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Review Article

ACNE VULGARIS: PATHOGENESIS, CURRENT THERAPEUTIC STRATEGIES, AND ADVANCES IN TOPICAL GEL-BASED DRUG DELIVERY SYSTEMS

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ABSTRACT

Acne vulgaris is one of the most prevalent chronic inflammatory skin disorders affecting adolescents and adults worldwide. It is characterized by the development of comedones, papules, pustules, nodules, and in severe cases, permanent scarring. The pathogenesis of acne involves multiple factors, including increased sebum production, follicular hyperkeratinization, colonization by *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and inflammation. Conventional treatment approaches include topical and systemic therapies such as antibiotics, retinoids, benzoyl peroxide, azelaic acid, salicylic acid, hormonal agents, and isotretinoin. Although these therapies are effective, their long-term use is often associated with adverse effects, poor patient compliance, and the emergence of antibiotic resistance. Topical gel formulations have emerged as a promising drug delivery system for acne management due to their non-greasy nature, ease of application, enhanced patient acceptability, and ability to provide localized drug action with minimal systemic side effects. Gels can effectively deliver both synthetic and natural anti-acne agents while improving drug stability, bioavailability, and therapeutic efficacy. This review discusses the etiology and pathogenesis of acne vulgaris, current pharmacological treatment strategies, and the significance of gel-based drug delivery systems. Furthermore, the classification, characteristics, preparation methods, evaluation parameters, and therapeutic advantages of gels in acne treatment are comprehensively summarized. The review highlights the potential of gel formulations as an effective and patient-friendly approach for the management of acne vulgaris and future advancements in topical dermatological therapy.

Keywords: Acne vulgaris, Topical gel, Drug delivery system, *Cutibacterium acnes*, Retinoids, Benzoyl peroxide, Antibiotics, Dermatological formulations, Anti-acne therapy, Skin disorders.

INTRODUCTION

Acne vulgaris or simply known as acne is a human skin disease characterised by skin with scaly redskin (seborrheas), blackheads and whiteheads (comedones), pinheads (papule), large papule (nodules), pimples and scarring. Acne affects skin having dense sebaceous follicles in areas including face, chest and back. Acne may be of inflammatory or non-inflammatory forms. Acne is usually caused

by increase in androgens level like testosterone mainly during puberty in both male and female (Benner and Sammons, 2013).

Etiology of Acne

Acne develops due to blockage of follicles, hyperkeratinization and keratin plug formation and sebum (microcomedo). With increased androgen production, sebaceous glands are enlarged and sebum production is increased. The microcomedo may enlarge to form an open comedo (blackhead) or closed comedo. Comedones occur as a result of clogging of sebaceous glands with sebum, naturally occurring oil and dead skin cells the naturally occurring commensal bacterium Propionibacterium acnes can cause inflammation and inflammatory lesions like infected pustules or nodules and papules in the dermis around the microcomedo or comedone resulting in redness, scarring or hyper pigmentation (James, 2005; Benner and Sammons, 2013).

Topical medication

Topical drugs are widely used and effective in patients with mild to moderate acne. Topical antibiotics, retinoids, benzoyl peroxide, azelaic acid and salicylic acid are commonly used in clinical treatment of acne. The choice of topical medication may be influenced by various factors, such as the patient's age, the location and extent of the lesions, the severity of acne, and the patient's individual preferences. Other considerations include skin type, potential side effects, drug interactions, and adherence to treatment regimens. In order to enhance the simplicity of the acne treatment and promote patient adherence, a variety of fixed-dose combination products available. Commonly used combinations include antibiotics with benzoyl peroxide, antibiotics with retinoic acid, and retinoic acid with benzoyl peroxide (Zaenglein *et al*., 2016).

Antibiotics

Propionibacterium acnes (*P. acnes*) plays a pivotal role in the pathogenesis of acne vulgaris. This bacterium colonizes the sebaceous glands and hair follicles of the skin, and its overgrowth can lead to inflammation and the formation of acne lesions. Topical antibiotics are commonly used in acne treatment as they exhibit both anti-*P. acnes* and anti-inflammatory properties. The topical application of antibiotics directly to the affected area can help reduce the bacterial colonization of the skin and hair follicles by *P. acnes*. The decrease in bacterial load can result in reduced inflammation and subsequently lead to a reduction in acne lesions.

At present, the commonly prescribed antibiotics for acne treatment include clindamycin, erythromycin, minocycline, and fusidic acid. Topical clindamycin can be utilized in combination with benzoyl peroxide and retinoic acids. It is generally well tolerated in a variety of concentrations and preparations such as lotions, foams, and gels.

Clindamycin 1% solution or gel is the preferred topical antibiotic for treating acne, while 2% erythromycin can be used in various topical products. However, due to higher resistance and weaker efficacy compared to clindamycin, it's recommended as a first-line treatment. To prevent drug resistance, the combination therapy with benzoyl peroxide or retinoic acid is often preferred. When used in combination with benzoyl peroxide, it can improve efficacy and reduce the development

of resistant bacterial strains, while improving patient compliance with treatment regimens (Dessiniotia and Katsambas, 2022).

Benzoyl peroxide

The mechanism of benzoyl peroxide is to decompose into benzoic acid and hydrogen peroxide, and then reduce the concentration of *Propionibacterium acnes* by generating free oxygen radicals. It also has anti-inflammatory and keratolytic properties, and currently there is no drug resistance, so it can be used as the preferred topical medicine for inflammatory acne. Research has demonstrated that benzoyl peroxide formulations at concentrations of 2.5, 5, and 10% exhibit comparable efficacy in the treatment of acne vulgaris. Nonetheless, increased concentrations can potentially elicit irritant dermatitis with adverse reactions like dryness, scaling, and erythema. Consequently, clinicians advise initiating therapy with a low concentration and a limited treatment area for cautious titration (Kumar *et al*., 2019).

Retinoids

Retinoids, derived from vitamin A, are commonly used to treat acne vulgaris due to their ability to regulate skin cell growth and reduce inflammation. They also help clear sebum from glands, dissolve pimples, and prevent atrophic scarring and pigmentation. Topical retinoids such as adapalene, tretinoin, and tazarotene are commonly used to treat acne vulgaris. Adapalene gel at 0.1% is the first non-prescription retinoid approved by the FDA for patients aged 12 and older. Topical retinoids can cause dry skin, irritation, and increased serum triglycerides. They also pose a risk of severe birth defects, so monthly pregnancy tests and thorough contraceptive counseling are essential (Lake and jaad, 2019).

The newly developed combination of adapalene (0.3%) and benzoyl peroxide (2.5%) is safe and effective for treating acne vulgaris in individuals aged 12 years and older. In a 24 weeks study, it showed a higher likelihood of reducing scarring compared to the placebo. Over 48 weeks, it consistently reduced acne and scarring, emphasizing its long-term efficacy (Falets *et al*., 2022).

Azelaic acid

Azelaic acid boasts multiple properties, including the dissolving of pimples, antibacterial and mild anti-inflammatory activities, as well as regulating follicular keratinization. Furthermore, its ability to reduce pigmentation by inhibiting abnormal melanocyte activity renders it highly beneficial for individuals with sensitive skin or pigmentation challenges. Categorized as a Category B medication during pregnancy, azelaic acid has been found to have high tolerability and can also be used in lactating women. A recent study found that 15% azelaic acid gel is as effective as 0.1% adapalene gel in treating inflammatory acne in adult women, with sustained therapeutic outcomes (Thielitz *et al*., 2015).

Salicylic acid

Salicylic acid is a mild anti-inflammatory and comedolytic agent used alone or with other medications to manage mild acne vulgaris, especially for patients who cannot tolerate retinoic acid or benzoyl peroxide. It's available in concentrations from 0.5 to 2%. Treatment starts with lower concentrations and increases as needed, up to two or three times daily. If there are adverse reactions like dryness or redness, the frequency of

application can be reduced. Higher concentrations can also be used for chemical peeling of the skin surface (Zaenglein *et al*., 2016).

Oral medication

Oral antibiotics

Severe acne cases with inflammation, as well as moderate to severe acne unresponsive to topical treatments, and conditions such as acne fulminans and acne conglobate may require oral antibiotics. Tetracycline antibiotics like doxycycline and minocycline, along with macrolide antibiotics such as erythromycin, roxithromycin, and azithromycin are commonly used for treating these types of acne (Skidmore *et al*., 2003).

Tetracycline antibiotics are the preferred choice for treating acne due to their strong anti-inflammatory effects, which include inhibiting neutrophil chemotaxis and reducing proinflammatory cytokine production. They also help reduce *p. acnes* levels. Other antibiotic classes like penicillin, sulfonamides, and cephalosporins are not recommended for acne treatment unless a patient has contraindications to tetracyclines and macrolides.

To prevent *p. acnes* resistance, it is not recommended to use oral antibiotics alone for acne treatment. They are often used in combination with topical retinoids and benzoyl peroxide. Once improvement is seen, topical agents can be used to maintain the effect. Overuse of antibiotics may lead to resistant strains of bacteria that contribute to acne (Dessinioti and Katsambas, 2017).

Retinoids

Systemic use of retinoid acid can suppress sebum production, hyperkeratosis, and the production of proinflammatory cytokines. Isotretinoin is the only orally administered retinoid approved by the FDA for the treatment of severe nodulocystic and recalcitrant acne, particularly acne that leads to scarring. Furthermore, isotretinoin is the only drug recognized for treating the four pathogenic mechanisms of acne: sebum overproduction,

hyperkeratinization, *propionibacterium acnes* colonization, and inflammation. It can be used for patients aged 12 years and older who are not pregnant and suffer from moderate to severe acne. The adherence and satisfaction with systemic use of isotretinoin were significantly higher compared to topical treatment and oral antibiotics. Common adverse effects encompass dryness and irritation of the skin and mucosa, myalgia, elevated triglycerides and aminotransferases, as well as severe teratogenic effects. It is recommended to conduct regular monitoring of liver function, serum cholesterol, and triglyceride levels at baseline during the course of treatment.

In addition, female patients of fertile age who opt to use isotretinoin must stringently adhere to contraception measures 1 month prior to the commencement of treatment, throughout the duration of treatment, and for 3 months following its conclusion. While the adverse reactions of viaminate are similar to isotretinoin, they tend to be relatively less severe (Shalita, 2001).

Studies have indicated that isotretinoin may be associated with an increased incidence of mood changes, such as depression and suicidal tendencies. Nevertheless, there is insufficient robust evidence to support this association. Therefore, it is advisable to avoid prescribing isotretinoin to patients who

exhibit significant depressive symptoms or have a diagnosis of depression (Chinese Society of Dermatology, 2019).

The initial dose of isotretinoic acid for acne treatment is typically 0.25 to 0.5 mg/kg/d, with a recommended routine dose of 0.5 to 1.0 mg/kg/d and a cumulative dose of 120 to 150 mg/kg, depending on efficacy and patient tolerance. The achievement of the appropriate cumulative dose may also lead to relief of acne. Regular doses of isotretinoin are associated with a decreased frequency of acne recurrence compared to low doses (Eichen *et al*., 2021).

Hormone therapy

Hormonal therapies commonly comprise combined oral contraceptives (COCs) and anti-androgen drugs. Studies have revealed that various hormones, including androgens, estrogen, insulin, insulin-like growth factors, and others, play a pivotal role in the pathogenesis of acne, with androgens being the most significant endogenous contributor (Kurokawa *et al*., 2009).

COCs can serve as a part of a comprehensive acne treatment plan. Women with contraceptive needs or menorrhagia may start using COCs early in the acne treatment process, and for women who do not respond favorably to other medications, COCs can be introduced as a supplementary treatment. Additionally, COCs can be used in combination with other oral drugs such as tetracyclines and spironolactone to achieve optimal therapeutic outcomes (Katsambas and Dessinioti, 2010).

Anti-androgen drugs, such as estrogen, progesterone, spironolactone, and insulin sensitizer, are commonly used in clinical practice to reduce the production of sebaceous lipids and alleviate acne symptoms. Spironolactone, a non-selective aldosterone receptor antagonist, exhibits potent antiandrogenic activity by decreasing testosterone production and competitively inhibiting the binding of testosterone and DHT to androgen receptors in the skin.

This ultimately leads to decreased sebum production and improved acne symptoms. Spironolactone is considered a long-term treatment option for hormonal acne with recognized safety and tolerance when used alone or in combination with COCs. Although generally well tolerated, dose-related side effects of spironolactone may include polyuria (29%), irregular menstruation (22%), breast tenderness (17%), breast enlargement, fatigue, headache, and dizziness. Due to its potassium-preserving diuretic properties, spironolactone carries the potential for hyperkalemia and hypotension. However, a study of 967 healthy female patients aged 18–45 who administered spironolactone for acne revealed no increased risk of hyperkalemia during treatment. Therefore, routine monitoring of potassium levels is unnecessary for female patients under the age of 45 with no additional comorbidities or symptoms (Blume *et al*., 2020).

Gels

Gels are semi-rigid systems in which the dispersion medium's strength is limited by threedimensional particle interaction or macromolecule solubility in the dispersed phase.

The word "gel" comes from "gelatin," and both "gel" and "jelly" can be traced back. In Latin, Gelu means "drop" and gel means "freeze" or "freeze". This origin illustrates the fundamental concept of liquids as solids that

do not flow but are elastic and retain some liquid properties. The term "gel" was first used to describe semisolids in the late 1800s, when chemists attempted to separate them based on phenomenological properties rather than molecular composition. The analytical methods needed to identify drug samples are not currently available (Loyd *et al*., 2011).

Gels are harder than jellies due to increased crosslinking, higher physical density, or simply less liquid. Gel-forming polymers produce a variety of hardnesses, ranging from sols to slimes, jellies, gels, and hydrogels.

Some gel systems are as clear as water, while others are cloudy due to incomplete molecular dispersion (soluble or insoluble) or the absence of light-scattering aggregates. With a few exceptions, the concentration of the gelling agent is usually less than 10%, ranging from 0.5% to 2. 0% more (Ofner *et al*., 2007).

Classification of gels

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties

Based on colloidal phases: They are classified into:

- Inorganic (Two phase system)
- Organic (Single phase system)

Inorganic (Two-Phase System)

The system consist of floccules of tiny particles rather than larger molecules and the gel structure will be unstable if the dispersed phase partition size is especially large and develops a three-dimensional structure throughout the gel. They must be thixotropic, which means that when disturbed, they transform from a semisolid to a liquid. Gel made of aluminium hydroxide and bentonite magma is two examples (Zatz, 2005).

Organic (Single Phase System)

On the twisted threads, there are large organic molecules that are continuously dissolved. The majority of organic gels are single-phase solutions made up of organic liquids such Plastic base and gelling agents like carbomer and tragacanthin.

Based on Nature of the Solvent Hydrogels (water based)

A hydrogel is three-dimensional networks of hydrophilic polymers that can grows in water and contain a significant quantity of water while maintaining their structural integrity due to the chemical or physical cross-linking of individual polymer chains. Hydrophilic colloids like silica, bentonite, tragacanth, pectin, sodium alginate, etc. provide an example. The hydrogel may be utilised as an ECG medical electrode, rectal medication delivery system, and sustained release drug delivery system.

Organogel (With a non-aqueous solvent)

A liquid organic phase is contained within a three- dimensional, cross-linked network in an organogel, a type of gel. The addition of a polar solvent causes the organo gelling or gelation of lecithin solution in organic solvents (Lachman *et al*., 2012).

Xerogels

Xerogels are solid-formed gels created by allowing materials to gently dry at room temperature while experiencing unrestricted shrinking. Viscous sintering takes place when a xerogel is heated over a certain point, thereby turning the porous gel into a thick glass. Examples include polystyrene, dry cellulose, and tragacanth ribbons. Gels are occasionally categorized as plastic gels, pseudo-plastic gels, and thixotropic gels because they display non- Newtonian flow.

Based on Physical Nature

Elastic gels

Agar, pectin, Guar gum, and alginates gels have an elastic property. At the point of junction, the fibrous molecules are joined by comparably weak connections such as hydrogen bonds and dipole attraction. If the molecule has a free -COOH group, a salt bridge of the type -COO-X-COO forms an extra bond between two adjacent strand networks. e.g.: Alginate and Carbopol (Florence and Attwood, 2001).

Rigid gels

This can be made from macromolecules with primary valence bonds connecting the framework. e.g. Silic acid molecules are kept together in a silica gel by the Si-O-Si-O link, resulting in a polymer structure with a network of pores (Das *et al*., 2010).

Characteristics of gels

Swelling

The gel expands and absorbs liquid as its volume increases. This could be considered the first stage of decomposition. The solvent penetrates the gel matrix, replacing gel-gel interactions with gelsolvent interactions. The limited swelling is usually caused by the degree of crosslinking in the gel matrix, which prevents complete dissolution. This gel swells significantly when the solvent mixture has a solubility parameter similar to the gelling agent (Fedina *et al*., 2020).

Syneresis

Many gels systems contract when standing. The interstitial liquid is expelled from the gel and accumulates on its surface. This process, known as syneresis, occurs not only in organic hydrogels but also in inorganic hydrogels. In general, syneresis increases as the polymer concentration decreases. The shrinkage mechanism is associated with the relaxation of elastic stresses that occur during gel solidification.

Ageing

Colloidal systems typically exhibit slow spontaneous aggregation. This process is known as aging. Aging in gels causes a dense gelling network to form over time. Inner demonstrated that the process is similar to the initial gelation process and continues once the fluid medium of the newly formed gel is lost. Gels are rigid because they contain a network of interconnected gelling particles. The network structure and properties of the gel are determined by the particle type and bond strength (Meng *et al*., 2022).

Rheology

Gelling agent solutions and flocculated solid dispersions are pseudoplastic, which means they flow non-Newtonian and have a decrease in viscosity as shear rate increases. The elongated structure of inorganic particles dispersed in water is disturbed by the applied shear stress, which causes the breaking of inter particulate bonds, resulting in a greater tendency to flow.

Evaluation parameters

Organoleptic characteristic

As rule, gels have a viscous consistency, they was homogeneous, transparent, fluid, elastics and plastic. The organoleptic characteristics were observed as a seeing form and which type of gel is see in vitro observation. The herbal gel was evaluated by color, odor and texture.

pH measurement

pH was measure of the concentration of hydronium ions in an aqueous solution. It was measures on a negative logarithm scale from 0 to 14. Acidic solution was below pH 7, with 0

being the acidic ph. Basic solution are above pH 7, with 14 being basic. When the existing in the environment of pH=8, the gel get the largest viscosity. The determination of gel measure by using pH meter (Jafari *et al*., 2008).

Viscosity

Viscosity was the measurement of the thickness of fluid. Gel preparation refers to fluid that have high viscosity of 2000-4000cps. The viscosity of gel plays an important part in the success. Viscosity was defined as a measurement of a fluids resistance to flow. The viscosity was determine by using brooke field viscometer (Kim *et al*., 2010).

Skin irritation test

The method uses the skin ethic reconstructed human epidermis model and involves the topical application of a chemical for 42 minutes. The preparation of gel was apply on wound and kept form 42 minutes and observe the any irritation may occur there, were no any itching or redness on wound.

Spread ability test

The gel was weighing to be as high as 0.5 g and then placed on graph paper coated with glass. Then, we put another glass above the gel mass. The gel diameter was calculated by measuring the diameter length of several sides Spread the formulate gel on the wound, it is spread easily and smoothly without any small particle (Ipsita *et al*., 2014).

Preparation of Gels

Gels are normally in the industrial scale prepared under room temperature. However, few of polymers need special treatment before processing. Gels can be prepared by following methods:

- Thermal changes
- Flocculation
- Chemical reaction

Thermal changes

Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reduced, the degree of hydration is decreased and gelation takes place. (Cooling of a concentrated hot solution will produce a gel).

E.g., Gelatin, agar sodium oleate, guar gummed, cellulose derivatives, etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method (Niyaz *et al*., 2011).

Flocculation

Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce age state, but inadequate to bring about complete precipitation. It is essential to ensure quick mixing to avoid local high concentration of precipitant.

E.g., Solution of ethyl cellulose, polystyrene in benzene can be gelled by quick mixing with suitable amounts of a non-solvent such as petroleum ether. The adding of salts to hydrophobic solution brings about coagulation, gelation is infrequently observed. The gels formed by flocculation method are Thixotropic in behavior. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is to “salt out”, the colloidal and gelation doesn’t occur (Goyal *et al*., 2011).

Chemical reaction

In this method gel is produced by chemical interaction between the solute and solvent.

E.g., Aluminium hydroxide gel can be prepared by interaction in aqueous solution of an aluminium salt and sodium carbonate an increased concentration of reactants will produce a gel structure. Few other examples that involve chemical reaction between PVA, cyanoacrylates with glycidol ether (Glycidol), toluene diisocyanates (TDI), methane diphenyl isocyanine (MDI) that cross-links the polymeric chain (Attwood, 2002).

CONCLUSION

Acne vulgaris is a common inflammatory skin disorder caused by increased sebum production, follicular blockage, bacterial colonization, and inflammation. Although conventional therapies such as antibiotics, retinoids, and benzoyl peroxide are effective, they may cause adverse effects and poor patient compliance. Topical gel formulations offer an effective alternative by providing localized drug delivery, improved patient acceptability, enhanced drug penetration, and reduced systemic side effects. Therefore, gel-based delivery systems represent a promising approach for the safe and effective management of acne vulgaris, with future potential for advanced and targeted dermatological therapies.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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