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Nanoemulsions A New Topical Drug Delivery System For The Treatment Of Acne

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ABSTRACT: The main aim of this review is to investigate published research that related nanoemulsions formulations as the for improving of acne and to evaluate the recent developments and future of nanoemulsions for acne care. Nanoemulsion, skin penetration, acne vulgaris, topical drug delivery using as keywords were sequentially searched three databases (PubMed, ScienceDirect, Google Scholar). Following the removal of duplications and irrelevant results, research articles and reviews were included in the final literature overview. Systemic therapy includes anti-inflammatory and antibiotics drugs that can bring on undesirable adverse. On the other hand, the low solubility in water of the drug and insufficient penetration through the skin limits the drugs's topical administration. Innovative topical nanoemulsion systems can be very impactful to decrease the side effects of drugs and provide tremendous drug penetration through the skin. They provide advantage over traditional topical medications by enhancing bioavailability of drugs, and the persistency of drugs in the skin layers. Furhmore, nanoemulsions have significant potential to overcome the drawbacks of the conventional dosage forms contains natural molecules and essential oils for acne thepaphy. Additionally, some comparative studies showed that nanoemulsions increase the permeability of the drug molecule through the skin more than other nanocarriers (SLN, NLC).

KEYWORDS: Acne vulgaris; drug delivery; nanocarriers; nanoemulsion; skin penetration; topical

1. INTRODUCTION

Acne that qualified with whiteheads and blackheads comedones, scaly red skin, large papules, pinheads, pimples, and possibly scarring, generally occurs in the chest, back, neck, and face [1]. Acne vulgaris is a inflamatory skin disorder that occur in any life period of people. Although acne seems in any period of life, it usually occurs in adolescence commonly. 85% of adolescent girls and 95% of adolescent boys affected by acne vulgaris and 20% of them have moderate to severe acne [2]. The prevalence of acne is higher in dark skin (black or spanish origin) women compared light-skinned women (Asian, Indian). Acne induce uncomfortableness, depression, deformity, and even persistent damage to the skin in adolescent individuals. It creates a lack of self-confidence and anxiety in patients and leads to low efficiency in daily life [3]. Acne is caused by the effect of hormones on the sebaceous glands. Excessive production of sebum causes epidermal hyperliferation. Preclude permanent scarring as full as possible, controlling and treating existing acne lesions, restrict the duration of the ailment, and to reduce morbidity is the main aim of acne treatment [3]. While planing treatment of acne, some individual patient's circumstances such as current medical condition, illness situation, the severeness of the wound, endocrine history, and the choice treatment of the patient must be taken into. The main substantial treatment of acne is improve physical appearance [4]. Acne can be treated with the topical or systemic application. In addition, using herbal preparations or other without medications treatments such as laser and phototherapy may be other ways to treat acne. Patients can apply topical products by themselves without needing health staffs. Additionally, topical therapy is an effective treatment owing to direct application to the affected area. Nevertheless, the Stratum Corneum (St. Corneum) outermost layer of skin form tremendous barrier system for drug agents. Low penetration of therapeutic agents from the skin causes non-effective treatment [5]. Especially, topical therapy can be non-effective for moderate to severe acne types due to these drawbacks. Systemic therapy can be added to treatment programs to support topical therapy for moderate to severe acne [1]. Oral antibiotics (erythromycin, doxycycline, and azithromycin, tetracycline, minocycline), isotretinoin and hormones constitute systemic therapy [6]. However, along with

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the oral administration of these drugs, some side effects may also emerge. Photosensitivity, cheilitis, nose bleeds, , temporary worsening of lesions, dry skin, secondary infection and increased serum lipids are among side effects of oral administration isotretinoin. Resistance to antibiotics is one of the problems restricting oral intake of antibiotics [7, 8]. Such problems indicate the need for new approaches that are effective in the treatment of acne.

1. CARE OF SKİN WITH ACNE VULGARİS

1.1. Pathogenesis of acne

The most important duty of the sebaceous gland is to secrete sebum [9]. Non-polar lipids that are synthesized from sebum glands constitute sebum [10]. Cholesterol esters, as well as squalene and wax esters, triglycerides, and some free cholesterols, constitute lipid mixture [11]. Various factors such as cell growth, the metabolic formation of lipids, endocrine metabolic process, and cytokine and chemokine release regulate sebum production. Impaired sebaceous gland activity associated with excessive sebum production and changes in sebum fatty acid balance, follicular hyperkeratinisation, disorders of the hormone nature, stimulation of infection and disfunction of the congenital and adaptative immunities are some of the causes that underlying acne vulgaris. These failures cause the pilosebaceous unit to fail, leading to the transformation of pores on the skin into microcomedones, even comedones and inflammatory lesions [2]. Bacterial antigens that settle in pores can aggravate inflammation [12, 11]. In the studies conducted to determine the relationship of acne with genetics, serious evidence has been found to prove that acne can be a hereditary disease [13, 14]. Factors such as ultraviolet rays and environmental pollution [15], diet, smoking [16], daily stress [17] can also trigger the formation of acne or make the existing acne worse. Major factors leading acne are shown in Table 1 [1].

Table 1. Major factors causing acne

Factor	Definition
Excessive sebum production	The most important factor causing acne formation is that the skin produces a large amount of sebum. Sebum provides the necessary environment for the formation of comedones and propionibacterium acnes (P. Acnes) bacteria to accumulate here.
Follicular hyper keratinization	Inhibition of the pilosebaceous canal causes enlargement of acne lacerations. The obstacle is produced by the growth of supportive keratinized cells within the channel, which creates an effect that blocks the flow of sebum. It can also cause relatively hyperproliferation of corneocytes due to irregularities in sebaceous lipids. The formation of comedones may be due to local linoleic acid deficiency in the pilosebaceous duct.
Abnormal bacterial function	Staphylococcus epidermidis and P. acnes tend to colonize skin with acne. P. acnes increases inflammation by stimulation of various chemotactic factors and separation of comedones.

1.2. Treatment of acne

Soreness, itching, and pain are some of the symptoms of acne. The psychological consequences are such that they cannot be underestimated [18]. Emotional disorders, thoughts of self harm, concerns, stress related signs, shameness, and unsocial are some of psychological results [19] that can be solved with effective treatment [20]. To provide effective treatments can take months [7]. Management should include a safe treatment and reduce psychological burden through emotional and social support. The main purpose of acne treatment can be listed as follows [21];

- Controlling and treating ongoing acne
- Preventing persistent blemish as much possible
- Limiting the length period of the disease and to minimizing morbidness

Present medical circumstance, ailment condition, the severeness of the wounds, endocrine report, and the treatment choice of the patient such oral or topical must be considered when planning a treatment regimen

[3]. Acne vulgaris be able to manage herbal preparations or without medication treatment (optical therapy) addition to topical and systemic therapy. Nevertheless, combination therapy is the most successful regimen for acne [3]. Topical therapy is effective to treat mild to moderate acne. Systemic therapy can be useful to support topical therapy at severe acne conditions [1]. Retinoids, antibiotics, and herbal agents are commonly used as topical products. Topical treatment affects only the application site and can cause irritation on the skin. To overcome this drawback lower concentrations are used in formulations [7]. Systemic antibiotics (e.g. doxycycline, erythromycin, minocycline azithromycin, and tetracycline), isotretinoin, and hormone treatment are used as systemic monotherapy or combination therapy with topical therapy to treat severe acne [6]. Treatment methods for acne are shown in Table 2 [3].

Table 2. Treatment methods for acne

Treatment Methods	Examples
Topical	**Retinoids:** Tretinoin, adapalene, tazarotene, isotretinoin, retinoyl-β-glucuronide, motretinide **Antibiotics:** Erythromycin, clindamycin **Others:** Dapsone, chemical peels, hydrogen peroxide, sodium sulfacetamide, sulfur, niacinamide, corticosteroids, triclosan, benzoyl peroxide, salicylic acid, azelaic acid
Systemic	**Retinoids:** Isotretinoin **Antibiotics:** Levofloxacin, minocycline, erythromycin, doxycycline, co-trimoxazole, roxithromycin, lymecycline, azithromycin, clindamycin **Hormonal:** Contraceptives **Others:** Zinc sulfate, clofazimine, ibuprofen, corticosteroids
Complementary and Alternative Medicines	Amaranth, achillea millefolium, black cumin, asparagus, arnica, basil oil, safflower oil, bay, birch, Eucalyptus dives, black walnut, antimicrobial peptides, borage, Brewer's yeast, benzoin, bittersweet nightshade, burdock root, cucumber, Du Zhong extract, coriander, commiphora mukul, calendula, chaste tree, chamomile, garlic, celandine copaiba oil, duckweed, fresh lemon, English walnut, geranium, grapefruit seeds, rose myrtle, green tea, jojoba oil, juniper twig, labrador tea, lemon grass, lemon, minerals, neem, pea, oak bark, orange peel, orange, probiotics, Withania somnifera, Oregon grape root, yerba mate extract, patchouli, petitgrain, pomegranate rind extract, poplar, pumpkin, turmeric, , rhubarb, Rosa damascena, onion, rosemary, vinegar, rue, sandalwood, pine, seaweed, soapwort, specific antibodies, stinging nettle, sunflower oil, , taurine bromamine, tea tree oil, thyme, , vitex, witch hazel, sophora flavescens, resveratrol and taraxacum officinale
Physical Treatment	Intralesional corticosteroids, cryoslush therapy, comedone extraction, electrocauterization, cryotherapy, and optical treatments

Topical treatment has less drawbacks compared to systemic treatment. While oral retinoids (isotretinoin) has some adverse effects such as nose bleeds, cheilitis, dry skin, secondary inflammation, imparmanent aggravete of wounds, photosensitivity, and enhanced serum fats, topical retinoids have minor problems such as their tolerability and cutaneous irritation. Furthermore, systemic antibiotic use poses a risk of developing resistance, while topical antibiotics are a minor concern. [7, 8, 22, 23]. On the other hand, topical drugs low penetration profile through the skin barrier is one of the major drawbacks. To overcome these shortcomings, topical drugs must be applied for a long period of time. This can create problems such as reducing patient compliance and boosts antibiotics resistance [24]. These disadvantages encouraged researchers to develop innovative and effective systems. Table 3 indicates some of the topical anti-acne drugs [1].

Table 3. Some of the topical anti-acne drugs

Drug	Mechanism of action	Advantages	Drawbacks
Topical retinoids (Isotretinoin, Adapalene, Tretinoin, Metretinide, Tazarotene)	They target the micro comedo precursor lesion of acne. They may show anti enflamatuvar properties	It targets abnormal follicular epithelial hyperproliferation, reduces follicular occlusion, micro comedones, and inflammatory acne lesion. It should be the first choice for most acne types and is much more effective in inflamed acne when combined with topical antimicrobials.	Burning sensation, irritant dermatitis, erythema, scaling,
Topical antibiotics (Clarithromycin, Clindamycin, Nadifloxacin , Erythromycin, Azithromycin)	It inhibits the growth of P. acne and reduces inflammation.	Erythromycin and clindamycin, which are also used as topical antibiotics, are the most preferred in the treatment of acne.	Erythema, peeling, itching, dryness, burning, bacterial resistance, cross resistance
New agents (Benzoyl peroxide, Clindamycin Tretinoin)	Prevent and eliminate the development of P. acne resistance.	Reducing both inflammatory and non-inflammatory acne lesions.	Skin irritation, burning, erythema, peeling, dryness, skin sensitivity
Natural agents (Tea tree oil, Azelaic acid)	It is effective for mild to moderate acne when applied topically at a concentration of 20%.	Act as antimicrobial, anti-inflammatory, and antioxidant.	Skin irritation

1.3. Novel topical approach

Recently, developments in formulation technology have enabled active molecules to penetrate deeper into the layers of the skin and increase the stability of the molecules. Thus, tolerability and efficiency are increased with lower molecular concentrations [25]. Innovative topical drug carriers are highly preferred in order to reduce the possible undesirable effects of drugs and increase the passage of molecules through the skin. To develop successful topical formulations, controlled release and biodegradation should be significantly considered [26]. Some innovative drug delivery systems (liposomes, transferosomes, emulsomes, nanoemulsions, microemulsions, niosomes, and nanolipid carriers) are widely accepted as enabling drug delivery through the skin. [27].

The primary advantages of nanocarriers are listed below [1].

- Large drug loading capacity
- Maintaining the physicochemical properties of the loaded drug
- Behaving as penetration enhancers
- Acting as a local repository for sustained drug release
- Targeting the drug molecule to the desired tissues without damaging other tissues
- Reducing harmful effects
- Contains drug molecules with different solubility
- Containing hydrophobic and lipophobic drugs simultaneously
- Provide protection from degradation such as oxidation and hydrolysis
- Provides rapid and effective absorption of the drug molecule.
- Increase bioavailability

- Increasing the residence time of the drug in the target area
- Improve the St. corneum characteristic

1.3.1. Colloidal dispersions

Nanocarriers encapsulate or carry drugs with sizes commonly between 1 - 200 nm. They can be used in different administration ways such as parenteral, oral, and transdermal. Various materials such as lipids, polymers, gold are used to manufacture nanocarriers to be utilized for the treatment of acne. A range of nanocarriers such as vesicular systems (Invasomes, niosomes, bilosomes, liposomes, cerasomes, ethosomes and cubosomes and), colloidal dispersions (microemulsions and nanoemulsions), polymeric carriers (micelles, nanoparticles, and nanosponges), lipidic nanoparticles (nanostructured lipid carriers (NLC), solid lipid nanoparticles (SLN)), nanocapsules and nanocrystals have been researched [28]. Nanocarriers that are applied topically are not used only for effective local administration, they are also used to transport active molecules to deeper tissues for systemic therapy [29].

Up to now, many formulation strategies have been investigated to deliver drug through the skin. Most skin products are colloidal dispersions include coarse emulsions, that is, containing immiscible oil and water phases. Nevertheless, there are some restrictions of conventional emulsions, such as bigger droplet size, low amount transportation through skin, immediate volatility of some ingredients, instability origin the environmental factors, and photo-instability, for achieving clinical therapy on skincare. Comprehensive researches have been performed with nanotechnology to overcome some problem of molecules that have highly irritant, less soluble, highly volatile, charged surfaces and photosensitive properties [30]. Nanoemulsion is considered as the best drug delivery system due to its fluid structure, significant interaction with skin cells, small droplet size, effective penetrating ability, and even its ability to transmit irritating, volatile and high molecular weight molecules [31]. Long term stability issues of nanoemulsions should be solved to encourage nanoemulsions as industrial products.

1.3.2. Nanoemulsions

Recently, nanoemulsions gained significant interest to be used for the treatment of acne. Nanoemulsions, consist of two immiscible liquids that have nano-sized droplets. The immiscible liquids consist of commonly oil and water. Emulsifiers and co-emulsifiers provide a homogeneous distribution of these two liquids by reducing the tension at the interface of two immiscible liquids [32-34]. They are isotropic, translucent, and heterogeneous systems. Nanoemulsions are stable thermodynamically and kinetically [31], droplet sizes are between 20 -400 nm, with uniform size dispersion [32, 35] and differ from other emulsions according to its physicochemical and biological properties. There are two main manufacturing methods to develop nanoemulsions. High pressure homogenizers, ultrasonication, and microplasticizers are high energy methods, while phase inversion and solvent displacement are examples of low energy emulsification methods [36-38]. Nanoemulsions have many advantages over conventional emulsions in terms of high stability, large interfacial area, rapid absorption through enterocyte internalization, ability to increase drug solubility and thereafter bioavailability [33, 34]. However, compared to other nanocarrier systems, nanoemulsions have advantages such as low likelihood of side effects, high drug loading for topical preparations, and high permeability through the skin [39, 6]. Foams, creams, gels, liquids, and sprays are the most common dosage forms to formulate nanoemulsions [40, 41]. Some of the patented nanoemulsion-based skin care products are listed in Table 4.

Table 4. Recent patents of topical nanoemulsion for acne

Patent claim	Patent no	Assignee	Reference
To reduce the amount of P. acnes by applying topical nanoemulsion to a person with acne, eliminating existing acne and preventing new acne formation.	US20190000761A1	NANOBIO CORP	[42]
A plant (Radix polygoni Officinalis, Radix Angelicae Sinensis, cactus, Radix Paeoniae Alba, saffron, honeysuckle, coix seeds) nanoemulsion acne cream treats acne's root causes and symptoms.	CN106389136A	NANTONG SNAKEBITE THERAPY INST	[43]
An herbal formulation of topical nanoemulsion for treating acne-related skin disorders. Nanoemulsion formulation contains an aqueous phase (comprising a therapeutic agent, rose water and/or lemon juice), an oil phase (containing essential oils such as tea tree oil, basil oil, rosemary oil, lavender oil, jojoba oil, bergamot oil, clove oil, and peppermint oil), a non-ionic surfactant, and an accessory surfactant.	RU2011131256 (A)	СУНЕВ ФАРМА СОЛЮШН ЛИМИТЕД	[44]
A method for treating and preventing acne or P. acnes infection in a subject comprising topically administering to the subject in need thereof an anti-acne nanoemulsion composition.	CA2750233 (A1)	NANOBIO CORP	[45]
Methods and compositions for transdermal delivery. Administration of a nanoemulsion (for example, nanoparticle composition) comprising at least one therapeutic drug such as botulinum toxin to treat disorders and/or conditions related to the dermis level of the skin. Such disorders include acne, hydrosis, bromhidrosis, chromhidrosis, rosacea, fallen hair, dermal infection, and/or actinic keratosis.	JP2018009026 (A)	ANTERIOS INC	[46]

Nanoemulsion droplets that contain drugs can penetrate through hair follicles easily owing to small diameter sizes, and target P.acnes colonization to prevent inflammation [47]. Because of their low water solubility and high volatility, some essential oils, which are known to be effective in the treatment of acne, tend to reduce their antimicrobial activities when they are prepared as commercial products [48]. The problem can be overcome by incorporating such natural actives into well-designed nanoemulsion-based delivery systems [49]. The high stability of nanoemulsion-based delivery systems for commercial preparations of such active substances is an important solution [50]. It is known that natural essential oils are used in the treatment of inflammatory diseases such as acne, especially in order to prevent antibiotic resistance in bacteria and the side effects of antibiotics [51]. It should not be forgotten that especially such natural active molecules, antimicrobial effects against pathogens are highly preferred by the public due to the safety of products of natural origin. Also, Ingredients as surfactants in nanoemulsion play a role to increase skin penetration in topical formulations [6]. The skin has hydrophobic character, therefore oil phase of nanoemulsion that has hydrophobic properties increases skin penetration of drug molecules [52]. Surfactant is one of the three main components of nanoemulsion with the oil and aqueous phase. Surfactants has properties that solubilize lipids of St. Corneum which comprise the main barrier of skin. Therefore, Surfactants act as penetration enhancers for drug molecules in topical formulations through the skin [53]. Since moistened skin is generally more suitable for the passage of drug molecules through the skin, the aqueous phase forming the nanoemulsion contributes to increased penetration through the skin [54].

Miastkowska et al. determined the release kinetics of the active ingredient from the nanoemulsion formulation by developing a loaded topical nanoemulsion carrier system of isotretinoin. [55]. Coconut oil as an oil phase and polysorbate 80 as a surfactant was used to formulate isotretinoin loaded o/w (% 0.05 wt) nanoemulsion. They determined drug release kinetics at 32°C using Spectra/Por Standard Regenerated Cellulose (RC) membrane. The amount of drug in the receptor medium was determined using the UV-Vis spectroscopy method. In results, they detected a zero order kinetic model for the drug release mechanism. As a result, it was found that isotretinoin loaded nanoemulsion can be used as a carrier for controlled drug release with long-term treatment efficacy and minimized undesirable effects.

Clares et al. developed retinyl palmitate (RP) loaded liposomes (LPs), solid lipid nanoparticles (SLNs) and nanoemulsions (NEs), to compare in terms of skin permeation, photostability and biocompatibility,

undesirable topical side effects [56]. In the results, they found that SLN showed better phosphostability for RP than LPs and NEs. After 38 hours, the cumulative amount of drug penetrating human skin was 6.67 ± 1.58 µg, 4.36 ± 0.21 µg and 3.64 ± 0.28 µg for NEs, LPs and SLNs, respectively. The highest flux was found in NEs compared to other carrier systems (NE: 0.37 ± 0.12 µg/h, SLN: 0.10 ± 0.05 µg/h and LP: 0.15 ± 0.09 µg/h). The skin retention was significantly higher in LPs than NEs and SLNs. Although the whole developed nanocarriers were found out biocompatible, the drug delivery systems that most disrupted the skin was NEs.

Saburi et al. to determine the therapeutic efficacy of tretinoin (TRE), coarse emulsion containing 0.05% TRE and trethionine loaded nanoemulsion (TRE-NE) were compared [57]. NE-TRE was developed by choosing the high energy method to create the nano-sized emulsion structure. The size and distribution of acne lesions on both sides of the face and porphyrin production were compared to determine the efficacy of the formulations by conducting a clinical study. In result of the pilot clinical study, after the topical application of NE-TRE, both acne lesions and the porphyrin production, was found to be improved importantly. It was concluded that nanoemulsion formulation may be appropriate in terms of therapeutic efficacy and sufficient loading capacity of TRE as a novel drug delivery system.

Poomanee et al. developed a nanoemulsion formulation loaded with Mangifera indica L. seed extract. They used the response surface methodology to improve the stability of the extract and the skin permeability [58]. The central composite design was utilized to optimize and evaluate some influencing factors (% co-surfactant (PEG-7 glyceryl cocoate), hydrophile-lipophile balance (HLB), and surfactant-to-oil ratio (SOR)) on physical properties of the nanoemulsions. Extract-loaded nanoemulsions were stored at diverse ambients conditions. Their antibacterial effects against Propionibacterium acnes and physicochemical properties to the initial situations were compared. Also, ex vivo skin permeation was explored. The extract-loaded nanoemulsions had nano-sized (26.14 ± 0.22) spherical droplets and PDI value was 0.16 ± 0.02. The nanoemulsion-based formulation had a more stable structure compared to the extract solution and reduced the microbial contamination of the extract. Ex vivo studies indicate that nanoemulsion contain extract can reach to deeper layer of the skin such as viable epidermis and dermis layers.

Najafi et al. developed nano-emulsions that contain 0.1% adapalene to assess therapeutic efficiency and its easing of using [59]. To determine the safety and efficacy of adapalene-containing nano-emulsion gel, it was compared with a commercially available gel containing the same amount of adapalene. As a result of the in vitro permeation test, no significant difference was found between the nano-emulsion gel contains adapalen and the commercially available gel in terms of the amount of active molecule passing through the skin. However, when the distribution of adapalene in the skin was examined, it was observed that the nanoemulsion gel containing adapalene was retained in the dermis in higher amounts than the commercial adapalene preparation. In vivo skin irritation test didn't show irritancy for the adapalene loaded nanoemulsion gel. After the treatment of rats for 90 days, histological analysis of liver and liver enzyme activity was investigated. The drug wasn't detected in the blood/liver in the results. Consequently, the researchers decided that adapalene loaded nano-emulsion gel can be very effective as a novel topical delivery system to treat acne.

In the next study they designed a study to assess efficacy and safety of the optimized tea tree oil nanoemulsion containing adapalene gel (TTO NE + ADA Gel) in comparison with 0.1% adapalene marketed gel (ADA Marketed Gel) [60]. A total of 100 patients were administered TTO NE + ADA Gel or ADA Marketed Gel at night once a day for 12 weeks. At 4, 8 and 12 weeks, the number of acne lesions (total, inflammatory and non-inflammatory) and acne severity index were evaluated by considering factors such as dryness, erythema, burning sensation and irritation. Compared to ADA Marketed Gel, there was a significant reduction in inflammatory and non-inflammatory acne lesions overall and at each measurement condition (p-value < 0.001 for all). The mean acne severity index was significantly reduced with TTO NE + ADA Gel (p value < 0.001). Dryness was higher in the TTO NE + ADA Gel group, but was also common in the control group. At the end of the study, it was concluded that TTO NE + ADA Gel is more effective in the treatment of acne vulgaris compared to the commercial product on the market.

Hosny et al. used isotretinoin, which is widely used in acne treatment and has a hepatotoxic effect, in form of nanoemulsion combinated with quercetin to wanted take advantage of the hepatotoxic protective property of quercetin [61]. The hepatotoxicity of topical application was evaluated in vivo. An enhanced steady-state flow (Jss) of the optimized formulation and increased percent permeability of ITT (52.11% ± 2.85%) and QRS (25.44% ± 3.18%) were confirmed by permeation studies. In in vivo animal studies, the optimized formulation in this study was found to have superior hepatoprotective activity compared to other drug formulations and commercially marketed products. It has been concluded that the optimized ITT

formulation according to the data obtained in clinical studies can be very safe and effective in the treatment of acne vulgaris.

4. CONCLUSION

Acne is a common inflammatory skin disease that has negative impact on human life quality. Both acne and acne treatment have been explored comprehensively. Since there is much pathogenesis of acne lesions there are diversity of many treatment methods available. Among these methods conventional topical, systemic therapy, or combination therapy for acne also found. However, undesirable side effects and antibiotics resistance restricts systemic therapy while insufficient active molecule penetration through the skin and insufficient solubility of the drug molecules in the topical formulation limits conventional topical therapy. The exploration was intensived on nanocarriers especially nanoemulsions that have great potential to overcome the drawbacks of systemic therapy and conventional topical therapy. Nanoemulsions are nano-sized novel drug delivery systems that offer less adverse effects and effective improvements in treatment of skin disorders as acne. Nanoemulsion has immense potential to solve solubility and bioavailability problems of the drug formulation compared to conventional creams. In addition, it has been seen in some comparative studies that nanoemulsions increase the permeability of the active molecule through the skin more than other nano-carriers (SLN, NLC). Nanoemulsions are also very useful to deliver natural drug molecules that have generally solubility and stability problems. In addition, nanoemulsion contains natural origin molecules shows high antimicrobial and healing effects with less side effects than reference antibiotics against acne. Further clinical studies on nanoemulsion formulations are needed. However, the industrial acceptability of nanoemulsion systems is low due to their unstable state in semi-solid dosage forms, scale-up problems, and insufficient clinical studies on human skin. In this review, based on the literature data, it could be concluded that nanoemulsion can present tremendous facility for the developing of innovative, a small amount dose and effectual theraphy systems to control acne disease.

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