# Topical Vehicle Formulations in the Treatment of Acne

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## ABSTRACT

Topical treatment is the mainstay of acne therapy. The most commonly prescribed topical medications for acne include benzoyl peroxide, clindamycin, and retinoids. Despite their effectiveness in treating mild to moderate acne vulgaris, these topical medications are found to be irritating, and are historically associated with poor tolerability and diminished patient adherence. Thus, choosing the right formulation that will be effective and well tolerated is essential. Novel formulations that optimize drug concentration and utilize improved delivery vehicles have helped to enhance the tolerability and efficacy, and allow for less frequent application or co-application of drugs that were previously considered incompatible. This article will review the goals of topical therapy for the treatment of acne, in addition to common therapies and their challenges. Advanced formulations and combination formulations of benzoyl peroxide, clindamycin, and tretinoin will also be discussed.

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## INTRODUCTION

Topical medication is a staple in the treatment of mild to moderate acne vulgaris. Not only is it an efficient way to deliver therapy to the source of the disease, but it also involves a decreased risk of systemic exposure to ingredients such as antibiotics and retinoids. However, local cutaneous irritation from the vehicle or the medication itself can lead to non-adherence and poor outcomes. Thus, choosing the right formulation that will be effective and well tolerated is essential. This can be challenging as the topical drug formulations for acne are numerous and complex. This article will review the goals of topical therapy for the treatment of acne, common therapies and their challenges, and newer therapies on the forefront.

Topical drugs are absorbed primarily by passive diffusion. There are three main methods of permeation of topical drugs through the stratum corneum: transappendageal, transcellular, and intercellular. Transappendageal transport occurs at the sweat glands or hair follicles and their associated sebaceous glands. This delivery system may be preferred for diseases of the pilosebaceous unit, such as acne or folliculitis, because it can be used to create a reservoir effect.[1,2] Diffusion via the transcellular and intercellular pathways differ because they depend more on the active molecule's characteristics. The transcellular route is the most common path, where drugs pass through corneocytes by repeated partitioning between lipophilic and hydrophilic compartments. In the intercellular pathway, drugs pass around the corneocytes via the lipid rich extracellular domains.[3]

There are several challenges to formulating topical drugs. As the active molecule passes through the epidermis, it may go through chemical changes that alter its efficacy at the target site. The active molecule may also be altered in the vehicle itself as it is applied to the skin.[3] Several methods can be utilized to improve drug delivery through the epidermis. For example, using an evaporating, volatile component in the vehicle will help to increase the concentration of the active drug on the skin surface when applied.[3] Vehicles usually include ingredients that disrupt the skin barrier, fluidize the lipid channels between corneocytes and alter partitioning of the drug into the cutaneous structures. Detergents, emulsifiers, and solubilizing agents can all be used as drug mediums to help disrupt the barrier and improve penetration of the active ingredient through the epidermis.[3]

When developing a vehicle delivery system for a drug, it is important to consider that it accommodates the drug being formulated and that it is suitable for application to the body site requiring treatment. The FDA recognizes the following topical dosage forms: solution, suspension, lotion, paste, gel, ointment, cream and "other" category including novel formulations such as aerosol, powders, and patches.[4]

In clinical practice, the optimal formulation needs to be effective and well tolerated. These are both features that help contribute to patient adherence with therapy, which can lead to better outcomes and lower long-term treatment costs. Poorer

adherence is directly related to poor treatment outcomes and patient dissatisfaction. A common cause of non-adherence is local cutaneous irritation, due to either the ingredients in the vehicle or the active drug itself.[5] As we review the current treatments for acne, it should be noted that the goals of formulations are as follows: reduce irritation, enhance therapeutic outcome, and promote patient adherence.[6,7] These goals can be accomplished by reducing the concentration of the active drug, delayed release of the active drug, and adding other ingredients to the formulation vehicle to repair the damaged epidermal barrier and offset the irritating effects of the drug.[3]

## Vehicles and Acne Therapy

Acne is a complex and chronic skin disease that commonly affects adolescents and adults. The etiology is multifactorial and the pathogenesis likely involves hormonal function, increased sebum production, follicular hyperkeratinization, proliferation of *Propionibacterium acnes* (*P. acnes*), and the propagation of various inflammatory cascades.[8,9] In fact, inflammation can persist throughout the course of lesion development and resolution, as evidenced by persistent inflammatory hyperpigmentation and erythema.[9] Given that acne is a chronic disease with a negative impact on psychosocial function and quality of life at all stages in the acne lesion cycle, it is critical to initiate effective therapy as early as possible to provide better treatment outcomes.

However, as described above, designing acne drug formulations is a complex and multifaceted process. Combination therapy is often required to address the different pathophysiologic associations with acne. This is challenged by the need to address the subsequent adverse events associated with the formulations, such as irritation and dryness. Fixed combination formulations for acne have simplified therapeutic decisions with once-a-day application, leading to improved adherence.[5] New formulations and delivery techniques, like microspheres and hydrating bases, have also been implemented to help reduce irritation, attributing to greater patient satisfaction.

## Common Acne Therapies

Topical treatment is the mainstay of acne therapy. The most commonly prescribed topical medications for acne include benzoyl peroxide, clindamycin, and retinoids.[10] Despite their effectiveness in treating mild to moderate acne vulgaris, these topical medications are found to be irritating, and are historically associated with poor tolerability and diminished patient adherence.[6,7] Current guidelines for treating acne vulgaris emphasize using both topical retinoids and benzoyl peroxide for maintenance therapy.[7]

Benzoyl peroxide (BPO) is a major workhorse in the treatment of acne. It is classified as a non-antibiotic antibacterial agent that is bactericidal against *P. acnes* due to its potent oxidizing activity.[11,12] It is effective against inflammatory and non-inflammatory lesions; however many benzoyl peroxide preparations are limited by their adverse events of dryness and irritation. Given the development of bacterial resistance to *P. acnes,* the utility of benzoyl peroxide has increased because *P. acnes* has not yet developed resistance to topical benzoyl peroxide.[13] As a result, BPO is often used in conjunction with both topical and systemic antibiotics, such as topical clindamycin, to reduce the development of *P. acnes* resistance.[12]

Antibiotic sensitivities to *P. acnes* arose in the 1980s with the introduction of topical formulations of erythromycin and clindamycin.[14] Clindamycin is a bacteriostatic agent for *P. acnes* and also exhibits anti-inflammatory activities.[11,15] Both BPO and clindamycin are currently the most widely prescribed antimicrobials for the treatment of acne, and they are even more effective when combined.[16,17] In a clinical trial comparing combination clindamycin phosphate 1% and benzoyl peroxide 5% gel formulation with matching clindamycin 1% gel monotherapy, total *P. acnes* count and clindamycin-resistant *P. acnes* count were significantly reduced after 16 weeks of treatment with the use of combination gel as compared to clindamycin alone. Moreover, in the group using the combination gel, the reduction in total *P. acnes* and clindamycin resistance *P. acnes* counts correlated with a reduction in total acne lesions.[17]

Current guidelines also emphasize the use of topical retinoids for treatment and maintenance therapy of mild to moderate acne vulgaris.[7] The mechanism of action of topical retinoids is anti-comedolytic; they regulate keratinization and target the microcomedone to reduce the formation of new acne lesions and can significantly interrupt disease progression.[18] Similarly to combination antimicrobial treatments, combination retinoid and BPO treatments have also been developed in recent years. In accordance with the general goals of topical formulations used in acne, the aim of combination retinoids/BPO formulations is to reduce irritation, enhance therapeutic outcomes and promote patient adherence.[6] This has been done by reducing the concentration of active drug, providing for delayed release of the active drug, or incorporating ingredients into the formulation vehicle that repairs the impaired epidermal barrier and offsets the irritating effect of the drugs.[5]

## Minimizing irritation with BPO and Tretinoin

*Hydrophase Base Formulations*

Benzoyl peroxide 4% in a hydrophase base and benzoyl peroxide 8% in a hydrophase base are both topical preparations that come in the form of a creamy wash and a gel. The hydrophase formulation is thought to reduce the irritation associated with the use of benzoyl peroxide.[11] Both the wash and the gel preparations are indicated for use in mild to moderate acne. They can be used as an adjunct with other acne treatment regimens, including antibiotics, retinoic acid products, and sulfur/salicyclic acid containing preparations.[11,19]

The BPO 4% and 8% creamy wash in a hydrophase base involves application to the face for a few seconds to minutes, followed by rinsing with water.[19] Despite its short contact time, clinically visible improvement can be expected by the third week of therapy, with maximum reduction by approximately 8 to 12 weeks.[11] In a clinical trial, benzoyl peroxide creamy washes were shown to have superior antibacterial activity compared to several other benzoyl peroxide products.[20] Moreover, a comparative study found greater physician preference for BPO 4% in hydrophase base as compared to BPO 3% cleansing lotion.[11]

As a gel vehicle, benzoyl peroxide 4% and 8% in a hydrophase base contain benzoyl peroxide as the active ingredient, in addition to purified water, cetyl alcohol, dimethyl isosorbide, fragrance, simethicone, stearyl alcohol, and ceteareth-20.[19] The solvent dimethyl isosorbide is of importance in this formulation because it helps to dissolve crystal residues of BPO left behind after water and other volatile solvents dissolve. This is thought to help reduce the irritation associated with BPO and improve its bioavailability.[11]

Sawleshwarker et al.[21] reported the results of a multicenter, open-labeled, non-comparative study to evaluate the efficacy and irritation potential of benzoyl peroxide 4% cream in a hydrophase base in acne vulgaris. At the end of the six-week trial period, 85.6% of patients had a good to very good effect with treatment. In fact, by the end of the second week of treatment, 36.9% showed good to very good improvement, and 43.6% of patients showed a fair response. The profile of side effects observed revealed that 53.8% of total patients did not have any irritation, 34.6% had minimal irritation, and only 11.6% had moderate to severe irritation. Patients' assessments were in accordance with these results; 72% of patients reported a satisfactory improvement at the end of 6 weeks, 23.6% reported a very satisfactory improvement, and only 4.4% reported an unsatisfactory response. Assessment of irritation after treatment showed that 53.8% of patients did not report any irritation, 41.4% had some irritation, and only 4.8% of patients reported troublesome irritation.[21]

## Dapsone

Systemic dapsone has been used for inflammatory conditions for many years, but the use of topical dapsone for acne vulgaris is relatively new.[3] Stabilizing topical dapsone has made creating a topical formulation challenging, but this has recently changed. The dapsone gel vehicle contains diethylene-glycol monoethyl ether (DGME), which facilitates permeation of the active drug into the skin and any undissolved drug, remains in the pilosebaceous unit. Through this method, the active dapsone molecule can accumulate in the skin without increasing systemic absorption.[22]

## Fixed Combination Formulations

*Antimicrobial Formulations*

Fixed combination clindamycin/benzoyl peroxide formulations are well established for the management of mild to moderate inflammatory acne vulgaris. The aqueous gel vehicle of clindamycin/benzoyl peroxide 5% contains two different and complementary moisturizers that are intended to counteract any potential irritation associated with benzoyl peroxide: glycerin 4% and dimethicone 1%.[23] Glycerin is a humectant, which is a hydroscopic substance that draws water from the epidermis/dermis to the stratum corneum.[24] If used without an occlusive though, humectants can increase transepidermal water loss (TEWL). Transepidermal water loss is a sign of barrier dysfunction seen in most inflammatory skin conditions. Occlusives, such as dimethicone, help to form a barrier to reduce TEWL while also conditioning the skin. Compared to non-treatment, the application of combination dimethicone and glycerin was shown to reduce transepidermal water loss.[24]

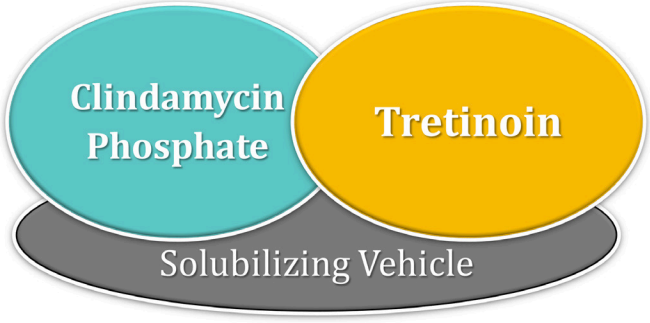
*Retinoid Combinations*

The other group of combination formulations features retinoids. These formulations contain either the first generation retinoids or the second-generation retinoids, such as the naphthoic-acid derivative adapalene. Adapalene is photostable and is not degraded in the presence of BPO.[25] The molecule has selective affinity for RAR-γ and RAR-β. It was found to have better tolerability than tretinoin with similar or greater reductions in inflammatory, non-inflammatory, and total lesion counts.[25]

The efficacy, safety, and tolerability of fixed combination adapalene 0.1% and benzoyl peroxide 2.5% have been well established in multiple controlled trials. Use of the combination formulation showed more significant reductions in inflammatory, non-inflammatory, and total lesion counts than either of its constituents alone or vehicle.[26-28] The tolerability of the fixed combination gel was similar to that of adapalene alone.[26]

Another fixed combination formulation containing a retinoid is topical tretinoin with clindamycin. This combination provides complementary methods of action in that the retinoid decreases

**FIGURE 1.** Novel combination gel: Clindamycin phosphate, tretinoin, and a solubilizing aqueous vehicle. Each gram of this novel combination gel contains 10 mg (1%) clindamycin as clindamycin phosphate, 0.25mg (0.025%) tretinoin, and a solubilizing vehicle containing Laureth-4.



microcomedone formation and extrudes comedones and the topical clindamycin has antibacterial properties and reduces inflammatory lesions.[15,18] It is also conveniently dosed as a once a day topical application. Combination tretinoin 0.025% and clindamycin phosphate 1.2% has been found to be effective in mild-to-moderate acne vulgaris in 3 pivotal phase 3 studies.[29-31] An alcohol-free, aqueous gel formulation of tretinoin 0.025% and clindamycin phosphate 1.2% has since been unveiled.[29]

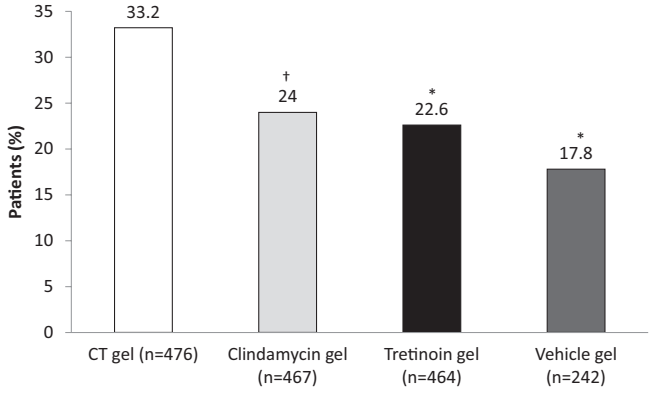
While clindamycin and tretinoin provide complementary methods of action, they are not readily combined into a single formulation. A combination acne treatment was developed to stabilize and solubilize tretinoin 0.025% and clindamycin phosphate 1.2% in an aqueous-based gel for once-daily treatment of acne vulgaris (Figure 1). The solubilized tretinoin is believed to have a faster rate of cutaneous delivery which may account for the favorable tolerability and low irritation potential.[29] One of the essential components of the vehicle is Laureth 4 (polyoxyether of lauryl alcohol). Laureth 4 is a clear, colorless liquid used in the manufacture of cosmetics and personal care products. It functions as both a surfactant and an emulsifier to help solubilize and disperse otherwise non-mixable substances, such as tretinoin and clindamycin.[33]

A multicenter, randomized, double-blind active drug- and vehicle-controlled study, evaluated solubilized tretinoin 0.025%/clindamycin phosphate 1.2% gel compared to its components alone and vehicle alone.[32] Those eligible for the study were patients greater than 12 years with active acne vulgaris on the face and an Investigator Global Assessment (IGA) score greater or equal to 2. Exclusion criteria included the following: nodulocystic acne at baseline, pregnant or lactating females, and patients with a history or presence of regional enteritis, inflammatory bowel disease, or history of antibiotic associated colitis.

Combined tretinoin 0.025%/clindamycin phosphate 1.2% gel provided a statistically significant improvement in acne as compared to its components alone or the vehicle. At 12 weeks, a higher percentage of combination treated patients achieved an ISGA score of 0 or 1 with a 2-grade improvement in IGA (33.2%), compared to clindamycin alone (24%), tretinoin alone (22.6%), and vehicle (17.8%) (Figure 2). Combination treated patients also had a greater mean percent reduction in total lesion number (55%), as compared to clindamycin alone (49%), tretinoin alone (50.5%), and vehicle (39.1%) (Figure 3). The reduction in inflammatory lesions was statistically significant for combination gel (60.4%) versus tretinoin gel (54.5%) and vehicle gel (43.3%), but not when compared to clindamycin gel (56.5%). Reduction in non-inflammatory lesions was statistically significant for combination gel (51%) versus clindamycin gel (42.9%) and vehicle gel (36%), but not compared to tretinoin gel (47.3%).[32]

In this trial, the combination formulation was found to have excellent tolerability. Observed local treatment-related adverse

**FIGURE 2.** Proportion of participants achieving an ISGA score of 0 or 1 with a 2 grade or greater improvement between baseline and week 12.
*$P$<0.002 versus CT gel; †$P$=0.001 versus CT gel.
(Adapted from Jarratt and Brundage, *J Drugs Dermatol.* 2012)[32]

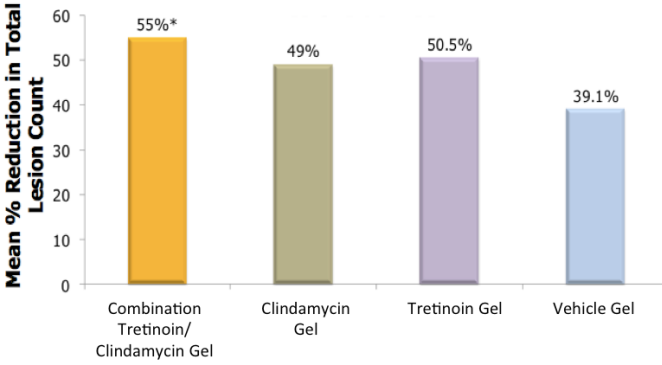



reactions (≥1%) were application site reactions, including dryness, irritation, exfoliation, erythema, pruritus, and dermatitis. Sunburn was also reported. The incidence of skin reactions peaked at 2 weeks and gradually decreased throughout the trial period.[32] These findings were consistent with previous reports of minimal adverse events and excellent tolerability of tretinoin gel/clindamycin phosphate formulation in other large, controlled clinical trials, including a 52-week trial.[30,31,34]

## CONCLUSION

Designing vehicle formulations for the topical treatment of acne vulgaris is complex and multifaceted. The optimal formulation must not only target the multifactorial etiology of acne, but also needs to be effective and well tolerated. This ultimately translates to more rapid clearance of disease and increased

**FIGURE 3.** Mean percent reduction in total lesions at week 12. At 12 weeks, a significantly higher percentage of combination treated patients had a greater mean percent reduction in total lesion number (55%), as compared to clindamycin alone (49%), tretinoin alone (50.5%), and vehicle (39.1%).
(Adapted from Jarratt and Brundage, *J Drugs Dermatol.* 2012)[32]



rates of patient satisfaction. The use of topical antimicrobials and retinoids for treating acne is well established; however, these topical medications are historically known for their local cutaneous irritation, inconvenient dosing, and subsequent poor compliance. Novel formulations that optimize drug concentration and utilize improved delivery vehicles have helped to enhance the tolerability and efficacy, and allow for less frequent application or co-application of drugs that were previously considered incompatible. Combination tretinoin/clindamycin gel and benzoyl peroxide in a hydrophase base are two examples of novel formulations, which have utilized these new technologies and can be used together for the complete treatment of acne. By decreasing irritation and increasing convenience, these novel formulations used together should improve adherence and lead to better therapeutic outcomes as well as decreased antibiotic resistance.

## DISCLOSURES

Dr. Hoffman has no conflicts of interest to disclose. Dr. Bhatia is an advisor, consultant, and investigator for Aqua/Almirall. Dr. Zeichner has served as an advisory board member, consultant, or speaker for Abbvie, Allergan, Bayer, Dermira, Galderma, Johnson & Johnson, La Roche Posay, Leo, L'Oreal, Ortho Dermatologics, Pfizer, Promius, Regeneron, Sanofi-Genzyme, Sun Pharma, and Unilever. Dr. Kircik has served as an advisor, investigator, consultant, and speaker for Allergan, Bayer, Galderma, Promius Pharma, Sun Pharma, Stiefel/GSK, LeoPharma, Taro, Valeant, and Warner-Chilcott.

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