil phase in nanoemulsion systems.

Nanoemulsion has the potential to improve the skin permeability of antipsoriatic drugs. Most of the antipsoriatic drugs possess high oil solubility and has a log *P* value of 3, which makes it suitable for being capsulated in emulsion.[111] Different types of oils has been investigated for their oil phase suitability in the antipsoriatic drug-loaded nanoemulsion system. A study by Ali *et al.* showed that Eucalyptus oil, which comes from a fast-growing evergreen tree native to Australia has excellent solubility and can enhance the skin permeation of beclomethasone dipropionate.[112] Likewise, Ghai and Sinha showed that triacetin has the maximum solubilization of talinolol.[113] Other compounds that are often used as an oil phase and as a permeation enhancer in emulsions for the topical delivery of antipsoriatic drugs are isopropyl myristate[114,115] and other natural oils such as soybean oil,[116] rice bran oil[117] and olive oil.[118]

Ali et al. investigated microemulsion system of babchi oil (Psoralea corylifolia) for the treatment of psoriasis, which improved permeation of the drug through the skin and increased patient compliance.[119] Babchi oil is used because its chief constituent psoralen is a photoactive furocoumarin that binds to DNA when exposed to UV light to form

photoproducts with a pyrimidine base. This action inhibits DNA synthesis and causes a decrease in cell proliferation.[120]

6.2 Selection of surfactant

The most important factor in the study of emulsion system is the selection of an appropriate surfactant which will efficiently emulsify or solubilize the chosen active ingredients in order to enhance the permeation of drugs.[121,122] There are four types of surfactants which could be used for the treatment of psoriasis: cationic,[123] anionic,[124] zwitterionic[125] and nonionic[126] surfactants. Nonionic surfactants are generally considered to be less irritating than ionic surfactants. They are also well known for their good biological acceptance[127,128] as well as insensitivity to electrolyte concentration and pH.[129] The hydrophilic-lipophilic balance (HLB) value has been proven to be very useful in choosing the best type of nonionic surfactant for any given oil phase. An important criterion for the selection of a nonionic surfactant is that the required HLB value to form nanoemulsions is greater than 10. Indeed, the right blend of low and high HLB surfactants leads to the formation of a stable nanoemulsion formulation.[130]

Surfactants are well known as skin penetration enhancers of drugs.[131] Either alone or in the form of micro or nanoemulsions, they were reported to enhance skin permeation of drugs by enhancing skin permeability and solubility.[132,133] The ethylene oxide-based surfactant is the most extensively investigated surfactant used in the treatment of psoriasis. For example, Tween 80 with HLB value of 15.0 was reported to accelerate fluticasone propionate,[134] tretinoin,[135] acitretin[136] and dithranol[137] permeation, whereas, Tween 20 (HLB value of 13.0) enhanced the betamethasone dipropionate and clobetasol propionate infusion in psoriasis.[138-

[141] Besides, the surfactant also improved the permeation of 5-flourouracil (used in cancer treatment) in a study with hairless mice.[142]

Vilasau et al. claimed that the mixture of surfactants could improve the stability of the emulsion system.[143] The mixture of Tween 20/Tween 80 and Span 80/Tween 80 has been proven to enhance the solubility of dithranol[137] and 8-methoxsalen,[144] respectively. The stability of emulsions can be related to two factors: (a) the chemical compatibility of hydrophilic head and tail groups and (b) better HLB value. Span 80 and Tween 80 possess an oleate-chain with 18 carbon atoms and one unsaturated bond, leading to a more stable O/W interface layer and subsequently higher emulsion stability. In comparison, Tween 20 has saturated laurate-chains with only 12 carbon atoms. Additionally, Tween 20 has a considerably higher HLB value than Tween 80.[145]

Investigations of glycolipids as nonionic surfactants in emulsions have been conducted since 1993. Alkyl polyglycosides (APGs) which are made from renewable raw materials, namely glucose and fatty alcohols, have an outstanding biodegradability, non-toxic, excellent skin- and environmental-tolerability and also have proven performance as surfactants in skincare products.[146-148] Microemulsions for use in colloidal drug delivery for diphenhydramine (DPH) using glycolipid (namely n-hexadecyl-β-D-triethylenglycol-glucopyranosid) as a surfactant or penetration enhancer was first reported.[149] The results showed that microemulsions containing glycolipid enhanced the penetration of DPH across the human breast skin. Recently, other glycolipids e.g. the branched-chain glycolipids have been used in a nanoemulsion system and was the potential enhancer for drug delivery system as compared to the formulation, which content the medium chain triglyceride only.[150]

6.3 Selection of co-surfactant

Typically, short chain alcohols are used as co-surfactants to modify the curvature and fluidity of the interfacial film, leading to the decrease of interfacial tension. Ethanol[151] and 1-butanol[152] were reported to decrease the fluidity of the interfacial film, which consequently reduce the apparent viscosity and increase the stability of the systems.[153] In fact, co-surfactants increase the maximum amount of incorporated water in the oil–surfactant system as compared to the co-surfactant free system. There have been investigations of the influence of co-surfactant on the transdermal delivery of hydrocortisone[154] and curcumin.[155] The studies show that ethanol produced the greatest enhancement in transdermal delivery followed by propylene glycol and isopropanol as compared to a co-surfactant free system. Besides, 1,2-alkanediols, especially 1,2-pentylene glycol was reported to enhance the penetration effects of dihydroavenanthramide D[156] and linoleic acid[157] which are used in the treatment of keloids and xerosis, respectively. 1,2-hexanediol, 1,2-butanediol, 1,2-ethanediol and glycerol can also be used as co-surfactants.[158]

7. Preparation of Nanoemulsions

Five methods may be applied for the preparation of nanoemulsions (covering the droplet radius size ranging from 50–200 nm)[159] namely, use of high pressure homogenisers;[160-162] microfluidization;[163-165] phase inversion composition (PIC);[167-169] phase inversion temperature (PIT)[170,171] and dilution of microemulsion.[172,173]

7.1 Use of High Pressure Homogenisers

The production of small droplets (submicron) requires the application of high energy. Simple calculations show that the mechanical energy required for emulsification exceeds the interfacial energy by several orders of magnitude. For example to produce an emulsion at $\varphi = 0.1$ with droplet diameter, $d_{32} = 0.6$ μm, using a surfactant that gives an interfacial tension $\gamma = 10$ mNm^{-1}, the net increase in surface free energy is $A\gamma = 6\varphi\gamma/d_{32} = 10^4$ Jm^{-3}. The mechanical energy required in a homogeniser is 10^7 Jm^{-3}, i.e. an efficiency of 0.1% ; The rest of the energy (99.9%) is dissipated as heat. The intensity of the process or the effectiveness (p) in making small droplets is often governed by the net power density ($\varepsilon(t)$) as illustrated above

$$p = \varepsilon(t)\, dt \qquad \mathbf{1}$$

where t is the time during which emulsification occurs.

Break up of droplets will only occur at high ε values, which means that the energy dissipated at low ε levels is wasted. Batch processes are generally less efficient than continuous processes. This shows why with a stirrer in a large vessel, most of the applied energy at low intensity is dissipated as heat. In a homogeniser, p is simply equal to the homogenizer pressure.

Several procedures may be applied to enhance the efficiency of emulsification when producing nanoemulsions: one should optimise the efficiency of agitation by increasing the interfacial dilational modulus, ε and decreasing the dissipation time. The emulsion is preferably prepared at high volume faction of the disperse phase and diluted afterwards. However, a very high φ value may result in the coalescence during emulsification. High amount of surfactant will create a smaller effective interfacial tension, γ_{eff} and this will possibly diminishes recoalescence. The

usage of surfactant mixture instead of single surfactant shows more reduction in γ the individual components. If possible dissolve the surfactant in the disperse phase rather than the continuous phase; this often leads to smaller droplets. It may be useful to emulsify in steps of increasing intensity, particularly with emulsions having highly viscous disperse phase.

7.2 Microfluidization

Microfluidization uses a high-pressure positive displacement pump operating at very high pressures (500 - 20,000 psi), which forces the product through the interaction chamber, consisting of small channels called micro-channels. The product flows through the micro-channels resulting in very fine particles of submicron range. The aqueous phase and the oily phase were combined together and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is introduced into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber of the microfluidizer repeatedly until the desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion. For example, a study to produce oil-in-water nanoemulsion containing aspirin has been reported. The results showed that microfluidization were capable of producing very fine nanoemulsions with the minimum droplet size ranging from 150 to 170 nm.[174]

7.3 Phase Inversion Composition (PIC)

A study of the phase behaviour of water/oil/surfactant systems demonstrated that emulsification can be achieved by three different low energy methods. (A) A stepwise addition of oil to a water

surfactant mixture.(B) A stepwise addition of water to a solution of the surfactant in oil. (C) Mixing all the components in the final composition and pre-equilibrating the samples prior to emulsification. For example, the system containing water/Brij 30/decane was chosen as a model to obtain O/W emulsions. The results showed that nano-emulsions with droplet sizes of the order of 50 nm were formed only when water was added to mixtures of surfactant and oil (method B) whereby inversion from W/O emulsion to O/W nano-emulsion occurred.[175]

7.4 Phase Inversion Temperature (PIT)

Phase inversion in emulsions can be one of two types. The first type is the *transitional inversion* induced by changing factors which affect the HLB of the system, e.g. temperature and/or electrolyte concentration. While another one is the *catastrophic inversion* which is induced by increasing the volume fraction of the disperse phase. *Transitional inversion* can also be induced by changing the HLB number of the surfactant at constant temperature using surfactant mixtures. For application of the phase inversion principle one uses the *transitional inversion* method using nonionic surfactants of the ethoxylate type. These surfactants are highly dependent on temperature, becoming lipophilic with increasing temperature due to the dehydration of the polyethyleneoxide chain. When an O/W emulsion is prepared using a nonionic surfactant of the ethoxylate type is heated, then at a critical temperature (the PIT), the emulsion inverts to a W/O emulsion.[176] At the PIT the droplet size reaches a minimum and the interfacial tension also reaches a minimum. However, the small droplets are unstable and they coalesce very rapidly. By rapid cooling of the emulsion (temperature 2 - 4^{o}C below the PIT), very stable and small emulsion droplets could be produced, which due to the changes in curvature H of the interfacial region, as the system changes from O/W to W/O. For O/W system and normal micelles, the monolayer curves towards the oil and H is given a positive value. For a W/O emulsions and

inverse micelles, the monolayer curves towards the water and H is assigned a negative value. At the inversion point (HLB temperature) H becomes zero and γ reaches a minimum.[173]

7.5 Dilution of Microemulsions

The simplest technique of preparing the nanoemulsion is through the spontaneous method, by stirring the emulsion mixture directly without involving any higher energy of emulsification. The conversion of microemulsion to nanoemulsion could also be promoted by the dilution of microemulsion with another material.[172] Normally the nanoemulsion can be formed by diluting the O/W microemulsion with water.[173] During this process, a part of the surfactant and/or cosurfactant diffuses to the aqueous phase. The microdroplets are no longer thermodynamically stable and consequently lead to the formation of a nanoemulsion. In contrast, the W/O microemulsion system reacts differently when diluted with water. The resulting nanoemulsion depends on the starting composition of the microemulsion. In addition, Pons et al. also reported that the dilution of the W/O microemulsion with water always gives a bigger droplet size compared to those produced by dilution of the O/W microemulsion.[177] In another dilution method of the microemulsion, alcohol is used as the cosurfactant.[178] In this case alcohol would diffuse from the oil into the aqueous phase causing the system to become no longer thermodynamically stable. The surfactant concentration in this system is not sufficiently high to sustain a stable minimum value of the droplet interfacial tension ($\gamma < 10^{-2}$ Nm^{-1}), thus converting the system to a nanoemulsion.[179]

8. Steric Stabilisation and the Role of the Adsorbed Layer Thickness

Since most nanoemulsions are prepared using nonionic and/or polymeric surfactants, it is necessary to consider the interaction forces between droplets containing adsorbed layers (Steric Stabilization).[180] When two droplets each containing an adsorbed layer of thickness δ approach to a distance of separation h, whereby h becomes less than 2δ, repulsion occurs as result of two main effects: (i) Unfavourable mixing of the stabilizing chains A of the adsorbed layers, when these are in good solvent conditions. This is referred to as the mixing (osmotic interaction, G_{mix}, and is given by the following expression,

$$\frac{G_{mix}}{kT} = \frac{4\pi}{3V_1}\phi_2^2\left(\frac{1}{2} - \chi\right)\left(3a + 2\delta + \frac{h}{2}\right) \qquad \mathbf{2}$$

where k is the Boltzmann constant, T is the absolute temperature, V_1 is the molar volume of the solvent, φ_2 is the volume fraction of the polymer (the A chains) in the adsorbed layer and χ is the Flory-Huggins (polymer-solvent interaction) parameter. It can be seen that G_{mix} depends on three main parameters: the volume fraction of the A chains in the adsorbed layer (the more dense the layer is the higher the value of G_{mix}). The Flory Huggins interaction parameter χ (for G_{mix} to remain positive, i.e. repulsive, χ should be lower than 1/2). The adsorbed layer thickness δ (ii) Reduction in configurational entropy of the chains on significant overlap - This referred to as elastic (entropic) interaction and is given by the expression,

$$G_{el} = -2\nu_2 \ln\left[\frac{\Omega(h)}{\Omega(\infty)}\right] \qquad \mathbf{3}$$

where v_2 is the number of chains per unit area, $\Omega(h)$ is the configurational entropy of the chains at a separation distance h and $\Omega(\infty)$ is the configurational entropy at infinite distance of separation. Combination of G_{mix}, G_{el} with the van der Waals attraction G_A gives the total energy of interaction G_T,

$$G_T = G_{mix} + G_{el} + G_A \qquad 4$$

Fig.3 gives a schematic representation of the variation of G_{mix}, G_{el}, G_A and G_T with h. G_{mix} increases very rapidly with decrease of h as soon as $h < 2\delta$, G_{el} increase very rapidly with decrease of h when $h < \delta$. G_T shows one minimum, G_{min}, and it increases very rapidly with decrease of h when $h < 2\delta$. The magnitude of G_{min} depends on the following parameters: The particle radius, R, the Hamaker constant, A, and the adsorbed layer thickness, δ.

(Fig.3. Should be placed here)

As an illustration, **Fig.4** shows the variation of G_T with h at various ratios of δ/R. It can be seen from **Fig.4** that the depth of the minimum decrease with increasing δ/R. This is the basis of the high kinetic stability of nano-emulsions. With nano-emulsions having a radius in the region of 50 nm and an adsorbed layer thickness of say 10 nm, the value of δ/R is 0.2. This high value (when compared with the situation with macroemulsions where δ/R is at least an order of magnitude lower) results in a very shallow minimum (which could be less than kT).

(Fig.4. Should be placed here)

The above situation results in very high stability with no flocculation (weak or strong). In addition, the very small size of the droplets and the dense adsorbed layers ensures lack of

deformation of the interface, lack of thinning and disruption of the liquid film between the droplets and hence coalescence is also prevented.[181]

9. Conclusions

Although significant progress has been made in understanding the mechanism of action of psoriasis and in identifying effective treatments, the search for the optimal treatment strategy for psoriasis still remains a major challenge. Many topical treatments are available for the treatment of psoriasis, but there is a lack of uniformity of approach which is acceptable for moderate to severe psoriasis. Psoriasis is a lifelong disease which causes the patients to have a continuous medication treatment. Thus, there is an urgent need to widen the medication prescription and always try to improve the treatment research, no matter from whichever methods, drugs used or the delivery therapy perspective. In addition, there is still no available treatment for psoriasis which is safe, effective, patient's compliance and affordable to completely cure the disease.

Nanoemulsions, as one of a novel carrier obviously have the potential to overcome many challenges associated with topical antipsoriatic therapy. This vehicle could possibly provide a better option 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. It helps patients to be more comfortable and confident with their own body. Hence, the psychosocial problem could be overcome.

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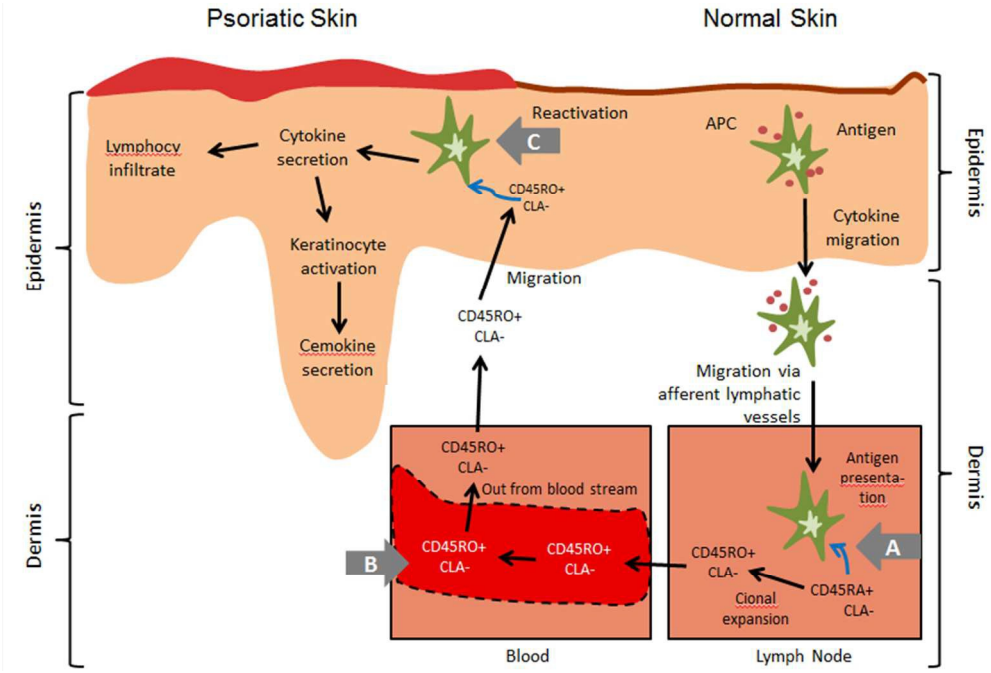
Figure Captions

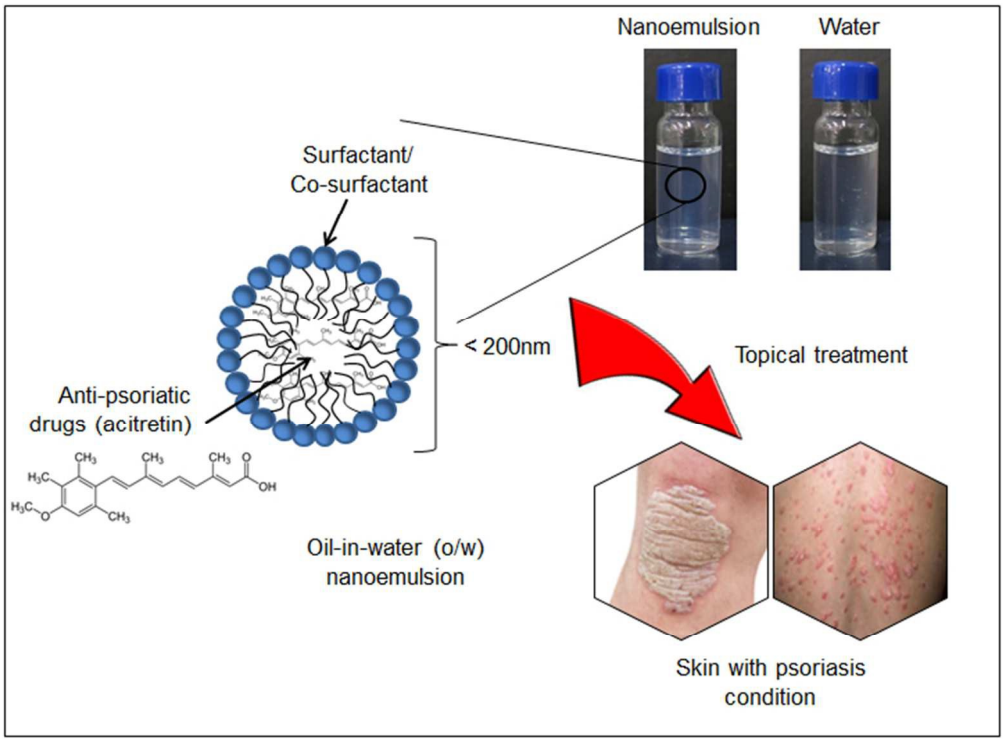
Fig. 1: The major pathway of psoriasis pathology

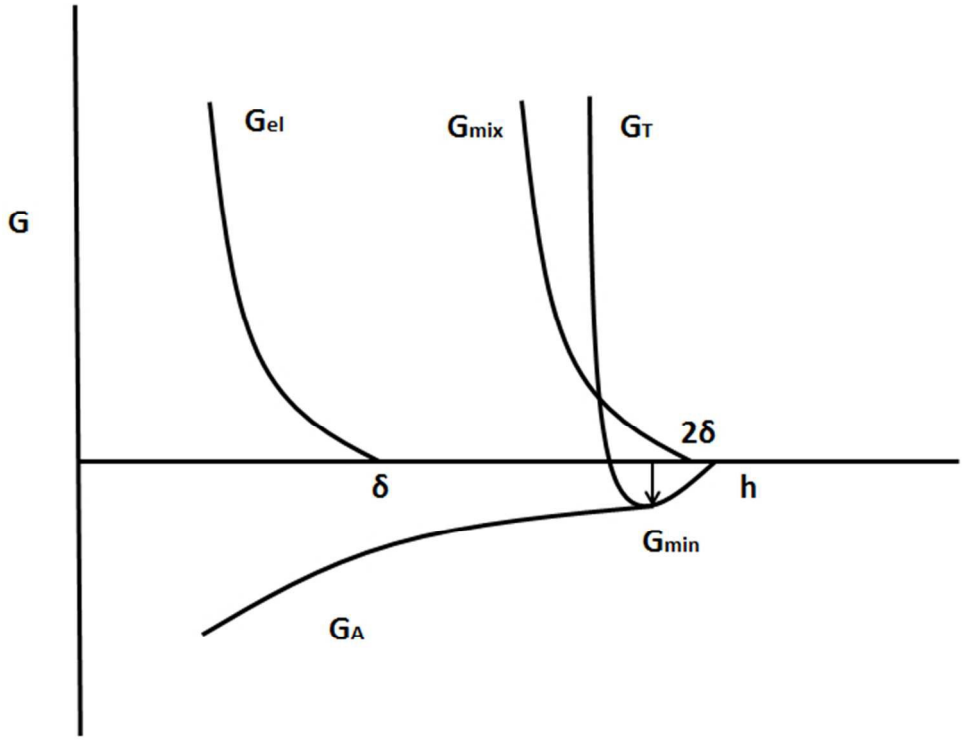
Fig. 2: Nanoemulsion system as a potential enhancer for topical drug delivery system

Fig. 3: Variation of G_{mix}, G_{el}, G_A and G_T with h.

Fig.4: Variation of G_T with h with increasing δ/R.







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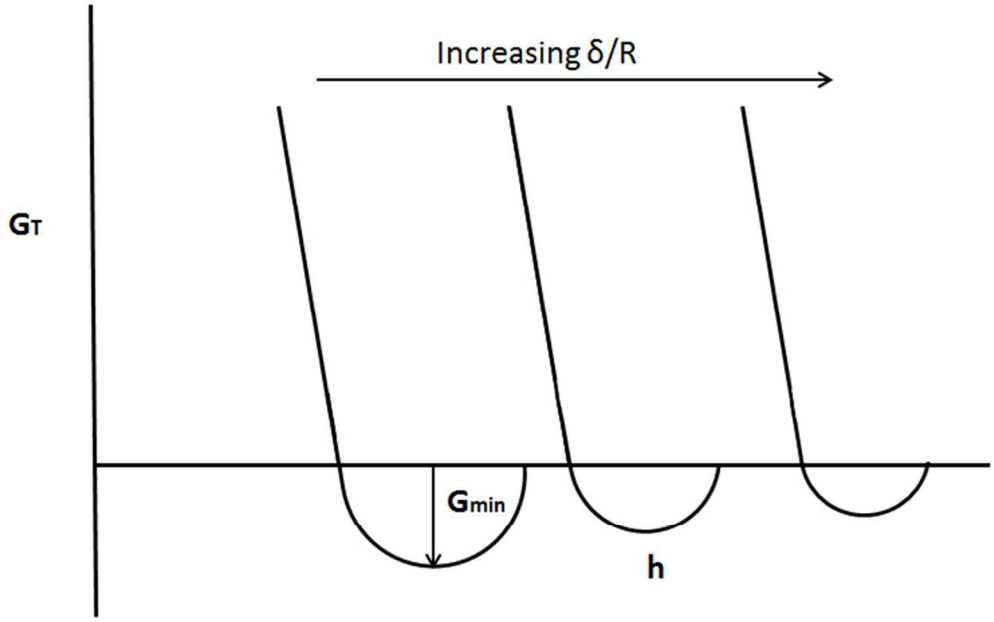

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Table 1

Examples of commercial topical formulation of antipsoriatic drugs (Retrieved from www.mims.co.uk)

Marketed Names	Drug	Form	Ref.
Calcipotriol® Ointment	Calcipotriol	Ointment	34
Capasal®	Coal tar	Shampoo	35
Carbo-Dome®	Coal tar	Cream	36
Ceanel® Concentrate	Cetrimide, Phenylethyl alcohol, Undecenoic acid (Antifungal and antibacterial)	Shampoo	37
Cocois®	Coal tar, Coconut oil, Salicylic acid, Sulfur	Oitment	38
Curatoderm®	Tacalcitol	Oitment	39
Curatoderm® Lotion	Tacalcitol	Lotion	39
Dermax® Therapeutic Shampoo	Benzalkonium chloride (Antifungal and antibacterial)	Shampoo	39
Dithrocream®	Dithranol	Cream	40
Dithrocream® 2%	Dithranol	Cream	34
Dovobet® Gel	Betamethasone/Calcipotriol	Gel	41
Dovonex® Ointment	Calcipotriol	Ointment	37
Exorex®	Coal tar	Lotion	42
Micanol®	Dithranol	Cream	43
Polytar® Plus Liquid	Coal tar	Solution	44
Psoriderm® Cream	Coal tar	Cream	45
Sebco®	Coal tar, Coconut oil, Salicylic acid, Sulfur	Ointment	45
Xamiol®	Betamethasone/Calcipotriol	Gel	46

Table 2

Comparison of nanoemulsions with other topical treatment

Drugs	Comparison	Ref.
Celecoxib	- The drug permeation and anti-inflammatory effects on carrageenan-induced paw oedema in rats of nanoemulsion were higher compared to the gel formulations.	74
	- Increase in bioavailability as compared to an oral capsule formulation in rats.	75
Indomethacin	- The drug permeation from nanoemulsions were higher compared to the conventional indomethacin	76
Aspirin	- Increased the efficacy of the drug compared to an aspirin suspension - Anti-inflammatory effects on carrageenan-induced paw oedema in rats of nanoemulsion were higher compared to the aspirin suspension	77
Ibuprofen	- The drug permeation from novel nanoemulsion were higher compared to the novel nanoemulsions	78
Ketoprofen	- High drug permeation rate from nanoemulsion compared to Fastun® gel	79

Table 3

The alternative techniques for drug delivery and its limitations

Technique	Principle	Antipsoriatic drugs	Limitations	Ref.
Liposomes	Bilayer vesicles formed from phospholipids and cholesterol	Calcipotriol	poor stability and limited penetration ability	[92]
Niosomes	Microscopic lamellar structures formed on admixture of a nonionic surfactant, cholesterol and a charge inducing agent, with subsequent hydration in aqueous media	Methotrexate, Cyclosporine	Less skin penetration, do not reach up to deeper skin layer	[93]
Nanostructured lipid carrier	Produced with solid and liquid lipids and surfactants, with distorted crystalline lattice	Calcipotriol, Methotrexate	Poor stability, low drug loading.	[94]
Ethosome	Composed of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatidic acid), high concentration of ethanol and water	Psoralen	Poor skin penetration, skin irritation	[95]
Solid lipid nano-particle	Produced with one single solid lipid and surfactants, with perfect crystalline lattice	Dithranol	Poor stability	[96]