

MINI REVIEW

Nanoemulsions: colloidal topical delivery systems for antiacne agents- A Mini-Review

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ABSTRACT

One of the common chronic inflammatory skin diseases is Acne Vulgaris that affects up to 80% of a teen-age population. The progress of acne lesions is due to colonization of Propionibacterium acnes (P .acnes) in hair follicles. Treatment of acne includes topical or systemic therapy or combination therapy, with a tendency to perform topical therapy in mild to moderate acne. Nanoemulsions, small oil droplet less than 200nm, which have been stabilized by surfactant(s) and/or co-surfactant in water, could be effective carriers for topical delivery of anti-acne agents. Interesting properties of nanoemulsions such as the improved efficacy of the drug, ease of production, ability to be used in various formulations and ability to load lipophilic drugs could make it an ideal carrier for this purpose. This review highlights applications of nanoemulsions for topical therapy of acne.

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INTRODUCTION

Acne vulgaris is a common chronic inflammatory disease which develops in any age, with a greater prevalence in adults. Acne is not life-threatening but can affect self-esteem in patients [1]. Clinical features of the disease include excessive oil production by sebaceous glands in the skin, non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules), nodules and cysts as well as different degrees of dermal scarring. Anatomical distribution of acne lesions are in the face, neck, upper chest, shoulders and back [2].

Acne is usually classified based on its severity as mild, moderate, or severe. Mild acne is characterized by the presence of minor pimples, whiteheads, and blackheads comedones, without inflammation. Patients with moderate acne have greater blackheads, papules and pustules, with

slight inflammation. Characteristics of severe acne include severe papules/ pustules comedones and cystic nodules that are often painful and can leave a scar on the skin [3].

In this review, pathogenesis of acne as well as conventional formulations for acne treatment are briefly explained. We then will focus on nanoemulsions as potential colloidal systems for delivering anti-acne agents.

PATHOGENESIS OF ACNE

A multifactorial mechanism is involved in the pathogenesis of acne (see the schematic shown in Fig. 1) [4].

Various factors including the presence of hormones, sebum, bacteria in the pilosebaceous units of dermis and keratinization of follicles have been associated in the literature with acne. An

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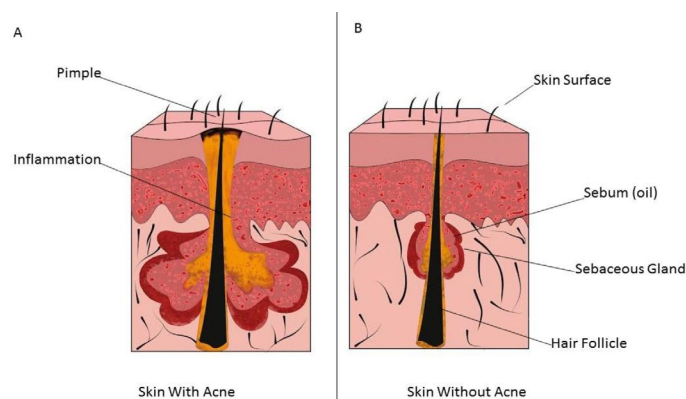


Fig. 1. Anatomic illustration of acne development in skin. A (skin with acne): development of acne due to increasing in sebum production in sebaceous glands that cause pilosebaceous canal obstruction, followed by inflammation and blackhead comedone, B (skin without acne): normal skin before acne with normal sebum production in sebaceous glands.

increase in sebum production is probably the main factor for the disease. Sebum provides a substrate for growth of *P. acnes* as a part of the bacterial flora of normal skin that is located within the follicles and needs the sebaceous constituent for nourishment. Hyperkeratinization of follicles which blocks flow of sebum in the pilosebaceous canal is another cause of acne. Further to a colonization of *Staphylococcus epidermidis* and *P. acnes* in pilosebaceous units, a cascade of events leads to inflammatory and non-inflammatory lesions. Such events include release of chemotactic factors, phagocytosis of bacteria by neutrophils and rupture of the follicular wall as a result of hydrolytic enzymes of neutrophils [5, 6]. A brief mechanism of acne pathogenesis is shown in Figure 2.

CONVENTIONAL TREATMENTS OF ACNE

Main treatment in mild to moderate acne is topical therapy. In severe conditions of acne, topical

therapy may also be used as additional support for systemic therapy [6]. Topical medicines which are commonly used are retinoids, antibiotics, and herbal agents and are commercially available in the dosage form of cream, gel as summarized in Table 1. Topical treatments only work where applied and some of them cause cutaneous irritation that can be minimized by using lower concentration formulations [5].

Systemic therapy is reserved for moderate and severe acne. Drugs that are used for systemic applications are isotretinoin, systemic antibiotics (e.g. tetracycline, doxycycline, minocycline, erythromycin, and azithromycin) and hormonal therapy [13]. Also, the combination of more than a single topical or systemic drug is a common approach in complicated cases as this method can target several pathogenic factors [14]. Several studies have shown combination therapy as an efficient therapy compared with monotherapy for

Table1. Topical drugs that are commonly used for acne treatment.

Drugs	Mechanism(s) of action	Major adverse effect(s)
Retinoids (Tretinoin, Adapalene, Tazarotene, Isotretinoin)	Regulation of hyperproliferation in follicular epithelial cells, anti-inflammatory effects	Skin irritation [7].
Antibiotics (Clindamycin, Erythromycin, Azithromycin)	Inhibition of growth of <i>P. acnes</i>	Change in normal skin flora, Antibiotics resistance [8, 9].
Herbal agents (Tea tree oil, Onion, Aloe-Vera, Rose oil)	Antimicrobial, Anti-inflammatory, Keratolytic, and antioxidant effects	Skin irritation [10-12].

acne treatment [15-17].

When comparing with systemic therapy, topical application of drugs shows substantially lesser adverse effects. For example, the only concern when using a topical form of retinoids is their tolerability and cutaneous irritation. Also, there is no important concern for topical antibiotics. While when taking orally, many side effects are expected from oral retinoids (isotretinoin) such as cheilitis, dry skin, nose bleeds, secondary infection, temporary worsening of lesions, photo sensitivity, and increased serum lipids. Antibiotic resistance is a concern in the systemic use of antibiotics [5, 8, 18, 19]. However, topical anti-acne drugs are less effective due to low penetration. To deal with this problem, patients should use the medicine for a long time that decreases patient compliance. Additionally, this may increase the risk of bacterial resistance [20]. Such problems indicate the necessity for developing novel topical formulations with improved efficacy.

APPLICATIONS OF NANOEMULSIONS IN TOPICAL DELIVERY SYSTEMS FOR TREATMENT OF ACNE

The main site of disease in acne is follicular recesses of the skin, so, any applied antiacne agent must accumulate in follicular recesses in

reasonable concentrations to be effective. Ease of use, production cost as well as safety and efficacy of formulations are also challenges ahead of a formulator.

Nanostructures provide many advantages for drug delivery systems. Improving efficacy of the active ingredient, controlling drug release profile and biological life-time as well as delivering multiple agents in a single preparation are some gains when “nano” is employed. In recent years, several reports have used various nanoparticles for delivering a drug in the treatment of acne [21-28]. In recent years, there has been a growing interest in the use of nanoemulsions as colloidal drug carriers for treatment of acne. For instance, in a research, extent and kinetics of drug deposition of tea tree oil through the follicular route were investigated in different formulations. The work demonstrated that microemulsion and liposomal formulations were more efficient for the delivery of tea tree oil [29].

Nanoemulsions are emulsions with a diameter less than 200nm. They are prepared using high energy emulsification methods (e.g. ultrasonication, microfluidizers and high-pressure homogenizers) or low energy emulsification ones (e.g. phase inversion and solvent displacement [30-38]. These nanocarriers offer advantages

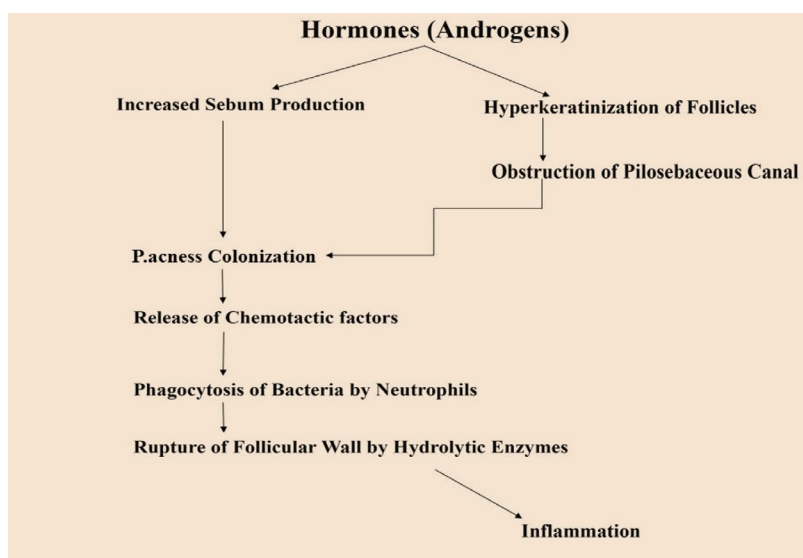


Fig. 2. Schematic of factors which are involved in the pathogenesis of Acne. Androgens affect sebum production and hyperkeratinization of follicles that cause colonization of P.acness in skin follicles and release of chemotactic factors from the bacteria which cause inflammation as the first stage of acne development in skin.

Table 2. Examples of nanoemulsions for acne therapy.

Antiacne drugs	Oil phase	Finding(s)	Ref
Clindamycin phosphate, Adapalene	Soybean oil	Enhanced stability and efficacy of the drug (in-vivo, in-vitro).	[54]
Dapsone	Isopropyl myristate or N-methyl-pyrrolidone	Improved <i>in-vitro</i> epidermal permeation and release rate of dapson	[55]
---	Lemongrass oil	Significant inhabitation zone against <i>P. acnes in-vitro</i> .	[56]
Nadifloxacin	Oleic acid	Significant activity against <i>P. acnes</i>	[57]
Clindamycin Phosphate	Olive oil	Proper physicochemical properties as anti-acne carrier	[58]
Isotretinoin	Coconut oil	Controlled drug release	[59]

of transparency, low viscosity, thermodynamic stability, ease of preparation, a high surface area that make them effective transdermal and topical drug delivery systems. Also, compared with other nanocarriers, they provide some substantial advantages including low skin irritation, high permeation ability, and high drug-loading capacity for topical treatment [39]. Nanoemulsions have been formulated in different topical dosage forms such as foams, cream, gels, liquids and sprays [40, 41]. Some nanoemulsion-based products have been patented for skincare products [42-45].

Several mechanisms participate in improving drug penetration in topical delivery of nanoemulsions containing anti-acne drugs. The Small size of nanoemulsion droplets can increase drug transportation through hair follicles as the main target for *P.acnes* colonization and oil production by Sebaceous glands [46]. Furthermore, many of nanoemulsion excipients act as permeation enhancers in topical applications. Due to hydrophobic characteristics of skin, the oil phase of the nanoemulsion having hydrophobic properties can improve permeation of active ingredients [47]. Surfactants are also well known as penetration enhancers in the skin. They have potential to solubilize lipids within stratum corneum (SC) as the main barrier for topical absorption of drugs

[48]. Penetration of the surfactant molecules into the lipid lamellae of the SC is strongly dependent on the partitioning behavior and solubility of surfactant [49]. Co-surfactants also can influence the transport behavior of the drug in the skin. For example, ethanol can increase lipophilic transport from SC through the formation of pores in SC [50, 51]. Also, since the hydrated skin is generally more permeable, water which is found in nanoemulsions is perhaps an ideal enhancer [52].

Table 2 lists the antiacne agents which have been formulated in nanoemulsions. Nanoemulsions also offer a great potential for boosting bioavailability of drugs, especially lipophilic drugs. Efficient transdermal drug delivery happens particularly with positively charged nanoemulsions [53].

Roy et al. reported a novel nanoemulsion with Soybean oil as oil phase loaded with clindamycin phosphate and adapalene. The preparation exhibited good therapeutic efficacy and improved permeability. A randomized clinical trial in Indian patients with the topical gel of this nanoemulsion showed better tolerance and efficacy than the conventional formulation for the treatment of acne vulgaris [54, 60]. In another study, nanoemulsion was prepared using isopropyl myristate which showed increased in-vitro epidermal permeation of dapsone while n-methyl-pyrrolidone as the oil

phase provided a greater solubilization of dapsone, and increased release rate of the drug [55]. Nanoemulsions of lemongrass oil (no chemical agent) and oleic acid loaded with nadifloxacin also showed improved zone inhibition properties against *P. acnes* as compared to clindamycin [56, 57]. In another study, clindamycin loaded in olive oil nanoemulsion showed good physicochemical properties as the anti-acne carrier [58]. In study of Miastkowska et al. release kinetic of isotretinoin from coconut oil nanoemulsions was investigated. A zero order kinetic model was suggested for the nano-formulation which could be used as controlled drug release carrier for acne treatment [59].

SELECTION OF NANOEMULSION COMPONENTS

Selection of appropriate components is an important step in the preparation of nanoemulsions. A nanoemulsion typically contains oil, surfactant, co-surfactant and water. These ingredients should be chosen properly to maximize the efficacy of the product.

SELECTION OF OIL PHASE

The oil is probably the most important excipient in a nanoemulsion, because it is the main part of a nanoemulsion in solubilizing lipophilic drugs. As the majority of antiacne drugs possess high oil solubility, nanoemulsions could be suitable carriers for encapsulating them. Different types of oil have been employed in antiacne nanoemulsions. Length of fatty acids chain in the molecular structure of the oil is a main factor determining the stability of nanoemulsions. Nanoemulsions with short chain oil often have low viscosity, while oils with long chain fatty acids produce stable nanoemulsions with larger particle size [61].

Although solubility of the active ingredient in the oil phase is an important criterion in the selection of oil, in some cases synergistic effects of oil phase with the active ingredient for the intended application becomes very important too [62]. For example, essential oils of eucalyptus and tea tree are being traditionally employed in the treatment of acne [63]. Nanoemulsions of such oils may be used as a combination therapy when the oil is both an active ingredient and a carrier for a second drug.

SELECTION OF SURFACTANT

Surfactants are amphiphilic molecules that consist of a non-polar hydrophobic portion which is attached to a hydrophilic portion. The hydrophobic part interacts readily with oil but is insoluble in water, while the hydrophilic part locates next to the water phase of the system [64]. Surfactants are usually classified as anionic, cationic and non-ionic. Non-ionic surfactants are less toxic than ionic ones. Examples of non-ionic surfactants include Tween, labrasol and Cremophor. Selection of an appropriate surfactant which efficiently emulsifies the oil is the most important factor in determining the stability of the product. HLB (hydrophilic lipophilic balance) value has been proven to be very useful in choosing the best type of surfactant for intended oil [64, 65].

SELECTION OF CO-SURFACTANT

Typically, short chain alcohols like ethanol and propylene glycol, are used as co-surfactants for decreasing interfacial tension and modifying fluidity of the interfacial layer. Co-surfactants also decrease viscosity and increase the stability of nanoemulsions. Additionally, they may help to dissolve hydrophilic surfactants or hydrophobic drugs in the oil phase [50, 66].

CONCLUSIONS

Although significant growth has been made in the treatment of acne, optimal treatment strategy can offer a promising potential for quick improvement with minimum adverse effects. Many topical and systemic treatments are available for treatment of acne. Nanoemulsions as nano-sized emulsions in carrying drugs have potential in topical anti-acne therapy. They offer better options in topical acne treatment due to enhancing penetration of the active ingredient(s). The correct selection of nanoemulsion components could enhance the efficiency of topical preparation.

A good combination of an active agent with an appropriate oil would even result in a better effect.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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