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Review Article

# AN INCLUSIVE REVIEW ON NOVEL DRUG DELIVERY STRATEGIES FOR AN EFFECTUAL DELIVERY OF BIO-ACTIVE DRUG MOLECULES IN THE TREATMENT OF ACNE

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## ABSTRACT

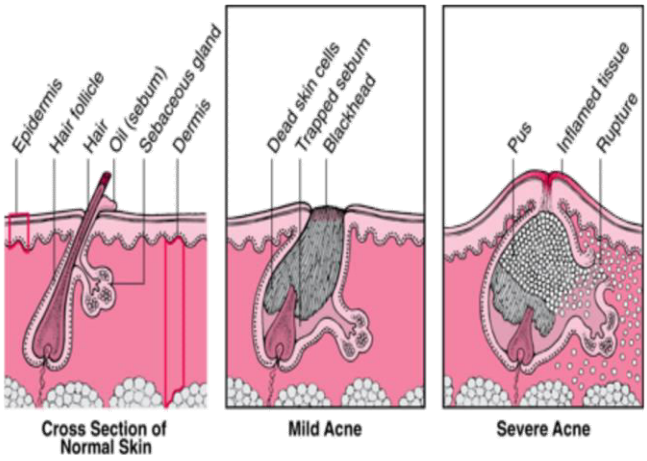
*Acne vulgaris* (acne) is chronic inflammatory human cutaneous disease, characterized by areas of skin with seborrhoea, comedones, papules, nodules, pimples and possibly scarring with lesions occurring on face, neck and back. This affects the pilosebaceous unit. Propionibacterium acnes and Staphylococcus epidermidis are common pus-forming microbes responsible for the development of various forms of acne vulgaris. Common therapies that are used for the treatment of acne include topical, systemic, hormonal, herbal and combination therapy. This multifactorial disease mostly occurs in adolescents; however, it can also affect neonates, prepubescent, children and adults. Near about 80-85% people throughout the world suffer from acne at some point in their life span. The majority of the acne sufferers exhibit mild to moderate acne initially, which progresses to the severe form in certain cases. Topical therapy is employed as first-line treatment in mild acne, whereas for moderate and severe acne, systemic therapy is required in addition to topical therapy. Currently, several topical agents are available that affect at least one of the main pathogenetic factors responsible for the development of acne. Although topical therapy has an important position in acne treatment, side effects associated with various topical antiacne agents and the undesirable physicochemical characteristics of certain important agents like tretinoin and benzoyl peroxide affect their utility and patient compliance. Novel drug delivery systems or nanotechnological approaches such as particulate (solid lipid nanoparticles and microspheres), vesicular (liposomes and niosomes), colloidal drug delivery systems (micro-emulsion and nano-emulsion) and miscellaneous systems (aerosol foams and micro-sponges) have been used to reduce the side effect of drugs commonly used in the topical treatment of acne. Topical treatment of acne with active pharmaceutical ingredients (API) makes direct contact with the target site before entering the systemic circulation which reduces the systemic side effect of the parenteral or oral administration of drug and designing of a novel, low-dose and effective treatment systems to control acne disease. The current review emphasizes the potential of various novel drug delivery strategies in optimizing and enhancing the topical delivery of antiacne agents. However, very few nanocarrier based formulations are available in the market for topical use and much progress is required in this field to improve anti-acne therapy.

**Keywords:** *Acne vulgaris, Propionibacterium acnes*, *Staphylococcus epidermidis,* Nanotechnological approaches, Antiacne agent.

## 1. INTRODUCTION

"Acme" is a Greek word of acne which means "Prime of life". *Acne vulgaris* (acne) is a chronic inflammatory disease of pilosebaceous unit affecting seborrhoeic areas (mainly face, chest, back), characterized by the presence of comedones, papular and pustular eruptions, purulent cysts and scars [1]. Acne affects approximately 650 million people or about 9.4% of the population globally. It affects almost 80-85% of people during their teenage years due to an increase in testosterone hormone level and sometimes persists into adulthood [2]. It is slightly more common in females than males (9.8% vs. 9.0%, respectively). In those over 40 years old, 1% of males and 5% of females still have problems. Acne affects 40-50 million people in the United States (16 %) and approximately 3-5 million in Australia (23%) [3]. Fig. 1 highlights the difference between a normal skin and the skin with acne. The current concept is that the pathogenesis of acne (Figs. 2-4) encompasses the interaction of several different pathogenic factors, namely follicular hyper keratini-zation, hormonally determined overproduction of sebum and changes in microbial flora in addition to immunological factors and inflammatory processes [4, 5]. Increased sebum

production and follicular hyperkeratosis result in the development of microcomedones, while changes in follicular milieu cause the intensive growth of *Propionibacterium acnes* (*P. acnes*) [6]. In the emergence of acne, other factors such as androgens, Peroxisome proliferator-activated receptor (PPAR) ligands, insulin like growth factor-1 (IGF-1) signaling pathway, regulating neuropeptides and environmental factors are probably involved, which interrupt the natural cycling process in the sebaceous gland follicle and support the transition of microcomedones to comedones and inflammatory lesions [7]. Despite acne not being a life-threatening disease, it has significant physical and psychological consequences such as permanent scarring, reduced self-esteem, social inhibition, depression, anxiety and suicidal tendency [8]. Since it can negatively affect the patient's quality of life, early and aggressive therapy is crucial, with successful treatment promoting much more than just cosmetic benefits [9]. Up to date, various clinical guidelines for management of acne have been proposed. Different factors, such as age of the patient, site of involvement, extent and severity of disease and patient preference may influence the choice of the therapy. According to the evolution, acne can be classified as mild, moderate or severe. Topical treatment is the first choice in mild and moderate acne, whereas systemic therapy is used to treat severe and moderate cases. The pathophysiological goal of acne treatment includes the normalization of keratinization, the reduction of interfollicular *P. acnes,* the reduction of inflammation, and the reduction of sebaceous gland activity. The options for the topical treatment of acne consist of agents with a primarily keratolytic action (retinoids and retinoid-like drugs, benzoyl peroxide, salicylic acid and azeilac acid) and antibiotics (clindamycin, erythromycin and erythromycin-zinc complex). Topical retinoids and similar drugs which include tretinoin, adapalene and tazarotene are the mostcommonly used topical agents [10-12]. The active substances and the conventional formulations for local acne treatment have numerous drawbacks, in terms of physico-chemical properties of the active ingredient, stability and limited possibility for penetration into the skin appendages. Numerous side-effects, such as skin irritation, redness, dryness, severe desquamation and photosensitivity occur due to the incapacity for targeted drug delivery to the pilosebaceous units and achievement of optimal concentration at the site of action. These side-effects diminish the patients` compliance [13, 14]. Hence, the patients are in search of topical products for skin use that are not only safe and efficient, but are also cosmetically acceptable and easy to use [13]. Novel delivery strategies for existing drugs and their modifications represent the recent changes in acne treatment, in addition to the development of new medications that target regulatory pathways involved in acne pathophysiology [15]. These novel drug delivery systems might minimize the problems associated with the conventional products in terms of penetration, retention, sustained release and therapeutic efficacy. Therefore, in the present review, our major aim was to explore the classification, causes, pathogenesis, current treatment options, and the role of novel carrier based treatment strategies of acne.




*(Adopted from: https://www.msdmanuals.com/professional/dermatologic-disorders/acne-and-related-disorders/acne-vulgaris)*

**Fig. 1: Difference between normal skin and skin with acne**

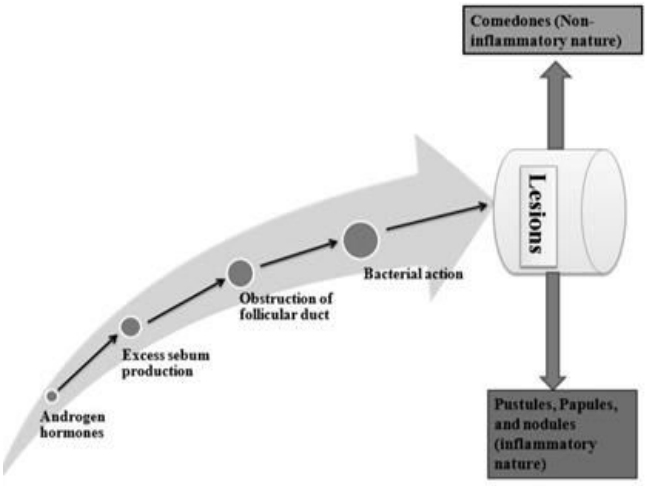



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**Fig. 2: Pathogenesis of acne**

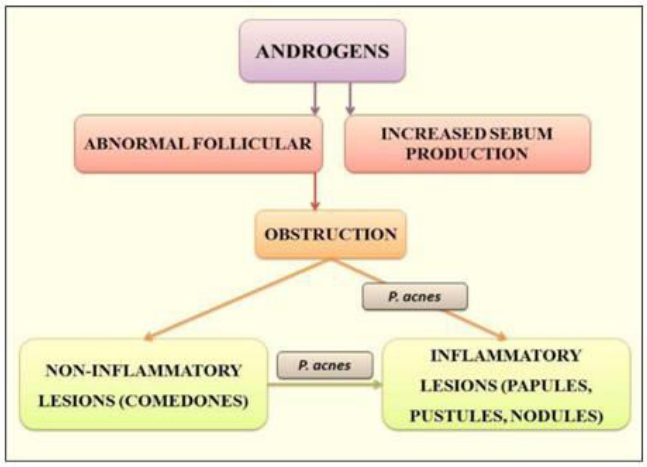
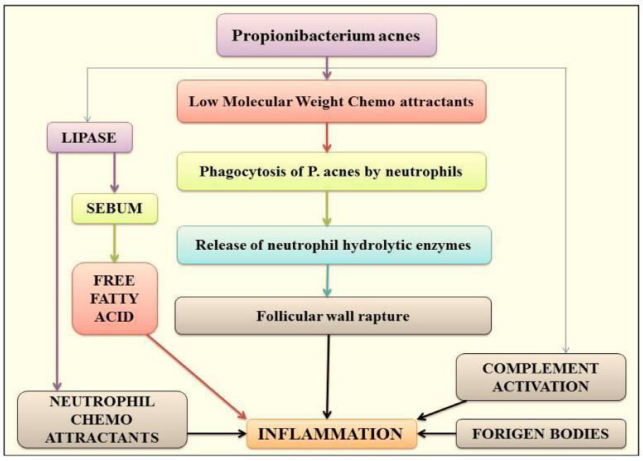



**Fig. 3: Role of androgen involved in pathogenesis of acne**




*(Adopted from: DOI: 10.3109/21691401.2014.916715)*

**Fig. 4: Basic mechanism of acne induction by *P. acne***

## 2. CLASSIFICATION OF ACNE

Acne is broadly classified into four classes such as papular, pustular, comedonal, and pustulocytic acne [3].

### 2.1. Papular Acne

This type of acne shows the presence of papules (10 to 25 in number) usually on the face, back, and posterior region of the body. Presence of bacteria, heat, oil, and dirt is responsible for the generation of this acne type. Inflammatory lesions of size below 5 mm may also be present in the affected area [16].

### 2.2. Pustular Acne

Pustular acne is characterized through the generation of the pustules in the areas like face, neck, and chest. Pustules consist of small bumps on the skin surface filled up with pus or fluid. They may be 20-25 in number [17].

### 2.3. Comedonal Acne

This type of acne consists of non-inflammatory or nonscarring comedones usually found in the area of facial skin. They may vary from 5-10 in numbers and are called microcomedones if their size is equal to or higher than 1 mm [18].

### 2.4. Pustulocystic Acne

This type of acne is characterized by the presence of cyst with extensive scarring in the groin, buttocks and armpit region. Cysts may be over 5 mm in diameter and they affect the deeper skin layers of the body [19].

### 2.5. Types of Acne According to Severity

***Mild Acne***

Fewer than 20 comedones or fewer than 15 inflammatory lesions, or total lesion count fewer than 30.

***Moderate Acne***

20-100 comedones, or 15-50 inflammatory lesions, or total lesion count 30-125.

***Severe Acne***

More than 5 nodules, or Total inflammatory count greater than 50, or Total lesion count greater than 125 [20].

## 3. CAUSES OF ACNE

Various factors such as environmental factors (humidity, heat, etc.), emotional factors, hormonal factors (Androgenic progestin), and micro-organisms are mainly responsible for causing acne.

- High humidity, heat and other conditions cause recurrent and elongated sweating can aggravate acne.
- Tight fitting clothes that confine air movement and avoid evaporation of skin moisture contribute to acne.
- Exposure to grime, cooking oils/smoke or industrial chemicals such as petroleum derivatives can cause occupational acne.
- Hair sprays can block the pilosebaceous gland cause acne.
- Products that contain comedogenic oils cause acne due to occlusive and plugging the follicles.
- Emotional factors will not cause acne but it subsidizes to acne together with severe or prolonged periods of stress or other emotional extremes.
- Androgenic progestin and oral contraceptives are contributors to acne.

- Some medications can exacerbate preexisting acne such as corticosteroids, androgens, azathioprine and bromides with a high progestin level, isoniazid, lithium, phenytoin, and thyroid preparations.
- Acne vulgaris is mainly caused by gram-positive, non-spore forming, micro-aerophilic and rod-like bacterium *P. acnes* [21].

## 4. CURRENT TREATMENT APPROACHES FOR ACNE

Treatment of acne in an individual patient depends on several factors. These factors include a clinical class of acne, size and number of lesions, severity of inflamemation, the oil content of the skin, presence of hyperandrogenism in females, and scarring content [22]. Final selection of treatment regimen depends upon the clinical class or type of acne. The main targets of treatment regimen are a reduction of bacterial number, inflammation, hyperkeratinization, and sebum content [23]. The nature of the patient's skin (whether oily or dry) plays an important role in the selection of vehicle to be used for delivery of anti-acne drugs [24]. Gels can be used for the patients with oily skin as they have the capability to cause dryness of the skin. Creams and lotions may be effective in patients with dry skin due to their moisturizing effect. Although, solutions cause dryness, they can easily cover large areas of the body and in areas having an excess of hairs, foams can be explored for delivery of anti-acne drugs [25]. Currently, acne can be treated by using topical, systemic, surgical, and photodynamic strategies.

### 4.1. Topical treatment of acne

Topical acne can be treated by using different antibiotics, acids, benzoyl peroxide and retinoids [26]. Pustular and inflammatory acne can be effectively treated by using clindamycin and erythromycin antibiotics. They are often used in combination with benzoyl peroxide or retinoids due to their inherent anti-inflammatory properties [27]. Topical clindamycin shows the same effects as that of oral antibiotics upon twice-daily dose administration. Clindamycin lotion can be more efficient compared to gel because it generates less skin dryness in patients [28]. Acidic compounds like salicylic acid and azelaic acid are also capable to eliminate acne when applied topically [29]. Salicylic acid can be implemented as an effective comedolytic and bactericidal agent in concentration 3-5%. This concentration is suitable to be applied on the face chest and back. Use of salicylic acid may promote the chances of hyperpigmentation in darker skin types [30]. Dicarboxylic acid, namely azelaic acid obtained from animal products and cereals also shows prominent topical anti-acne effect. It causes a reduction in stratum corneum thickness by reducing hyperkeratinisation [31]. Patients having sensitive skin can easily tolerate azelaic acid compared to other topical agent. It is more suitable to be used in pregnant women compared to topical retinoids [32]. Furthermore, retinoids are also used for topical acne treatment. Retinoids are the examples of comedolytic agents which are derived from the vitamin A. Retinoids have the capability to block the comedones formation by controlling follicular keratinisation. They may also show anti-inflammatory effect to some extent [33]. Retinoids increase penetration of other topical anti-acne drugs into pilosebaceous unit. Use of benzoyl peroxide with retinoids must be avoided as it inactivates retinoids. The use of retinoids is recommended at night as they are photolabile in nature [34]. Tretinoin is the most commonly used retinoid for anti-acne effect which is a prodrug in nature. It shows efficient anti-acne effect in the concentration range 0.03- 0.05% [35]. Adapalene (also known as Differin) is a synthetic retinoid, which shows the high efficacy of acne removal, less irritation, and lack of photosensitivity at concentration range 0.1-0.3% [36]. Newly developed retinoid, tazarotene is very effective in reducing comedones and open papules without causing dryness and irritation. It increases patient compliance by acting as a skin moisturizer [37]. Table 1 gives an overview of various conventional delivery systems used for acne treatment [38].

### 4.2. Systemic treatment of acne

Systemic treatment of acne is done by using various bioactive molecules like retinoids, hormones, and antibiotics [39]. Acne showing resistance towards conservative treatment is generally exposed to systemic retinoid therapy. Isotretinoin is the main example of systemic retinoid. It can effectively reduce sebum production, follicular keratinisation and surface concentration of causative bacteria [40]. It is supposed to cause complete remission of lesions in patients upon administration of a dose of 1 mg/kg/day for 4 to 8 months. Systemic administration of isotretinoin generates side effects like conjunctivitis, cheilitis, and dryness of body parts like mouth, nose, and skin [41]. It is also categorized as a teratogenic molecule causing cardiac and nervous system abnormalities [42]. Systemic antibiotics are usually employed for the treatment of inflammatory acne. These antibiotics reduce the fatty

acid content of sebum and inflammatory substances produced by the WBCs, ultimately, minimizing inflammation rate. Doxycycline and minocycline are examples of systemic antibiotics belonging to the class tetracycline used for effective acne removal [43]. Minocycline is administered at a dose of 50 - 100 mg (twice daily) for the treatment of pustular acne. Its absorption rate enhances when taken on an empty stomach [44]. Doxycycline is an excellent choice for treatment of inflammatory and pustulocystic acne. It is administered as 100 mg twice daily dose. Administration of doxycycline in a patient less than 9 years of age is contraindicated [45]. Erythromycin is another example of systemic antibiotic used for acne treatment. It is administered as 250-500 mg twice daily dose and considers being safe in pregnant patients. It should be administered with food as it is capable to generate nausea in the patients [46]. For the treatment of severe pustular acne, use of azithromycin at a dose of 250 mg thrice a week is also suggested [47]. Table 2 describes the side effects of various systemic antibiotics used for the treatment of the acne. Oral contraceptives are also preferred nowadays by patients due to their high advertisement in the media. Hormones are not suitable for all the female patients with acne. Main hormonal drugs used for the treatment of acne include spironolactone, prednisone, ethinyl estradiol, and levonorgestrel [48]. Spironolactone is usually taken in a dose of 25-100 mg twice daily for approximately six months. It shows side effects like menstrual irregularities and weakness [49]. Administration of prednisone at a dose of 2.5-5 mg daily for 6 months can be beneficial for acne treatment, however side effects like adrenal suppression can be observed in patients [38]. Estradiol and levonorgestrel are examples of other hormonal drugs used for acne eradication in 20 - 100 µg daily doses for six months. Side effects observed for these drugs are thrombosis, melasma, and gain of weight [50].

**Table 1: Conventional formulations used for topical acne treatment [38]**

| Bioactive Mol. | Conventional Formulations | Side Effects |
|---|---|---|
| Benzoyl peroxide | Lotion | Peeling, itching, redness, dryness, burning, dermatitis |
| | Gel | Dryness, erythema, peeling, dermatitis |
| Clindamycin | Lotion | Peeling, itching, redness, dryness |
| | Cream | Erythema, desquamation |
| Tretinoin | Lotion | Erythema, scaling, burning, Itching, rash, pruritus |
| Erythromycin | Lotion | Erythema, scaling, burning |
| | Gel | Dryness, erythema, peeling, dermatitis |
| Glycolic acid | Lotion | Itching, rash, pruritus |
| Adapalene | Cream | Erythema, scaling, dryness, burning, stinging, irritation |
| | Gel | Erythema, scaling, dryness, burning, stinging |
| Tazarotene | Cream | Erythema, scaling, burning |
| Azelaic acid | Cream | Itching, rash, pruritus |
| Tea oil | Cream | Burning, itching, irritation, stinging |
| Salicylic acid | Gel | Erythema, dryness, dermatitis |
| Dapsone | Gel | Peeling, itching, redness, burning |
| Sodium sulfacetamide-sulfur | Emollient | Dryness, irritation, redness, scaling, stinging, or burning |

**Table 2: Side effects of systemic antibiotics used for efficient acne removal [38]**

| Antibiotic | Side Effects |
|---|---|
| Doxycycline | GI upset, photosensitivity |
| Minocycline | Vertigo, hyperpigmentation of skin and oral mucosa,expensive |
| Erythromycin | GI upset, emergence of resistance of *P. acnes* |
| Azithromycin | Gastrointestinal upset |
| Oxy/Tetracycline | GI upset, vaginal candidiasis, decreased compliance |

### 4.3. Surgical treatment of acne

Surgical removal of acne involves the process known as comedone extraction [51]. In this method, comedonal lesions healed by extracting their content using comedone extractor. Comedone extractor is a device with a small loop on one or both ends. This extractor is placed over the comedone and pressure is applied over it in a perpendicular direction to the skin leading to the removal of comedone [52]. This procedure gives therapeutic compliance to the patient by reducing the number of lesions immediately compared to the medical therapy [51].

### 4.4. Photodynamic treatment of acne

Selective tissue destruction can be achieved by using photodynamic therapy (PDT) [53]. In this therapy, a photosensitizing agent is applied to the affected area and allowed to incubate for minutes to hours. Later on, the area is exposed to a light source for the activation of photosensitizing agent. 20% aminolevulinic acid solution or its methyl ester (MAL) is actively absorbed by the sebaceous gland of acne lesions. These lesions are more responsive towards the photoactivated MAL. Red wavelength light is employed for acne treatment and exposure time is 3-4 hours [54]. PDT combats most of the side effects caused by other therapeutic methods, however, it is a very costly technique and not affordable by all the patients [55].

## 5. NOVEL DRUG DELIVERY SYSTEM FOR THE TREATMENT OF ACNE

Novel drug delivery strategies play an essential role in refining the topical delivery of anti-acne agents by enhancing their dermal localization with a concomitant reduction in their side effects. Pointing is the capability to direct the drug-loaded system to the site of attention. Controlled drug release and following biodegradation are important for developing successful formulations [56]. Potential releases mechanisms involve desorption of surface-bound/adsorbed drugs, diffusion through the carrier matrix, carrier matrix erosion, or combined erosion/diffusion process. Novel carriers are gaining wide acceptance, which include utilization of carriers such as niosomes, liposome, emulsomes, transferosomes, micro emulsion, nano emulsion, and nano lipid carriers that are efficient to transfer the drug across the skin [57].

The main advantages of nanocarriers are:

- Excellent entrapment efficiency;
- Maintain the physiochemical properties of entrapped drug;
- Act as penetration enhancers;
- Act as local depot for sustained release of drugs;
- Deliver the drug molecule to target site without effecting the normal organ or tissue;
- Minimize the toxic effects;
- Accommodate drug molecules with a wide range of solubility;
- Accommodate both lipophilic and hydrophilic drugs;
- Provide protection from hydrolysis and oxidation;
- Provide rapid and efficient penetration of the drug moiety;
- Increase the rate and extent of absorption of the drug;
- Increase the residence time of drugs; and
- Improve the horny layer properties.

### 5.1. Liposomes

Liposomes are most widely used drug delivery vehicles for optimized delivery into specific skin layers [58]. Liposomes are vesicular structures composed of amphiphilic lipids having aqueous core and capability to encapsulate both hydrophilic and lipophilic drug molecules [59, 60]. This property makes them suitable carrier for topical delivery of anti-acne drugs. Efficacy of elastic liposomes loaded with isotretinoin-hydroxypropyl beta-cyclodextrin (HP-beta-CD) inclusion complex was evaluated by Kaur *et al.*, in sprague dawley rats and male albino rabbits. Liposomal formulation showed 4-5 folds higher transdermal flux of isotretinoin compared to a free drug-CD complex solution in rat skin. Irritation studies carried out in male albino rabbits revealed a reduction in irritation genera-ted by liposomal formulation compared to free drug solution and drug-CD complex solution [61]. Later on, Pornpattananangkul *et al.*, developed lauric acid loaded liposomes (LipoLA) for effective eradication of acne infection in the ICR mouse. Liposomal formulation (LipoLA) showed effective *invivo* eradi-cation of *P. acnes* from infectious sites in mouse ear model and reduction of acute toxicity in animal skin compared to free benzoyl peroxide and salicylic acid [62]. After topical application, liposome can improve drug deposition within the skin at the site of action, reduces systemic absorption and minimizes the side effects thereby providing localized effect [63]. They can target the drug to skin appendages in addition and increase the systemic absorption [64]. The major disadvantage of liposomal formulation is related to its stability aspect. The stability

issue of liposomes remains an area, which is surrounded by a number of problems; due to the formation of ice crystals in liposomes, the subsequent instability of bilayers leads to the leakage of entrapped material. The physical instability is also faced by liposomes. The oxidation of cholesterol and phospholipids leads to the formulation instability. Chemical instability indicates the hydrolysis and oxidation of lipids. The destabilization of liposomes is due to the lipid exchange between the liposomes and HDLs [65].

### 5.2. Niosomes

Niosomes are unilamellar or multilamellar vesicles wherein an aqueous phase is encapsulated in highly ordered bilayer made up of nonionic surfactant [66].They are nonionic surfactant vesicles by which skin penetration and accumulation are increased in the superficial skin strata [67]. Liu and Huang carried out an *in-vitro* evaluation of curcumin loaded niosomes containing lauric acid for effective elimination of acne. Niosomal formulation showed curcumin reservoir formation in neonate pig skin at concentration of 0.43µg/ml of curcumin and a significant reduction in *P. acnes* content *in-vitro* [68]. Niosomes can enhance the residence time of drug in the stratum corneum and epidermis, while systemic absorption of the drug can be reduced [69-72]. They also increase the horny layer properties by reducing transepidermal water loss and increasing the smoothness via replenishing lost skin lipids [67, 73, 74]. Both Niosomes and liposomes are equiactive in drug delivery potential and both increases the drug efficacy as compared with that of free-drug. Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy. One of the reasons for preparing niosomes is that they assume higher chemical stability of the surfactants than that of phospholipids which are used in the preparation of liposomes. Due to the presence of ester bond, phospholipids are easily hydrolysed [75]. Although niosomes are superior to liposomes, they have some stability problems associated with them such as physical stability of fusion, aggregation, sedimentation and leakage on storage. The major issue is the hydrolysis of encapsulated drugs which limits the shelf life of the dispersion in niosomes [76].

### 5.3. Aspasomes

Aspasomes are novel vesicular carriers recently investigated by Gopinath *et al.*, which are formed by using ascorbyl palmitate, cholesterol and dicetyl phosphate. Aspasomes can gain importance in acne therapy as the potential of ascorbic acid derivatives in acne treatment has been realized. They can be fabricated by the typical film hydration method. Aspasomes have been characterized by conventional techniques for bilayer formation and thermal behavior by differential scanning calorimetry (DSC) analysis. Their advantages in dermal delivery of therapeutic agents are similar to that of liposomes. Moreover, their inherent antioxidant potential can be complementary to the topical acne therapy [77].

### 5.4. Microemulsions

Microemulsions are colloidal translucent dispersions containing oil, surface active agent, co- surfactant, and water. A microemulsion may be oil in water (o/w) or water in oil (w/o) in nature [78]. High solubilization capacity of microemulsions makes them able to carry high amounts of bioactive molecules [79]. Various studies have discovered the significance of micro-emulsion for dermal and transdermal delivery both *in-vitro* and *in-vivo*. Due to the high solubilization capacity, a large quantity of drug can be incorporated in this formulation. The components of microemulsion can interact with the lipid layers of stratum corneum and changes its structural integrity leading to enhance transdermal permeation of drug [80]. Liu and Huang studied the antimicrobial activity of curcumin-loaded myristic acid micro-emulsions against *Staphy-lococcus epidermidis*. Curcumin distribution in neonate pig skin was visualized using confocal laser scanning microscopy. Curcumin (0.86 mg/mL) in the myristic acid micro-emulsion could inhibit 50% of the bacterial growth, which was 12 times more effective than curcumin dissolved in dimethyl sulfoxide (DMSO). The cocktail combination of myristic acid and curcumin in the microemulsion carrier synergistically inhibited the growth of *S. epidermidis* [81].

### 5.5. Nano-emulsion

Nano-emulsions (NEs) can also be defined as “ultrafine emulsions” because of the formation of droplets in the submicron range. A nano-emulsion seems to be transparent and translucent with a bluish color. The small-size droplets give them characteristic stability against creaming, sedimentation, flocculation, and coalescence. It allows the effective transport of active ingredients to the skin [82]. Lin et al., developed lipid nanocarriers, NEs, and nanostructured lipid carriers (NLCs) that combine Tretinoin and tetracycline for the

efficient topical delivery to treat acne vulgaris. The antibacterial activities of the nanosystems against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *P. acnes* were evaluated using an agar diffusion assay. NEs and NLCs exhibited high entrapment of Tretinoin which ranged 60-100%. This is the first report examining skin permeation and antibacterial activities of dual-drug nanocarriers for acne treatment [83].

### 5.6. Surfactant-free emulsions

Emulsifier-free formulations are a developing area for dermatologic and cosmetic products. Most skin care products are emulsions, that is, a mixture of two or more materials that are not miscible with each other. As a result, they require the addition of surfactants (emulsifiers) that stabilize the formulation and increase its shelf life. Furthermore, once these surfactant agents are applied on the skin, they tend to emulsify and remove the natural lipids of the epidermis. Accordingly, the pharmaceutical industry has been developing surfactant-free emulsions as alternatives to conventional formulations using stabilizers, such as polymeric emulsifiers or solid particles. These stabilizers produce sufficiently stable products with a cosmetically pleasant appearance [84]. Dominguez-Delgado et al. prepared and characterized surfactant-free emulsions of Triclosan intended to be used for the treatment of acne. Differential scanning calorimetry, transmission electron microscopy, and scanning electron microscopy studies suggested that Triclosan-loaded emulsions show good encapsulation efficiency (95.9%). Emulsions, being free of surfactants or other potentially irritant agents, can be a good option for the delivery of Triclosan to the skin, representing a good alternative for the treatment of acne [84].

### 5.7. Polymeric nanoparticles

Release pattern or transport of a bioactive molecule can be modified easily by its encapsulation in a nanocarrier. Polymeric nanoparticles may be suitable carriers to deliver the drugs topically [85-87]. Polymeric nanoparticles are defined as colloidal particles having a size range of 10-400 nm [88, 89]. Poly(lactic-co-glycolic acid) and chitosan are the examples of widely used polymers for the preparation of topical nanoparticulate systems [90-92]. Domínguez-Delgado *et al.*, developed triclosan loaded Eudragit® E 100 nano-particles and evaluated them for *in-vitro* skin permeation using pig ear skin. Prepared nanoparticles showed equivalent penetration power compared to commercial cream in the skin and high skin retention of drug compared to free drug solution. Thus, drug-loaded nanoparticles were considered an effective alternative to treat acne [84].

### 5.8. Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLN) were introduced in the year 1991 and they embody an alternative carrier system to tradition colloidal carriers such as emulsions, liposomes, and polymeric carriers. Solid lipid nanoparticles (SLNs) are particles made from solid lipids with a mean diameter between approximately 50 and 1000 nm, which are normally stabilized by lecithin [93, 94]. The reasons for the ever-increasing applications of lipid based system are many fold and include the following: lipids enhance the oral bioavailability and reduce plasma profile variability, better characterization of lipoid excipients and an improved ability to address the key issues of technology transfer and manufacture scale-up. The occlusive nature of SLNs makes them capable to enhance the moisture content of the skin. Castro *et al.*, prepared retinoic acid-loaded SLNs and evaluated them *in-vitro* for the treatment of acne. The addition of amines to glyceryl behenate based SLNs improved their encapsulation efficiency and *invitro* skin permeation power [95]. Later on, tretinoin loaded SLNs were developed by Shah *et al.*, using biocom-patible microemulsion as a template. Prepared SLNs showed the ability to encapsulate 48% of the drug at a particle size of 175 nm indicating its effectiveness to treat acne [96]. The release rate of the drug from SLNs depends on the presence of the drug in the solid lipid matrix. If the drug is localized only in the outer shell, burst release will be obtained and not controlled release. If the drug is homogeneously distributed within the lipid matrix, however, controlled release can be achieved [97, 98]. Some of the parameters, which hinder the use of SLN, are particle growth, unpredictable gelation tendency, and unexpected dynamics of polymeric transitions.

### 5.9. Nanostructured lipid carriers (NLCs)

Tailored solid lipid nanoparticles (SLNs) are known as nanostructured lipid carriers (NLCs) [99, 100]. Structurally, they show incorporation of the liquid lipids in solid lipid matrix. NLCs have less organized crystalline structure due to the presence of liquid lipids promoting high loading capacity for the accommodation of bioactive molecules in them compared to SLNs [101-103]. Stecová *et al.*, carried out a comparative assessment between SLNs, NLCs, and microspheres

loaded with cyproterone acetate for treatment of acne *in-vitro* in human skin. Prepared NLCs showed 2-3 fold increase in drug absorption *in-vitro* compared to microspheres and SLNs [104]. Table 8 describes an overview of research focusing on the use of NLCs for acne treatment [105-108].

### 5.10. Microspheres

Microsphere technology improves the treatment tolerability, encourage adherence, and contribute to better long-term therapeutic outcomes. Microsphere technology removes the quick delivery of high concentrations of active drug to the application site and instead facilitates controlled release of potentially irritating drugs. It is associated with improved treatment outcomes and minimal irritation. Microsphere formulations of topical tretinoin and benzoyl peroxide (BPO) currently on the market have demonstrated good efficacy and tolerability and are expected to encourage adherence and long-term therapeutic benefit [109]. Eichenfield et al. studied the safety and efficacy of Tretinoin microsphere gel (TMG) 0.04% pump in children aged 9-11 years with acne vulgaris. The results showed that greater improvement in the least-squares mean change in non-inflammatory lesions with TMG 0.04% than with vehicle (-19.9 vs. -9.7, $p$=0.04) and a significant difference in Investigator Global Assessment of improvement at Week 12 between the children treated with TMG 0.04% pump and those treated with vehicle ($p$= 0.02), but there were no discernible differences in static acne severity scales. This study confirmed statistically significant differences in the reduction of non-inflammatory lesions between TMG 0.04% pump and vehicle in patients aged 9-11 years with acne vulgaris [110].

### 5.11. Microsponges

Microsponges are biologically inert particles prepared of synthetic polymers with the capacity to store a volume of an active agent up to their own weight. Additionally, the particles assist to defend the entrapped active compound from physical and environmental degradation. The microsponge technology can be utilized in a variety of formulations, but is more frequently manufactured as gels. Microsponge delivery system when applied to the skin, the release of drug can be controlled through diffusion or other variety of triggers, including rubbing, moisture, pH, friction, or ambient skin temperature [111]. Controlled release of drug from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Microsponges are capable of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Microsponge polymers possess the ability to load a wide range of actives providing the benefits of enhanced product efficacy, mildness, tolerability, and extended wear to a wide range of skin therapies [112, 113]. Jelvehgari et al. developed microsponge delivery system of BPO for the treatment of acne and athletes foot. The micrograph of microsponges showed that they were spherical in shape and contained pores. One of the research studies showed that an increase in the ratio of drug: polymer resulted in a reduction in the release rate of BPO from microsponges which were attributed to a decreased internal porosity of the microsponges [114].

### 5.12. Hydrogel

Hydrogels are the network of polymer chains that are water-insoluble and sometimes they are found as a colloidal gel in which water is the dispersion medium. Hydrogels are superabsorbent natural or synthetic polymers [115, 116]. Hydrogels are three dimensional, hydrophilic networks that hold large amount of water or biological fluids, similar to biological tissues. Because of this unique property, hydrogels show good biomedical applications. By tuning, the physicochemical properties of the hydrogels suitable modulated drug delivery system are generated [116].

### 5.13. Aerosols foams

Aerosol foams have converted an increasingly standard type of topical formulation for a variety of skin conditions including acne vulgaris. Foams are preferred for application on large hairy surfaces like the chest, back, and in the face as cleansers due to easiness of application. The vehicle base of the foam can have a liquid or semi-solid consistency that shares the same physicochemical characteristics of conventional vehicles like creams, lotions and gels, but it maintains desirable properties such as moisturizing, fast-drying effects or higher drug bioavailability. The aerosol base is dispensed through a gas pressurized can that discharges the foam. The product characteristics (i.e., texture, bubble size and thickness, viscosity, stability and spreadibility) are determined by the type of formulation and the dispensing containers that are selected to suit the specific treatment needs [117]. Del Rosso successfully prepared sodium sulfacetamide 10%-sulfur 5% emollient foam in the treatment of acne vulgaris. Recently, an emollient foam sodium sulfacetamide

10%-sulfur 5% formulation indicated for topical therapy of acne vulgaris, rosacea and seborrhea dermatitis has become available [118].

### 5.14. Fullerenes

Fullerenes (resemble a hollow sphere) are molecules composed entirely of carbon. Once fullerenes come into contact with the skin, they migrate through the skin intracellularly, as opposite to affecting over cells. So, a fullerene could be used to "trap" active compounds and then release them into the epidermis on the skin after the application. Moreover, fullerenes, themselves, are thought to be potentially potent antioxidants [119]. Inui et al. developed polyhydroxylated fullerene (capable of potent radical-scavenging activity) and investigated its inhibitory effects *in vitro* on sebum production in hamster sebocytes and in *P. acnes* lipase activity. These results suggested that fullerene could be a beneficial skin care reagent for controlling acne vulgaris by suppressing sebum in the inflammatory response and by reducing *P. acnes* lipase activity [120]. Literature on fullerenes proved that they can be tolerated and can hold substantial promise in dermatologic and cosmetic applications.

### 5.15. Lipospheres

Lipospheres are lipid-based encapsulation system, used for topical drug delivery of various medicaments. Lipospheres consists of water dispersible solid microparticles, which have diameter ranging from 0.1 to 100 $\mu$m. In liposphere, solid hydrophobic fat core is stabilized by a layer of phospholipid molecules embedded in their surfaces, which are a potential group of penetration enhancers [121-125]. Better physical stability, high dispersability in aqueousmediumand prolonged release of various types of drugs including anti-inflammatory compounds, local anesthetics, antibiotics, and anticancer agents are possible using this type of system [126-128].

### 5.16. Polymers

Polymers are large molecules, which consist of repeating structural units of monomers connected by chemical covalent bonds. In dermatology, the new acrylic acid polymer turns into gel in presence of water by trapping water into microcells. A stable gel-like formulation containing hydrophilic compound as solution and lipophilic compound in the form of suspension is easy to use, and it releases the active compound after single application. For example, an antiacne formulation that combines clindamycin (1%) and benzoyl peroxide (5%) utilizes this novel polymerbased gel technology and provides excellent tolerability and efficacy. Despite the availability of numerous effective medical therapies for acne vulgaris, issues of safety, compliance, and less than ideal efficacy help drive the search for alternative treatments for this exceedingly common clinical problem. Recently, scientists have developed effective vaccine for *P. acnes*-associated inflammatory acne, consisting of a cell wallanchored sialidase of *P. acnes* or killed-whole organism of *P. acnes* [129, 130]. They also hope to develop a future bacterial therapy for overcoming problems seen with the continuous use of antibiotics such as a building up a bacteria resistance. These scientists of the 21st century are convinced that acne is not due to dirt and that scrubbing skin can lead to worse problems. Therefore, in the future, it is possible to explore the use of micro- and nanocarrier-based drug delivery systems in advanced form with increase in effectiveness for treatment of acne.

Table 3 shows the various applications of novel nanocarriers systems in the effective treatment of acne [131]. Recently, nanotechnological carriers have created new possibilities of acne treatment due to their several advantages over conventional treatment strategies. Therefore, scientists are exploring this field of nanomedicine for effective acne removal. A list of patents regarding the use of nanotechnological carriers for treatment of acne is given in Table 4.

**Table 3: Applications of nano-carrier systems for treatment of acne**

| Nano-carrier | Bioactive molecule | Results/Applications |
|---|---|---|
| Solid lipid nanoparticles | Isotretinoin (ITR) | Increasing the therapeutic performance of all types of acne, including recalcitrant, severe and nodulocystic |
| Solid lipid nanoparticles | Tretinoin (TRE) | Increase the therapeutic effectiveness of drug for treatment of various skin diseases including acne and psoriasis |
| Solid lipid nanoparticles | Retinoic acid | Reduce skin irritation without reducing efficacy, for the topical treatment of acne |

| | | |
|---|---|---|
| Solid lipid nanoparticles | All-trans retinoic acid (RA) | Improve the entrapment efficiency of RA in SLN using a low surfactant/lipid ratio |
| Solid lipid nanoparticles | Tretinoin (TRE) | Increase the therapeutic effectiveness of drug for treatment of various skin diseases including acne |
| Microspheres | Adapalene | Improve the therapeutic index of drug for the treatment of acne |
| Microspheres | Tretinoin (TRE) | Showed excellent safety and efficacy of drug for the treatment of acne in the preadolescent population |
| Microspheres | Tretinoin (TRE) | Showed anti-inflammatory effects against acne after oral administration of Isotretinoin |
| Microspheres | Tretinoin (TRE) | Tretinoin gel microsphere 0.1% showed better cutaneous tolerability profile (Lucky and |
| Microspheres | Tretinoin (TRE) | Showed greater therapeutic efficiency against mild-to-moderate acne. |
| Liposomes | Clindamycin | Showed therapeutic effectiveness acne vulgaris in pig ear skin. |
| Liposomes | Benzoyl peroxide (BPO) | Showed a significantly greater antibacterial efficacy for Propionibacteria and |
| Liposomes | Tretinoin (TRE) | Allows reduction of the concentration of the active agent without a decline in efficacy for acne vulgaris. |
| Liposomes | 5-aminolevulinic acid (5-ALA) | Reduced inflammatory facial acne in Asians, with a low risk of persistent phototoxic effects |
| Liposomes | 5-aminolevulinic acid (5-ALA) | Improved inflammatory acne with minimal side effects in Asians (An et al. 2011). |
| Niosomes | Isotretinoin | Great potential for skin targeting, prolonging drug release, reduction of photo degradation, reducing skin irritation and improving topical delivery of drug |
| Niosomes | Curcumin | Curcumin-loaded vehicles could efficiently accumulate in the skin and inhibit*P. acnes* |
| Micro-emulsion | Thai basil oil, Holi basil oil | Showed therapeutic activity against *P. acnes*. |
| Nano-emulsion | Adapalene, Clindamycin | Showed more efficacious and better tolerated for the treatment of acne vulgaris in Indian patients |
| Aerosols foams | Povidone iodine | Act as skin cleanser in the management of acne vulgaris |
| Micro sponge | Tretinoin (TRE) | Showed an excellent treatment of face acne vulgaris |
| Fullerenes | Fullerenol C60(OH)44 | Beneficial skin care reagent for controlling acne vulgaris by suppressing sebum in the inflammatory response and by reducing *P. acnes* lipase activity |
| Fullerenes | Fullerenes | Fullerene gel help in controlling acne vulgaris with skin care benefit. |

**Table 4: Patents regarding the use of nanotechnological carriers for the treatment of acne**

| Title of Patent | Brief Description | Inventors | Patent Number |
|---|---|---|---|
| Use of PVP-Iodine liposomes for treatment of acne | This invention describes the method of preparation of liposomes loaded with PVP-Iodine complex and their characterization | Karen Reimer, Wolf-gang Fleischer, Michael Hopp | US20120294933 A1 |
| Application of ginkgo extract nanometer liposomes in acne removing and dermatosis treatment | This patent explains the preparation of nanometer liposomes containing ginkgo extract (0.001-8.0%) and their capability to eliminate acne pathogens from the skin with minimum irritation | Lei Hong, Wang Qing | CN103751231 A |
| Liposome composition for treating acne containing conjugate of lysophosphati-dylcholine and chlorine e6 | his invention describes the preparation method of liposomes enclosing 0.001% to 5% by weight of lysophosphatidylcholine and chlorine e6 and their anti-acne efficacy | Hong Geun Ji, Hyo Gyoung Yu, Young Rong Woo, Dong KIM, Se Hee Jo, Kun Na, Hyung Park | US 9457083 B2 |

| | | | |
|---|---|---|---|
| Anti-acne microemulsion system and preparation method thereof | This patent gives a description of the preparation method of microemulsion system loaded with Pogostemon extract and its efficacyto treat acne | Wei Kejie, Law Yan, Lin Jiancong | CN104523473 A |
| Compound aloe microemulsion composition and its preparing method | This invention deals with the method of preparation of microemulsion of size range 1 - 100 nm loaded with aloe extract and its anti-acne efficacy following topical delivery | Floor Layer, Hou Deqiang, Feng Yuqin, Shen Fuan, Rao Yan, Fang Li Song, Shen Yuan | CN1292728 C |
| Polymeric nanoparticles for photosensitizers | This patent gives a description about the utility of hypocrellin-B loaded poly (lactide-co-glycolide) nanoparticles for effective removal of acne | Azita Haddadi, Ragupathy Madiyalakan, Thomas Woo | WO2013020204 A1 |
| Solid lipid nanoparticles of roxithromycin for hair loss or acne | This invention describes the method of preparation of solid lipid nanoparticles loaded with roxithro mycin (0.1 to 10.0%) and their therapeutic effect against hair loss and acne | Krysztof Cal, Hanna Wosicka | WO2014077712 A1 |
| Process for preparing solid lipid sustained release nanoparticles for delivery of vitamins | This invention deals with the method of preparation vitamin (Vitamin D3 and retinoic acid) loaded sustained release nanoparticles forthe treatment of diseases like acne, hyperpigmentation and osteoporosis | Indu Pal Kaur, Manoj Kumar Verma | US20140348938 A1 |
| Preparation for the topical application of anti-androgenically active substances | This invention discloses the development method of lipidic nanoparticles or nanoemulsion which can be explored for the effective elimination of acne, alopecia, and hirsutism | Karl Theodor Krae mer, Karl-Heinz Nietsch, Rainer Pooth, Uwe Muenster, Wolfgang Mehnert, Monika Schaefer-Korting | CA2483786 A1 |
| Topical formulation comprising adapalene microspheres and clindamycin | This patent describes a stable fixed dose topical formulation containing adapalene loaded microspheres and free clindamycin in combination for the treatment of acne | Ulhas Rameshchandra Dhuppad, Nitin Babulal Bhamre, Sunil Sudhakar Chaudhari, Girish Ramkrishna Trivedi, Akhilesh Dayanand Sharma, Prashant Dongre | WO2009116086 A3 |
| Topical nano drug formulation | This invention discloses a method of preparation of nanostructured lipid carriers (NLCs) loaded with spironolactone and their anti-acne efficacy in the gel form | Hamidreza, Kelidari, Majid Saeedi | US20170020896 A1 |

## 6. CONCLUSION

In present review, we have discussed about the whole global consequence of the disease by familiarizing drug delivery systems or by modifying the current ones as chemotherapy regimen for acne. Particulate, vesicular, and colloidal drug delivery approaches have their important place in acne therapy. From the above study, we can conclude that the above nanotechnology approaches has an enormous opportunity for the designing of a novel, low-dose and effective treatment systems to control acne disease. From the future perception, development of vaccines using combined strategic approach like nanocarriers can play a major role in the treatment of acne.

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