



THE POTENTIAL ADVANTAGES OF LIPID NANOPARTICLES IN TREATMENT OF ACNE

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ABSTRACT

Acne is a disfiguring disorder of the skin with significant cosmetic morbidity that may lead to serious psychological and social dysfunction. The skin disease comes in two forms. The most well-known form is Acne vulgaris (referred to as acne), which mostly manifests in teens but may continue into the early 20s. The second form is called Acne rosacea (referred to as rosacea) and mostly affects 30- to 60-year-olds. The two forms, despite sharing a common prefix, are quite unrelated in their respective pathophysiology, have different approaches to treatment and hence are considered two separate conditions. Conventional drug delivery system is efficient in management of acne but poor patient compliance and adverse effects limits its efficacy. Lipid nanoparticles are novel nanolipid carriers made from biocompatible lipid which reduces toxicity; improve physical stability, skin hydration and film formation. Furthermore lipid nanoparticles protect the encapsulated drug from degradation. Thus current review focused on potential use of lipid nanoparticles for management of acne.

Keywords: Acne, Rosacea, Solid lipid nanoparticles, Topical drug delivery, Nanolipids, Acne vulgaris.

Article info:

Received: July 6, 2018

Revised: August 19, 2019

Published Online: Oct, 2019

DOI: <https://doi.org/10.31069/japsr.v2i3.2>

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INTRODUCTION

Acne is a chronic inflammatory disease of the pilo sebaceous follicles and prominently affects skin sites with high density of sebaceous glands. Four major factors plays key role in formation of acne are; enhanced sebum secretion, hyper cornification of sebaceous duct, *Propionio bacterium acnes*, and inflammation and host reaction. It predominantly affects the adolescent population (approximately 85%).^[1] Rosacea is a disorder of the skin characterized by erythema, telangiectasia, papules, and pustules of the face and, in its most extreme form, can cause bulbous deformity of the nose (rhinophyma).^[2] It mostly affects middle aged to elderly adults, being more common in fair-skinned people. Acne rosacea is inflammatory disorder of the skin associated with an over-reactivity of capillaries in the skin to heat and chemical stimuli.

While the etiology of acne rosacea is not clearly understood, it involves vascular dilatation with an increased susceptibility to flushing. The cause in some literatures is reported to be linked to the increased pathogenic presence of the bacterium *Staphylococcus epidermidis*.^[3] In others, it was reported that the available evidence supported that rosacea was not caused by an underlying bacterium and that rather, it was a complex inflammatory disorder.^[4] From the nineteenth to twentieth century, almost all the treatments were based on conventional drug delivery system for management of acne. Conventionally available dosage forms works by the following mechanisms, anti-inflammatory effect,

hormonal manipulation, killing *P.acnes* and prevention of pore blockage.^{[5] [6]} In spite of various available treatments for management of acne, many patients develop problematic side effects. Furthermore some of systems cause skin dryness, peeling and skin irritation.^{[7] [8]}

Most of the conventional formulations produce side effects that diminish the patient compliance. To overcome the drawbacks of conventional drug delivery systems, development of lipid carrier based drug delivery came into existence. Nano-carrier based drug delivery reduces irritancy of drugs and improves penetration of drug into the hair follicles.^[9] The anti-acne therapeutics loaded lipid particulate system for topical application is advantageous compared to conventional available topical delivery system. Furthermore the entrapped drug in lipid matrix of particulate system represents an innovative and alternative approach for reducing side effects and preserving their efficacy. This article focuses on the role of Solid lipid nano-particles (SLNs) as nano-delivery system for delivery of anti-acne drugs.

Pathogenesis of acne

Hormones, sebum, follicle fallout, bacteria are major factors contribute in formation of acne. The major factors associated with acne include:

1. *Increased sebum production*: Is one of the most important factors associated with development of acne. The role of sebum in the pathogenesis of acne is its associative role in comedogenesis as well as providing the substrate for *P. acne* growth. Figure 1 highlights the basic mechanisms involved in pathogenesis of acne. ^[10]
2. *Follicular hyper keratinization*: Obstruction of pilosebaceous canal due to follicular hyper keratinization is another cause for development of acne. Obstruction is produced by the growth of keratinized cells within the channel that blocks the flow of sebum. ^[10]
3. *Reactive oxygen species (ROS)*: Rosacea skin has higher production of ROS than normal skin. UV radiation generates ROS, which mediates cytokine production by tumor necrosis factor (TNF- α) in keratinocytes, induces chemokine production by TLR2 stimuli in monocytes, stimulates fibroblasts and alters matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP) expression. All these effects of ROS together result in enhanced inflammatory reactions and degeneration of collagen and matrix in dermis, as seen in rosacea. ^[11] Figure 2 show sequences of events leading to acne primarily induce by ROS.
4. *Staphylococcus epidermidis*: *Staphylococcus epidermidis* plays a role in the pathogenesis by its ability to stimulate TLR-2 receptors. Figure 3 highlights mechanisms of formation of acne primarily induce by *Staphylococcus epidermidis*.

Causes of acne

Various factors such as emotional factors, environmental factors (humidity, heat etc.), hormonal factors (androgenic progestin) and microorganisms are responsible for causing acne. ^[10]

- High heat and humidity cause recurrent and elongated sweating can aggravate acne.
- Tight fitting clothes that obstruct air movement and evaporation of skin moisture contribute to acne.
- Hair spray can block the pilo sebaceous glands cause acne.
- Comedogenic oil containing products can cause acne due to occlusive and plugging the follicle.
- Oral contraceptives and androgenic progestin can contribute to acne.
- Acne vulgaris is mainly cause by gram-positive, micro-aerophilic and non-spore forming bacteria *P. acnes*.
- *H. pylori*, a bacteria found in the gut, stimulates the production of bradykinin, a small polypeptide cause dilation of blood vessels. Experts suggest that this bacterium may responsible for causing rosacea.
- Genetic causes: Individuals with a family history of rosacea were more likely to develop rosacea.

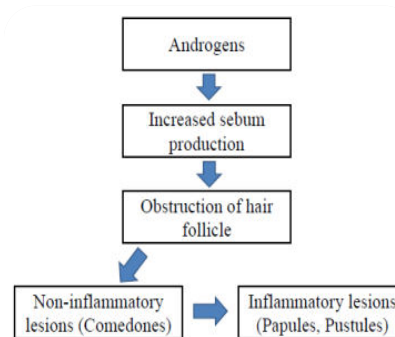


Figure 1: Role of androgen in formation of acne.

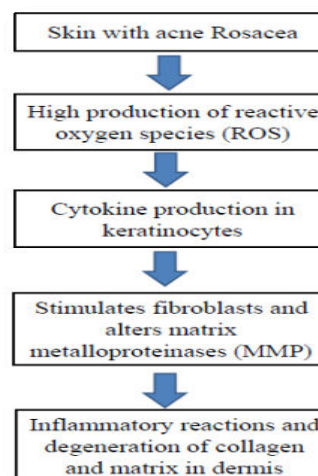


Figure 2: Mechanisms of acne induction by ROS.

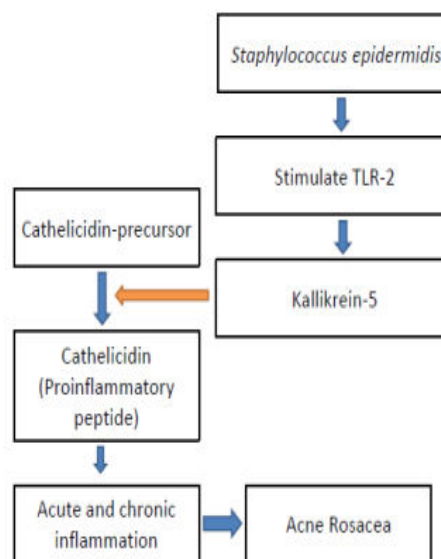


Figure 3: Mechanisms of formation of acne induced by *Staphylococcus epidermidis*.

Grades of acne

Based on intensity and severity, acne divided into four grades (Comedonal, Papular, Pustular, Severe pustulocystic). Table 1 highlights various grades and their characteristics. In general, rosacea is characterized by episodes of flushing and telangiectasias of the face, especially about the nose and cheeks. While these

patients may develop papules, pustules, or cysts, there are no comedones associated with this condition (as in acne vulgaris). This is the prime differentiating point of rosacea from acne: the absence of the central comedones. Patients with rosacea may develop granulomatous papules of the nose and cheeks, which, in the most severe form, result in the bulbous deformity known as rhinophyma.

Table 1: Characteristics of various grade of acne





Acne grade	Picture	Characteristics of acne
Comedonal acne		<ul style="list-style-type: none"> • Consist of comedones only. • Less than about 10 on the face. • None on the trunk. • No scarring and non-inflammatory in nature. • Comedones that are 1 mm or larger are called microcomedones.
Papular acne		<ul style="list-style-type: none"> • Consist of 10 – 25 papules on the face and trunk with mild scarring. • The presence of inflammatory lesions (less than 5 mm in diameter). • Papular acne is caused due to bacteria, oil, dirt and heat. • Mostly found on the face, back and posterior parts.
Pustular acne		<ul style="list-style-type: none"> • It is a subset of acne vulgaris. • Pustules are small bumps on the skin that fill with fluid or pus. • Consists of more than 25 pustules with moderate scarring. • These bumps can form on any part of the body, but they are most common on the back, neck, chest and face.
Severe Pustulocystic acne		<ul style="list-style-type: none"> • Consist of nodules or cysts with extensive scarring. • Inflammatory lesions over 5 mm in diameter. • Extensive nodules and cysts. • Appear on the buttocks, groin, and armpit area, and anywhere else where sweat collects in hair follicles and perspiration ducts. • Cystic acne affects deeper skin tissue than does common acne.

Rosacea can be divided into four subtypes based on which symptoms predominate in the individual. (erythematotelangiectatic, papulopustular, phymatous, and ocular), with erythematotelangiectatic rosacea is the most common. [12] Table 2 highlights various subtypes and characteristics of rosacea. The intensity of rosacea has been categorized into four stages. [13] [14]

Stage 1 is characterized by frequent blushing with easy irritation of the skin. Stage 2 occurs when a vascular component is present, leading to persistent blushing and early telangiectasias. Stage 3 involves a deeper erythema with telangiectasias increasing and papules and pustules appearing. Stage 4 occurs when nasal edema, called rhinophyma, develops, and ocular inflammation begins. In

severe cases, rosacea can progress to irreversible disfigurement and loss of vision.

Table 2: Characteristics of various subtypes of acne Rosacea

Rosacea subtypes	Picture	Characteristics
Erythematotelangiectatic rosacea		<ul style="list-style-type: none"> • Flushing and persistent central facial erythema with visible blood vessels • Burning and stinging
Papulopustular rosacea		<ul style="list-style-type: none"> • Persistent central facial erythema • Transient papules or pustules
Phymatous rosacea		<ul style="list-style-type: none"> • Thickened skin irregular • Surface nodularities and enlargement • Rhinophyma
Ocular rosacea		<ul style="list-style-type: none"> • Watery or bloodshot appearance of eyes • Foreign body sensation, stinging or burning, dryness • Itching, light sensitivity, telangiectases of the conjunctiva • Blurred vision

Updates on Management of Acne

General measures

It is necessary to educate patients at the initial stage regarding chronic relapsing nature of disorder, and to advise the patients to avoid recognized triggers. General measures to manage acne are to maintain skin hydration and barrier function, photoprotection (avoidance of sunlight exposure and use of sunscreen agent). Colour-correcting powders cover-up can be helpful to mitigate the psychological impact of rosacea.^[15]

Topical approach

Topical therapy is mainly indicated in mild to severe acne and is inevitable in acne treatment.^{[8][16]}

A combined topical and systemic treatment is recommended in more severe form.^[17] Table 3 takes overview of topically applied drugs for treatment of acne. The available drugs directly or indirectly affect the pathogenesis of acne. Selection of drug is based on predominant type of acne lesions. The therapeutic success of drug is depending on a regular application of drug over a prolonged period of time.^[18] However adverse effects associated with commonly used topical agents (Table 3) affects the patient compliance.

In mild to moderate type of rosacea, topical treatment is first line approach. Metronidazole 0.75%, 1% (Cream, gel, lotion), azelic acid 15% gel and ivermectin 1% cream are US FDA approved formulations for treatment of rosacea. Brimonidine tartrate 0.33% gel was approved by FDA for treatment of facial erythema associated with acne rosacea. ^[19]

Systemic approach

Systemic therapy is first line treatment in moderate and severe acne. Drugs employed for systemic delivery are shown in Table 4.

Table 3: Overview of topical anti-acne agents

Topical drugs	Mechanism of action	Adverse effect
Topical retinoids (Tretinoin, Adapalene, Tazarotene, Isotretinoin, Metretinide)	<ul style="list-style-type: none"> Target the abnormal follicular epithelial hyper proliferation, Reduces follicular plugging, micro comedones, Non-inflammatory and inflammatory acne lesion. 	Irritant dermatitis, erythema, scaling, burning sensation
Topical antibiotics (Clindamycin, Erythromycin, Clarithromycin, Azithromycin, Nadifloxacin)	<ul style="list-style-type: none"> Inhibit the growth of <i>P. acne</i> and reduce inflammation. Topical antibiotics such as erythromycin and clindamycin are the most popular in the management of acne. 	Erythema, peeling, itching, dryness, burning, bacterial resistance, cross resistance
New agents (Clindamycin, Benzoyl peroxide, Tretinoin)	<ul style="list-style-type: none"> Prevent and eliminate the development of <i>P. acne</i> resistance. 	Skin irritation, burning, erythema, peeling, dryness, skin sensitivity
Metronidazole	<ul style="list-style-type: none"> Ability to decrease reactive oxygen species generation and inactivate existing reactive oxygen species production as well as its antibacterial properties. 	Skin irritation
Herbal agents (Azelaic acid, Tea tree oil)	<ul style="list-style-type: none"> Reducing both inflammatory and non-inflammatory acne lesions. Act as antimicrobial, anti-inflammatory, and antioxidant. 	Skin irritation

Table 4: Overview of systemic anti-acne agents

Systemic drug	Mechanism of action	Adverse effect
Systemic antibiotics (Tetracycline, Doxycycline, Minocycline, Erythromycin, Azithromycin)	<ul style="list-style-type: none"> Inhibit the growth of <i>P. acne</i> and reduce inflammation. Mainly moderate-to-severe inflammatory acne. Tetracycline's and derivatives still remain the first choice. 	Gastrointestinal upset, vaginal candidiasis, pigment deposition in the skin & teeth
Hormonal therapy	<ul style="list-style-type: none"> Prevent the effects of androgens on the sebaceous gland and probably follicular keratinocytes 	Hyperkalemia, menstrual irregularities

Topical Delivery of Drugs

The Lipophilic Nature of the Skin

For any topical system, the drug transport process begins by drug partitioning out of the dosage form and into the uppermost stratum corneum, which comprises of intercellular lipid domains. The stratum corneum is regarded the principle barrier to the entry of external chemicals. For a drug to enter the stratum corneum and form a drug reservoir, it must have sufficient lipophilicity. However, although very highly lipophilic drugs may be able to enter the stratum corneum with relative ease, they may not be able to partition to the same extent into the more aqueous viable epidermis. Thus, a molecule must have optimum lipophilicity.

Next, the molecular size of the molecule also plays a role in the fate of the drug in the skin. Molecules larger than 500 Da permeate poorly. Thus, as a general rule of thumb, candidate molecules are only selected for topical delivery if their molecular size is below 500 Da. ^[20]

Solid Lipid Nanoparticles

Background, definition, method of preparation, advantages and disadvantages

Parenteral fat emulsion was the first dosage form developed in 1960s for incorporation of lipophilic drugs in lipid droplets and was developed as the first generation lipid nanoparticles, called SLNs. [21] [22] SLNs are composed of solid lipid dispersed in an aqueous solution of surfactant as stabilizer. Biocompatibility of SLNs can be achieved by using biocompatible and biodegradable lipids and surfactants. The mean diameter of SLNs ranges from 40 to 1000 nm. Also, owing to their miniscule size, nanoparticles are readily able to be taken up by cells, allowing an accumulation of drug at the target site, forming a reservoir for prolonged drug release. SLN provide following features: physical stability, low toxicity, controlled release and protection of encapsulated drug from degradation, film formation, controlled occlusion, skin hydration, physical stability and the possibility of drug release modulation, if well tolerated excipients are used. Another important benefit of SLNs as compared to other colloidal drug delivery systems (liposomes, niosomes, etc.) and to nanoemulsions is their great kinetic stability and rigid morphology. [23] Moreover, SLNs can be prepared by organic solvent free technique and can be easily scaled up, e.g., by high pressure homogenization, melt homogenization ultrasonication. SLNs are prepared using solid lipids (i.e., lipids that are solid at room temperature as well as at body temperature). NLCs are prepared using a solid lipid as well as a lipid. These lipids are biocompatible and biodegradable with GRAS (Generally Recognized as Safe) status.

Potential disadvantages of SLN are expulsion of drug during storage and low drug loading capacity.

Merits of Solid lipid nanoparticles for Topical Drug Delivery

The characteristic features that make SLNs an ideal carrier for dermal delivery and rosacea treatment are as follows:

1. Improved body/tissue tolerance and less stringent regulatory requirements due to utilization of physiologically acceptable lipids.
2. Ability to entrap hydrophilic as well as lipophilic drugs by using various techniques of fabrication.
3. The protection of labile compounds against chemical degradation has been shown, e.g. for retinal, coenzyme Q-10, and tocopherol.
4. Depending on the produced SLNs type, modulation of drug release is possible depending upon the requirements. SLNs with a drug-enriched shell show burst release as well as sustained release characteristics whereas NLCs with a drug-enriched core lead to sustained release. In vivo studies on sunscreen oxybenzone have shown that SLNs can significantly reduce the amount released in the skin as compared to conventional emulsions. [24] Thus, SLNs may serve as a local depot for the sustained release of dermally active compounds thus offering reduction in frequency of administration and side effects of the drug.
5. SLNs can be used in order to increase the water content of the skin which may help in combating the skin dryness caused by most of the antirosacea agents.
6. SLNs show a UV-blocking potential, i.e. they act as physical sunscreens on their own and is a benefit for

rosacea patients since they are advised to use sun-protection whenever moving outdoors.

A topical drug delivery system may have the following disadvantages:

- 1) A topical drug delivery system for application to the facial skin must be free from tackiness and residue in order to allow quick application when required.
- 2) It must also have good cosmetic and emollient properties to manage dry and inflammatory conditions like rosacea.
- 3) The inclusion of a sensory component may be desirable to achieve product acceptability and patient compliance.
- 4) The drug must have sufficient solubility in a solvent/s or in a formulation base in order to achieve the target concentration at the site of application.

Table 5 highlights recent research on lipid nano-carriers based acne treatment.

Table 5: Overview of research on topical drug delivery of lipid nanoparticles for acne treatment

Drug	Method of preparation
Neem oil	Double emulsification method [25]
Juniper oil	O/W emulsification combined high shear homogenization [26]
Tretinoin	Hot high pressure homogenization [27]
Isotretinoin	Hot microemulsion technique [28]
Retinoic acid	High pressure homogenization [29]
Benzoyl peroxide	Solvent evaporation technique [29]

Neem oil was encapsulated into SLNs for topical delivery. Neem oil-loaded SLNs dispersion was obtained from mixture of soya lecithin and cholesterol using double emulsification method. Drug-lipid compatibility was assessed using FTIR spectroscopy. Scanning electron microscopy (SEM) revealed spherical and smooth shaped SLNs. *In-vitro* release behavior of SLNs in phosphate buffer (pH 7.4) was analyzed using Franz diffusion cell. The study showed limited percentage of drug release over the 12 hrs. Results demonstrated that SLNs are a promising strategy for topical delivery of neem oil. [25]

Juniper oil loaded SLNs were formulated using O/W emulsification combined high shear homogenization techniques for topical delivery. Compritol and Precirol were selected as lipid matrix for encapsulation of juniper oil. SEM images revealed spherical, non-aggregated and smooth shaped SLNs. Evaporation of volatile content from juniper oil loaded SLNs was investigated

in terms of percentage weight loss. Relatively low percentage (3-12%) of oil evaporation from SLN was reported. Exposure time required by fixed amount of oil, SLNs to kill standardized inoculum of *P.acnes* was determined. Lipid nanoparticles were reported to kill 60% microorganisms at the end of 1.5 hrs whereas 100% reduction in microbial count was reported in case of juniper oil. Results concluded that, colloidal particles were suitable carrier for delivery of anti-acne drug.^[26]

Tretinoin was encapsulated into SLNs and chitosan SLNs for topical delivery in Acne vulgaris. Tretinoin-loaded SLNs dispersion was obtained from Myristyl myristate as lipid matrix and Pluronic F68 as stabilizer using hot high pressure homogenization. Cytotoxicity evaluation of tretinoin loaded SLNs on HaCaT cell lines revealed more than 90 % cell viability which indicated low toxicity to cells. Antibacterial activity of SLNs was assessed by determining minimum inhibitory concentration on standard stocks of *P.acnes* and staphylococcus aureus.

Tretinoin chitosan SLNs inhibited growth of bacteria at low concentration. Scanning electron microscopy (SEM) revealed spherical and smooth shaped SLNs. Particle size and zeta potential were measured using Zetasizer Nano ZS; the reported values of both were 162.7 nm and -31.9 mV. The results demonstrated that drug loaded SLNs exhibit antibacterial activity against bacteria involved in acne.^[27]

Isotretinoin loaded SLNs for topical delivery in Acne vulgaris was also formulated. Isotretinoin-loaded SLNs dispersion was obtained from Compritol as lipid matrix and Tween 80 as stabilizer using hot microemulsion technique. Particle size and zeta potential were measured using Zetasizer Nano ZS. Permeation of drug across skin of hairless Laca mice was assessed using Franz diffusion cell. *In-Vivo* anti-acne activity was assessed in Testosterone-induced acne model. Significant reduction in acne papule after 4 weeks treatment was reported in mice treated with isotretinoin SLNs.

CONCLUSION

Acne is a chronic inflammatory disease of skin. Rosacea is a disorder of the skin characterized by erythema, telangiectasia, papules, and pustules of the face and, in its most extreme form, can cause bulbous deformity of the nose. Almost all the treatments were based on conventional drug delivery system for management of acne. To overcome the drawbacks of conventional drug delivery systems, development of lipid carrier based drug delivery came into existence. The antiacne therapeutics loaded lipid particulate system for topical application is advantageous compared to conventional available topical delivery system. Thus SLNs is novel way for topical drug delivery for better management of acnes and useful tool for future research.

ACKNOWLEDGEMENT

Authors are extremely thankful to the referred authors.

CONFLICT OF INTEREST

The author declares that they have no competing interests.

Skin irritation potential of drug loaded SLNs and marketed formulation was checked using hairless Laca mice skin. Nano-colloidal system showed better tolerability on mice skin as compared to marketed formulation.^[28]

Retinoic acid was encapsulated into lipid nanoparticles for topical drug delivery. Compritol and polyoxyl 20 cetyl ether were selected as lipid matrix and stabilizer respectively. Retinoic acid loaded SLNs dispersion was prepared using hot high pressure homogenization. Particle size and zeta potential were measured by photon correlation spectroscopy using Zetasizer Nano ZS. Drug-excipient compatibility was assessed using differential scanning calorimetry. *In-vitro* antimicrobial activity of drug loaded SLNs against acne causing microorganisms was assessed using well diffusion technique. SLNs showed improved antimicrobial activity against *S. aureus* and *S. epidermidis* when compared to the blank formulation. Results suggested that the Retinoic acid loaded SLNs was a promising alternative for the topical therapy of acne. Benzoyl peroxide is an effective topical agent in management of acne.^[29]

SLNs loaded with benzoyl peroxide were formulated to reduce the side effects of the drug i.e., cutaneous irritation and erythema. Excipients were selected based on their solubilization potential of Benzoyl peroxide. Benzoyl peroxide loaded SLNs dispersion was prepared by solvent evaporation technique using Precirol ATO5. *In-vitro* drug release behavior of SLNs was assessed using Franz diffusion cell. Benzoyl peroxide SLN optimized using 2³ full factorial design provided high occlusion factor, low permeation rate, increased drug deposition, reduced skin irritation and strong antibacterial activity in contrast with marketed product. The authors concluded that desired goals were achieved by factorial design approach in shortest possible time with minimum number of experiments. The developed BPO-SLN system provided controlled drug release, thereby reducing the well-known side effects.^[30]

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