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Review Article

Novel Drug Delivery System and Its Uses in the Treatment of Acne

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Acne is a common inflammatory skin disease which affects the pilosebaceous units of the skin. It can have severe psychological effects and can leave the patient with severe skin scarring. There are four well-recognized pathological factors responsible for acne which is also the target for acne therapy. In this review, different treatment options are discussed, including topical (i.e., retinoids, and antibiotics) and systemic (i.e., retinoid, antibiotics, and hormonal) treatments. Since the general public has been shown an increasing interest in more natural and generally safer treatment options, the use of complementary and alternative medicines (CAM) for treating acne was also discussed. The use of physical therapies such as comedone extraction, cryoslush therapy, cryotherapy, electrocauterization, intralesional corticosteroids and optical treatments are also mentioned. Acne has been extensively researched with regards to the disease mechanism as well as treatment options. However, due to the increasing resistance of Propionibacterium acnes towards the available antibiotics, there is a need for new treatment methods. Additionally, the lack of necessary evidence on the efficacy of CAM therapies makes it necessary for researchers to investigate these treatment options further.

Keywords: Novel drug delivery system, Acne, Retinoids, Tretinoin, Adapalene and Benzoyl peroxide.

INTRODUCTION

Acne is a medical condition describing blocked skin pores that result in lesions. For a variety of reasons that aren't entirely understood, skin pores can become plugged with sebum, the natural oil produced by skin's sebaceous glands. Once plugged, dead cells and bacteria become trapped in the pore, resulting in the lesions common to acne. The most common lesions are called 'comedones'. Comedones come in two basic varieties, 'white heads' and 'black heads'. A

white head is a plugged pore that has begun to bulge outward from the skin due to bacteria, dead skin cells, and other contaminants that have become trapped inside.^[1] The bulging dome shape often takes on a white appearance. Black heads are simply comedones that have become opened, revealing the dark follicle plug within. Acne comedones are often referred to as pimples or zits. Microcomedones are a less common form of acne lesion, sometimes referred to as papules. These are basically small comedones that form from localized cellular

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reactions to the processes that cause acne.^[2] That usually occur in clusters and are sometimes too small to see, but can be felt as a series of little bumps along the skin surface. In more severe forms of acne, pustules, nodules and cysts can form. A pustule is like a normal comedone, but larger due to a higher amount of dead white cells, or pus, trapped inside the plugged sebaceous follicle. Nodules are a more severe form of papules, extending deeper into the skin tissue and resulting in large raised lesions that are usually inflamed, and painful to touch. Cysts are very large fluid filled sacs that can result from pustules or nodules. Though none of these forms of acne are dangerous or life threatening, they can leave scars and are sometimes very disfiguring. What causes the plugged pores that result in acne is a question that scientists and doctors still haven't been able to completely agree upon. Today, most theories seem to point to a combination of factors that include genetics, hormone changes, and stress. For years it was believed that diet was a strong component to acne, but most evidence today suggests that hormones and stress are more likely to be the culprits.

CAUSE OF ACNE

Acne develops as a result of blockages in follicles hyperkeratinization and formation of a plug of keratin and sebum (a microcomedo) is

the earliest change. Enlargement of sebaceous glands and an increase in sebum production occur with increased androgen (DHEA-S) production at adrenaeche. The microcomedo may enlarge to form an open comedone (blackhead) or close comedone (whitehead).^[3] Whitehead are the direct result of sebaceous gland becoming clogged with sebum, a naturally occurring oil, and dead skin cells. In these condition the naturally largely commensal bacteria propionobacterium acnes can cause inflammation, leading to inflammatory lesion (papules, infected pustules, or nodules) in the dermis around the microcomedo or comedone, which results in redness and may result in scarring or hyperpigmentation.

- **Genetically-** There is a much greater chance for the children to have acne if their parents had acne in their teenage years, as the genes carry information from the parents to children. This form of acne cannot be avoided until and unless the advancement of medical sciences leads to the deletion of the culprit genes.
- **Hormonal-** There is production of the androgen hormones during the adulthood years and this hormone activates the stimulation of the oil producing glands in the skin and this leads to the clogging of the pores and in turn results in the causation of pimples and blackheads.
- **Stress-** This is not a proven fact whether the



stress causes the initiation and formation of acne lesions, but this can surely aggravate the acne pimples and can also aggravate any condition of the skin that you are suffering from

- **Diet-** It is not surely known that the diet can cause the formation of acne pimples as is the case with stress, but there are some experts who believe that the allergies to certain foods can cause the trigger of the acne problem in an individual.

TREATMENT

The main goal of acne treatment is to control and treat existing acne lesions, prevent permanent scarring as far as possible, limit the duration of the disorder and to minimize morbidity. The patient should be informed on the aims involved in preventing new acne lesions while allowing the existing ones to heal. Patients should also be made aware that it may take 3–6 weeks until an improvement can be observed. [4] Individual patient factors must be taken into account when determining a regimen for the treatment of acne. Some of these factors are the current medical condition, disease state, severity of the lesions, endocrine history and the preferred treatment of the patient.

Topical Treatment

Topical products have the advantage of being applied to the affected area directly; thus

decreasing systemic absorption and increasing the exposure of the pilo-sebaceous units to the treatment.[4] However, a major side effect of topically applied anti-acne products is skin irritation. Preparations for topical application are available as various formulations, including creams, gels, lotions, solutions and washes. Topical therapy is based on the type and severity of acne. Mild acne is often treated with topical retinoids, or a variety of diverse treatments such as azelaic acid, salicylic acid and benzoyl peroxide. Mild to moderate inflammatory acne can be treated with topical anti-inflammatory agents as well as topical antibiotics . The different topical anti-acne drugs target different pathophysiological factors and a few of the common topical treatments will be discussed below.

Retinoids

Topical retinoids can be used as mono therapy for inflammatory acne, in combination with more severe forms of acne or as a maintenance treatment. They generally control the formation of microcomedones, reduce the formation of lesions and existing comedones, decrease sebum production and normalize desquamation of the epithelium. They target the microcomedones and suppress comedone formation. They may also show anti-inflammatory properties. Gollnick and Krautheim gave the following suggestions on the



use of topical retinoid: (1) the use of topical retinoid is vital for maintenance treatment; (2) retinoids can repair the scarring and hyperpigmentation of the skin; (3) this class of drugs should be first choice of treatment for most of the acne types; and (4) when combined with topical antimicrobials it is more effective in inflammatory acne. A common side effect during the first few weeks of topical retinoid treatment is a flare up of acne. This should, however, clear as the patient continues with the treatment . Only some of the most common topical retinoids (i.e., tretinoin, adapalene and tazarotene) used in acne treatment will be discussed.

Tretinoin

Tretinoin is a form of vitamin A. It is a standard comedolytic agent used in acne treatment to regularize desquamation of the epithelium, which prevents blockage of pilosebaceous units. It also seems to have anti-inflammatory properties. It has been a topical treatment for acne for over three decades.

Adapalene

Adapalene is a synthetic retinoid analogue which is most commonly used as a first line topical retinoid treatment for Acne vulgaris. It normalizes the cell differentiation of the follicular epithelium and prevents comedone formation. It also shows anti-inflammatory action on the acne lesions.

Tazarotene

Tazarotene is a synthetic acetylenic pro-drug which is converted to tazarotenic acid in keratinocytes. It is one of the newer retinoids used for acne treatment. It affects the keratinocyte differentiation and proliferation in the epithelial tissue and may also show anti-inflammatory properties . It is regarded as a second line treatment after no response was observed after previous tretinoin or adapalene treatment, as it may cause skin irritation in acne patients.

Other Retinoids

Other retinoids used for topical treatment of acne include isotretinoin, retinoyl α -glucuronide and motretinide. However, according to Zaenglein , these topical retinoid formulations are unavailable in the USA, although they are commonly used in the European Union. Of these three retinoids, only isotretinoin is available as a topical formulation in South Africa.

Antibiotics

Topical antibiotics are generally used for mild to moderate inflammatory acne. They have activity against P. acnes, and therefore act on the surface of the skin to reduce the stimulus for inflammation of the lesions . Due to certain side effects and lesser effectiveness of topical chloramphenicol and tetracyclines, these drugs are less frequently used. The most popular topical antibiotics used in acne treatment are



erythromycin and clindamycin, but, in recent years, the continuous use of these antibiotics has led to the increasing development of resistance against *P. acnes* strains. Therefore, it is recommended that mono therapy with topical antibiotics are used for only a short time period (12 weeks) and that the antibiotics should be combined with benzoyl peroxide, zinc or retinoids to prevent bacterial resistance . The use of oral and topical antibiotics in combination to treat acne should be avoided.

Erythromycin

Erythromycin is a macrolide antibiotic that attaches to the 50S ribosomal unit of bacterium and prevents translocation, which is necessary for protein synthesis of the bacteria . It is active against *P. acnes* and reduces the colony on the surface of the skin and within follicles. It has been regarded as a very effective topical antibiotic in acne therapy, but recently it was discovered that erythromycin is up to 60% resistant to *P. acnes* which makes it less desirable. This has led to interest in the future development of other topical antibiotics.

Clindamycin

Clindamycin is classified as a lincosamide antibiotic. It is a semi-synthetic derivative of the antimicrobial agent, lincomycin. Clindamycin attaches to the 50S ribosomal subunit and inhibits protein synthesis of the bacteria and as

with erythromycin; it also inhibits *P. acnes* on the surface of the skin .

Diverse Treatments

Other topical treatments used for acne, such as for example chemical peels, benzoyl peroxide, dapson, etc. will be discussed in the following section.

Salicylic Acid

Salicylic acid is known as a keratolytic agent whose mechanisms of action is to dissolve the intercellular cement which holds the cells of the epithelium together. It has a minor anti inflammatory effect, enhances penetration of certain substances and at low concentrations it is fungistatic and bacteriostatic. Salicylic acid is found in a number of over-the-counter products for acne treatment.

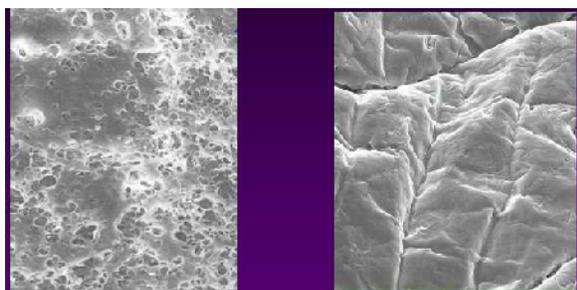
Chemical Peeling with Hydroxy Acids

Chemical peels involve facial resurfacing whereby removal of the epidermis stimulates re-epithelization and skin rejuvenation . Chemical peeling also appears to reduce hyperpigmentation and superficial scarring of the skin. This therapy can be divided into different groups according to its penetration depth and destruction. Alpha-hydroxy acids (i.e., glycolic acid and lactic acid) and beta-hydroxy acids (i.e., salicylic acid) are the most common chemicals used in chemical peels. A much higher concentration of salicylic acid (20%–30%) is

present in chemical peels than found in daily acne cleansers. There exist little evidence/data that peels are relatively safe to use. Therefore, it should be regarded as a complementary treatment rather than a first-line treatment.

Benzoyl Peroxide

Benzoyl peroxide is a topical disinfectant, originally employed as a peeling agent for treating acne. It possesses diverse properties, making it both a comedolytic and an antibacterial agent, with no effect on sebum production. Benzoyl peroxide has proven bactericidal activity against P. Acnes by releasing free radical oxygen, which degrades the bacterial proteins. Bershad stated that in addition to its successful treatment of inflammatory acne, benzoyl peroxide Also decreases the Insoluble benzoyl



Soluble benzoyl peroxide (Novel drug) .



Benzoyl peroxide cream

number of comedones on the skin. Benzoyl peroxide is an important treatment for mild to moderate acne and, although it can be used as monotherapy for a period of 6–8 weeks, is often combined with topical antibiotics in order to reduce the resistance of the P. acnes species and to increase the efficacy of treatment . Gollnick and Krautheim suggested that benzoyl peroxide is best combined with topical retinoids. However, it has been found that all retinoids (except for adapalene) are unstable when combined with benzoyl peroxide and should therefore be applied separately . The main side effects of benzoyl peroxide include burning, dryness, erythema, peeling or stinging .

Azelaic Acid

Azelaic acid is a natural dicarboxylic acid that inhibits protein synthesis of the P. acnes species. It is an effective agent because it has bacteriostatic, anti-inflammatory, antioxidant and anti-keratinizing properties. Thusfar, no bacterial resistance of P. acnes exists with azelaic acid. It has also been suggested that when azelaic acid is used in conjunction with clindamycin, benzoyl peroxide or α -hydroxy acids it will be more effective. Sulfur In the past, sulfur was frequently used in preparations for acne. This active has, however, become unpopular due to its bad odor. Sulfur is a chemical that has demonstrated to have mild keratolytic and bacteriostatic



properties. Sulfur is reduced to hydrogen sulfide inside the keratinocytes which is said to break down keratin in the skin. According to Akhavan and Bershad, sulfur also has activity against P. acnes.

Niacinamide

Niacinamide is an active amide of vitamin B3 and is composed of niacin (also known as nicotinic acid) and its amide. It may also be referred to as nicotinamide. Its mechanism of action can be explained as the inhibition of sebocyte secretions, resulting in less sebum production which reduces the oiliness of the skin. It also has anti-inflammatory properties which have proved to be beneficial in pustular as well as papular acne. Topical application of a 4% niacinamide has led to significant improvements to acne all over the world.

Topical Corticosteroids

Topical corticosteroids can be used in certain conditions, as for example to treat very inflammatory acne. The treatment period should, however, be short and proof of their efficiency should still be determined.

Triclosan

Triclosan is an antibacterial agent (antiseptic) which can be used to treat acne. It was determined that bacterial populations did not develop resistance to triclosan under clinical

conditions. No adverse effects are anticipated when triclosan containing products are used as recommended.

Sodium Sulfacetamide

This agent belongs to the sulfonamide antibacterial group. It is bacteriostatic by inhibiting deoxyribonucleic acid (DNA)-synthesis through competitive antagonism of para-aminobenzoic acid (PABA). Sodium sulfacetamide has activity against a number of gram-positive and gram-negative agents, but is generally only used when other topical agents cannot be tolerated by patients.

Dapsone

Dapsone possesses antibacterial and anti-inflammatory activity, although its precise mechanism of action against acne is still unknown. However, it has recently been suggested that dapsone's mechanism of action in the treatment of acne may be due to antimicrobial and anti-inflammatory effects. Dapsone gel (5%) can be used to reduce inflammatory as well as non-inflammatory acne lesions. This agent's lower cost makes it more favorable for use in developing countries; however, it is not recommended as first-line therapy.

Systemic Treatment

Oral systemic treatment is required when acne is



resistant to topical treatment or if it manifests as nodular lesions or leaves scarring. It is the preferred choice in the treatment of inflammatory lesions. Systemic treatment may also be required to prevent social embarrassment and psychological impairment in people suffering from acne. The most common systemic treatment includes isotretinoin, oral antibiotics and hormonal agents .

Retinoids

Isotretinoin is a systemic retinoid and derivative of vitamin A. It is currently being used as a first line treatment for severe nodular or inflammatory acne and is the only known medication which has the potential for the suppression of acne in the long term. It can also benefit patients with mild to moderate cases of acne that have proved resistant to topical or other oral agents in the past. It is also considered as a first line treatment in severe acne of the face and trunk, acne that causes scarring and acne that causes psychological complications .

Currently, isotretinoin is the only drug available which has an effect on all four pathogenic factors of acne . Isotretinoin causes de-differentiation of the sebaceous gland, decreasing the sebum production which will lead to a change in the ecosystem of the cutaneous bacterial flora, ultimately reducing *P. acnes* colonization in the follicles. It also causes the shedding of the

keratinocytes. Isotretinoin treatment is normally over a course of 16–24 weeks. It is necessary to closely monitor patients who use isotretinoin because of its harmful side-effects .

Antibiotics

Oral antibiotics are generally indicated for moderate to severe inflammatory acne, acne that shows resistance to previous topical treatment or for acne that covers a large surface area of the body. Acne is often treated with oral antibiotics such as macrolides (erythromycin, clindamycin, azithromycin and roxithromycin), fluoroquinolones (levofloxacin), tetracyclines (doxycycline, minocycline and lymecycline) and co-trimoxazole . These antimicrobial agents inhibit the growth of *P. acnes* and the synthesis of inflammatory mediators released from *P. acnes*. The success of the antibiotic treatment is based on the ability of the agent to reach the lipid environment of the pilosebaceous follicles in the dermis, which is the area where *P. acnes* colonize. Tetracyclines are very popular because they are effective and inexpensive. Doxycycline and minocycline are preferred because they cause less gastrointestinal irritation, and they are more lipid soluble, penetrating the pilosebaceous follicle more efficiently. The tetracycline family exhibits both anti-inflammatory as well as antibacterial properties. Additionally, less resistance in *P. acnes* have been reported with



the tetracyclines than the macrolides . Not many studies have been performed to determine the efficacy of azithromycin in the treatment of acne, whereas clindamycin (topical) and erythromycin (topical and oral) have been well recognized as acne treatments. Erythromycin and clindamycin have little anti-inflammatory activity and mainly work by reducing the levels of P. acnes. Since these antibiotics are used repetitively at low doses for extended periods of time during acne treatment, increasing resistance has developed overtime which has resulted in limited use of these agents. To reduce resistance and improve the efficacy, oral antibiotics should be combined with topical benzoyl peroxide or retinoids. Additionally, the duration of treatment should not exceed 12 weeks when feasible. It has also been suggested that if a patient is a good candidate for treatment with isotretinoin, long-term antibiotic treatment is unfeasible .

Hormonal

Sebaceous glands are androgen dependent and therefore the effect of androgen on sebaceous glands can be treated with hormone therapy. Hormonal treatment can be used as an alternative for adolescent and adult females. These hormones are most commonly given in the form of oral contraceptive pills. The contraceptive hormones reduce the sebum production that is initially induced by androgen. It increases the

synthesis of sex hormone-binding globulin which in turn decreases biologically active free testosterone in the female body. Although all contraceptives can be used to treat hormone related acne, progestins are usually preferred because they possess no androgen activity . Oral contraceptives can be used alone or in combination with other therapies to treat acne in Women. The treatment period of acne with hormonal anti-androgens must be at least for 12 months and oftentimes even longer as the favorable effect of hormonal agents will only be visible after 3-6 months of treatment. Spironolactone is an alternative drug which can also be combined with oral contraceptives in the treatment of hormone related acne. Its mechanism is based on the fact that it is an androgen receptor blocker. It is especially effective for patients with inflammatory acne .

Diverse Treatments

Other oral treatments that can possibly be used as adjunctive acne therapy include zinc sulfate, ibuprofen (due to its anti-inflammatory effect) and doxycycline. Systemic corticosteroids can be used for initial treatment of inflammatory manifestations (Acne fulminans). It can also be used to manage aggravation of acne when treating with systemic isotretinoin . It has been recommended that severe inflammatory Acne vulgaris, Acne fulminans and Pyoderma facialis



be treated with oral prednisone (0.5–1.0 mg/kg daily) for a period of 4–6 weeks, after which the dosage can be decreased gradually.

Complementary and Alternative Medicines (CAM)

More efficient and safer treatment options are needed for the treatment of acne. Numerous CAM therapies have been noted and/or promoted for use as acne treatment and are generally regarded as safe. Botanical therapies have the added benefit of possessing several modes of action due their composition consisting out of a range of possible active components. It has been proposed that CAM therapies influence the androgenicity, increased sebum activity, infection, inflammation and hyperkeratinization associated with acne. However, in most cases evidence for their use is inadequate and one should still be wary of the possible harm and side effects these plant-derived products can lead to. Some researchers are of the opinion that botanicals may lessen resistance when used as alternatives to or in combination with antibiotics. This should, however, still be verified with clinical studies. Various articles list all the possible plant/herbal remedies for acne. Some of these ingredients do however have some anti-inflammatory, moisturizing and soothing properties. Therefore, theoretically, these ingredients should be able to help relieve some

of the drying effects caused by the more vigorous acne therapies and the erythema associated with inflammatory acne. The absence of clinical data on the efficacy of these complimentary remedies is of big concern and need to be addressed by future research. For the purpose of this article, only a few of the major CAM therapies will be discussed in detail. There is, however, a strong possibility that the range of CAM therapies being used by acne patients is much larger than the series of treatments mentioned in this review.

Basil Oil

Advocated topically applied basil essential oils for the treatment of acne include *Ocimum sanctum*, *Ocimum basilicum* and *Ocimum gratissimum*. Since ancient time, Thai basil oils such as *O. basilicum* L. (sweet basil) and *O. sanctum* L. (holy basil) have been used as traditional medicine to treat ringworm and insect bites. Studies showed that topical application of a preparation containing *O. gratissimum* oil in a cetomacrogol blend base were more efficient and reduced lesion counts faster than a 10% benzoyl peroxide lotion. A study on Thai basil oils showed that *O. basilicum* and *O. sanctum* showed promise to be used for acne treatment as they exhibited antimicrobial activity against *P. acnes*. The formulations containing *O. basilicum* showed a higher anti-*P. acnes* activity than the *O. Sanctum* containing formulation.



Copaiba Oil

Copaiba oil-resin has traditionally been used as an antiseptic, anti-inflammatory and healing agent. Da Silva et al. conducted a double-blind placebo controlled clinical trial in which the copaiba oil was prepared into a topical gel to determine its activity against *Acne vulgaris*. After 21 days of treatment, the copaiba oil gel stopped the outbreak of new pustules, healed pre-existent pustules and reduced the area of erythema. The authors concluded that copaiba oil may be used in the treatment of mild acne, although larger studies are necessary to confirm.

Green Tea

Green tea possesses anti-inflammatory, antioxidant, antimicrobial and antimutagenic properties which can be ascribed to its high content of polyphenols, including catechins (flavan-3-ols). The main catechins found in green tea include epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG) and epicatechin (EC) of which EGCG is the most abundant polyphenol found in green tea. Polyphenon-60 from green tea is a mixture of polyphenolic compounds. Topical application of polyphenon-60 in patients with mild-to-moderate acne (in vivo testing) decreased the average amount of open-comedos and pustules. However, polyphenon-60 showed no improvement on closed-comedos. In vitro studies

to determine the underlying mechanism by which polyphenon-60 has this therapeutic effect on acne showed that this compound suppresses the inflammation process. Yoon et al. conducted in vitro studies in which it was determined that EGCG directly targets three pathological processes of acne as it has sebo-suppressive effects, it inhibits the growth of *P. acnes* and it has anti-inflammatory effects. They also found that EGCG may reverse the modified keratinization of follicular keratinocytes associated with acne. These results were followed by a double-blinded, split-face clinical trial which showed that the mean inflammatory and non-inflammatory lesion counts significantly decreased after eight weeks of treatment with an EGCG solution when compared to the baseline values. Results obtained from a double-blind, placebo-controlled, randomized clinical trial showed that when green tea extract was given orally it was found to be effective against acne lesions in mild-to-moderate acne cases. Compared to the control, the green tea extract significantly decreased the inflamed and total lesion counts, although no significant effect was observed on the non-inflamed lesion count. A topical 3% green tea emulsion was found to decrease the sebum production of the cheeks of healthy male volunteers over a 60 day period.

Minerals



Minerals have been used for healing purposes since prehistoric times. The minerals being used for therapeutic intents are mostly clay minerals such as kaolinite, palygorskite, smectites and talc. Clay minerals can be used to treat acne, blackheads and spots. Generally it is applied as a face mask consisting of a warm mixture of water and clay which will open pilosebaceous orifices, stimulate perspiration and sebaceous secretions. A mix of minerals (consisting primarily of halloysite, sericite and talc) obtained from ores indigenous to Korea showed to inhibit the growth of *S. Epidemidis* and *P. acnes*. Dead Sea black mud showed marked antimicrobial action when test microorganisms (*P. acnes*) were added to the mud where after they lost their viability. Additionally, when Dead Sea mud was placed on *P. acnes* inoculated agar plates, a growth inhibition zone was observed. Another mineral commonly used both systemically as well as topically for the treatment of *Acne vulgaris* includes zinc which was mentioned earlier.

Antimicrobial Peptides

Natural antimicrobial peptides represent promising therapies for treating acne as they are unlikely to provoke drug resistance in microorganisms. However, some authors have stated that development of peptide-based drug resistance has been proven experimentally, although, when compared to conventional

antibiotics it is considered to arise at a much slower pace.

A synthetic peptide, derived from epinecidin-1 (from the marine organism *Epinephelus coioides*), have shown bactericidal properties against *P. acnes* by means of destroying its membrane. In another study, antimicrobial peptides derived from ranid frog skins showed a high potency against *P. acnes*. Wang and co-workers purified a snake cathelicidin-derived antimicrobial peptide, cathelicidin-BF, from the venoms of *Bungarus fasciatus*. When tested in vitro it was observed that cathelicidin-BF possessed potential antimicrobial activity against *P. acnes*, comparable to that of the antibiotic, clindamycin. Additionally, this antimicrobial peptide showed some anti-inflammatory effects and inhibited *P. acnes*-induced O₂ production. All these properties suggested the potential use of cathelicidin-BF for treating *Acne vulgaris*.

Resveratrol

Considering the pathophysiology of acne, the ideal drug should be capable of reducing the inflammatory response as well as inhibiting *P. acnes*. As a result resveratrol is emerging as a new approach in treating acne as it possesses anti-proliferative, anti-inflammatory and *P. Acne* inhibiting properties. Resveratrol is a natural phytoalexin which is produced by certain spermatophytes, such as for example grapes. A



single-blind, vehicle-controlled pilot study was performed in which resveratrol (trans-isomer) was formulated into a gel with a carboxymethylcellulose base. This formulation was applied on the right side of the face of volunteers with inflammatory Acne vulgaris in the facial area for 60 days and compared to the left side of the face on which the control (hydrogel vehicle) was applied. All the volunteers had a noteworthy reduction in pustular lesions and inflammation with an overall noticeable clinical improvement on the side of the face treated with resveratrol. The resveratrol-treated side of the face also showed a significant decrease of macrocomedones and microcomedones when compared to the vehicle-treated side of the face. It seemed as though resveratrol inhibited the keratinocyte hyperproliferation process. Resveratrol was found to inhibit *P. acnes* growth when tested in vitro. It was bacteriostatic at lower concentrations (50 mg/L and 100 mg/L) and bactericidal at the highest concentration tested (200 mg/L). The inhibiting effect of resveratrol compared well with the activity of frequently used acne treatments benzoyl peroxide and erythromycin.

Novel drug delivery system and its use in treatment ACNE:

The method by which a drug is delivered can have a significant effect on its efficacy. Some

drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Novel drug delivery strategies can play a pivotal role in improving the topical delivery of antiacne agents by enhancing their dermal localization with a concomitant reduction in their side effects.

This novel formulation helps by encouraging collagen production in the skin. It helps improve overall skin tone and luster and improves the appearance of fine lines. It is made of a combination of collagen and Hyaluronic acid. Light, oil-free lotion contains finely milled prescription-grade medicinal agents to heal blackheads and blemishes and helps prevent future breakouts. The advanced delivery system in Repairing Lotion is soothing and safe for entire face.

Novel Topical Delivery Systems:



Targeting is the ability to direct the drug-loaded system to the site of interest. Controlled drug release and subsequent biodegradation are important for developing successful formulations.

Potential release mechanisms involve:

- (i) Desorption of surface-bound /adsorbed drugs;
- (ii) Diffusion through the carrier matrix;
- (iii) Diffusion (in the case of nanocapsules) through the carrier wall;
- (iv) Carrier matrix erosion; and
- (v) A combined erosion /diffusion process.

1. Aerosol Foams:

Aerosol foams have become an increasingly popular type of topical formulation for a variety of skin conditions including acne vulgaris. 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, density, persistence, stability, and spreadability) are determined by the type of formulation and the dispensing container that are selected to suit the specific treatment needs. In acne, foams may be preferred for application on large hairy surfaces (e.g., chest and back) or on the face as cleansers, because they are easier to apply.

2. Liposomes:

Liposomes are frequently used as vehicles in pharmaceuticals and cosmetics for a controlled and optimized delivery to particular skin layers. Liposomes are spherical vesicles whose membrane consists of amphiphilic lipids (i.e., lipids that are hydrophilic on one side and lipophilic on the other side) that enclose an aqueous core, similar to the bilayer membranes of living cells. Because liposomes offer an amphiphilic environment, they may encapsulate hydrophilic substances in their aqueous core and lipophilic substances in their lipid bilayer. This unique dual release capability enables the delivery of two types of substances once they are applied on the skin; each differs in its effects on skin permeability, which may enhance the desired therapeutic benefit.

3. Nanoemulsions:

Nanoemulsions are a class of emulsions (i.e., water-in-oil or oil-in-water formulations) that are characterized by the dispersion of very small-sized droplets when mixed. Nanoemulsions are not formed spontaneously, as they require unique thermodynamic conditions, specialized manufacturing processes, and specific surfactants that can stabilize the nano droplets. Nanoemulsions are suitable for the transport of lipophilic compounds into the skin and, therefore, they may be an ideal vehicle for use in acne to



increase the penetration of the active compounds inside the lipophilic environment of the pilosebaceous unit. In addition, nanoemulsion particulates will not clog the pores and they can produce additional therapeutic effects, such as increased skin hydration and viscoelasticity.

4. Polymers:

Polymers are large molecules consisting of repeating structural units, or monomers that are connected by covalent chemical bonds. These compounds serve as the building blocks of natural (e.g., paper and amber), biological (e.g., proteins and nucleic acid), or synthetic (e.g., plastics and polyethylene) materials. Today, applications for synthetic polymers can be found in nearly every industry, and their versatility has given rise to technological advancements within the pharmaceutical sector that address a variety of medical needs. For example, in dermatology, there are new acrylic-acid polymers that turn into a gel in the presence of water by trapping water into microcells. Inside these aqueous microcells, hydrophilic compounds can remain in a solution, where as non-hydrophilic compounds may be dispersed in suspension. The result is a stable gel-like formulation that is easy to use and releases the active compounds once they are applied on the skin. Moreover, these polymerbased gels can be mixed with other excipients, such as moisturizers and emollients,

to provide additional clinical benefits. Recently introduced anti-acne formulations that combine clindamycin 1% with benzoyl peroxide 5% utilize this novel polymer-based gel technology that exhibits efficacy and excellent tolerability.

5. Microsponges:

Microsponges are biologically inert particles that are made of synthetic polymers with the capacity to store a volume of an active agent up to their own weight. Furthermore, the particles serve to protect the entrapped active compound from physical and environmental degradation. The micro sponge technology can be utilized in a variety of formulations, but is more frequently manufactured as gels. Once applied on the skin, microsponges slowly release the active agents.

6. Emulsifier Free Formulations:

Emulsifier-free formulations are also a growing area of development for dermatologic and cosmetic products. Most skin care products are emulsions, i.e., a mixture of two or more materials that are not miscible with each other; as such, according to the second law of thermodynamics, they are inherently unstable. As a result, they require the addition of surfactants (emulsifiers) that stabilize the formulation to guarantee an adequate shelf life. Furthermore, once these surfactant agents are applied on the skin, they tend to emulsify and remove the natural lipids of the epidermis. Consequently, the



pharmaceutical industry has been developing surfactant-free emulsions as alternatives to conventional formulations by using stabilizers, such as polymeric emulsifiers or solid particles, in order to yield sufficiently stable products with a cosmetically pleasant appearance.

7. Fullerenes:

Fullerenes are molecules composed entirely of carbon that resemble a hollow sphere. Once fullerenes come into contact with the skin, they migrate through the skin intercellularly, as opposed to moving through cells. Therefore, a fullerene could be used to 'trap' active compounds and then release them into the epidermis once they are applied on the skin. Moreover, fullerenes, themselves, are thought to be potentially potent antioxidants. Data are reported in the literature showing that fullerenes are well tolerated and they hold substantial promise in dermatologic and cosmetic applications.

Conclusion

The increasing importance of appearance and the influence of disfiguring on psychologic health confirm the significance of the disease "acne". Although during the past 50 years dramatic progress has been made concerning the development of treatment modalities, the pathomechanism is still not fully understood. Molecular biology combined with molecular

immunology and pharmaceutical research is necessary to clarify these issues.

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