# Chemical Stability and Tolerability of Topical Benzoyl Peroxide 5%/Clindamycin 1% Gel in Combination With Topical Retinoids and Sunscreens

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Acne vulgaris is a multifactorial disease that is typically treated with a combination of agents, including benzoyl peroxide (BP), topical antibiotics, and topical retinoids. Because of concerns regarding potential chemical instability (especially with BP and retinoids) and/or skin irritation, it is frequently suggested that product application be separated by at least 8 hours.

The objective of this study was to evaluate the chemical stability of BP 5%/clindamycin 1% gel when combined with adapalene, tretinoin, and specific sunscreen ingredients (ie, avobenzone, octinoxate, oxybenzone, octisalate, and homosalate). Triplicate test samples were prepared by admixing equal volumes of BP 5%/clindamycin 1% gel (tube formulation) with each retinoid and sunscreen ingredient. Chemical stability was assessed using stability-indicating high-performance liquid chromatography to determine drug concentrations at baseline (immediately after admixture) and at 1, 2, 4, 6, and 24 hours after admixture.

Optimal treatment of acne vulgaris usually requires rational combination therapy.[1] The topical combination of BP, clindamycin, and a retinoid uses multiple mechanisms of action to target different points in the pathogenesis of acne vulgaris.[1-3] Although other modes of action may be operative, recognized mechanisms of action and the clinical implications of each agent are summarized in Table 1.[1-7]

To achieve favorable therapeutic results with topical therapy in clinical practice, it is important that the agents used are effective and safe. In addition, skin tolerability and compatibility of applied products, especially with concurrent use, are important considerations. The required frequency of topical drug application may markedly affect patient compliance, with once-daily use associated with the greatest potential for optimal compliance.[8,9] The compatibility and stability of topical agents applied concurrently or sequentially is an important clinical consideration, as incompatibility may require a significant interval between applications. Consequently, the treatment regimen may become more complicated and negatively affect patient compliance.[10-12] For example, because tretinoin is photolabile and unstable in the presence of BP, it is applied in the evening, and formulations containing BP are applied in the morning. This regimen allows for avoidance of tretinoin exposure to light and an interval between tretinoin and BP applications of at least 8 to 12 hours.[10,12] Studies have demonstrated that adapalene is photostable and is sustained in the presence of BP when tested during a 24-hour period.[11-13] When formulated in the microsphere vehicle, tretinoin is photostable; in the presence of BP, tretinoin microsphere gel is at least 97% stable for up to 8 hours and approximately 70% (68.4%–71.5%) stable during a 24-hour period.[12,13]

The tube gel combination of BP 5%/clindamycin 1% may be used with a topical retinoid to treat acne vulgaris.[1,2]

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TABLE 1

**Commonly Used Topical Agents for Treating Acne Vulgaris: Mechanisms of Action and Clinical Implications[1-7]**

| Agent | Mechanism of Action | Implications |
|---|---|---|
| Benzoyl peroxide | Reduction in *Propionibacterium acnes* colony count | Marked reduction in inflammatory lesions (papules and pustules) |
| | | Moderate reduction in noninflammatory lesions (open and closed comedones) |
| | | Reduced risk of antibiotic-resistant *P acnes* strains when used in combination |
| Clindamycin | Reduction in *P acnes* colony count | Marked reduction in inflammatory lesions (papules and pustules) |
| | | Moderate reduction in noninflammatory lesions (open and closed comedones) |
| | | Additive therapeutic benefit when used in combination with benzoyl peroxide |
| Topical retinoids | Modulation of epidermal cellular differentiation, with reduction in hyperkeratosis | Marked reduction in noninflammatory lesions (open and closed comedones) and inflammatory lesions (papules and pustules) |
| | Down-regulation of toll-like receptor 2 | Inhibition of inflammatory cascade |
| | Down-regulation of some matrix metalloproteinase enzymes involved in dermal matrix degeneration | Potential reduction of acne scarring |

This formulation has been shown to be effective and well tolerated. The traditional use of combination therapy with BP-containing formulations and older tretinoin formulations (nonmicrosphere vehicle) has dictated that individual products be applied several hours apart at different times of the day. However, the chemical compatibility of the BP 5%/clindamycin 1% tube gel with each of the commercially available topical retinoids is important, as maintenance of stability of all active ingredients may allow for sequential application of products once daily, provided skin tolerability proves to be acceptable. Compatibility with sunscreens is also important, as sunscreens are commonly recommended to patients as a routine component of skin care.

## Methodology and Results of Chemical Stability Studies

BP 5% and clindamycin 1%, formulated as the patented combination tube gel product, were individually admixed in equal amounts by weight with adapalene 0.1% gel, tretinoin microsphere 0.1% gel, and a patented sunscreen containing avobenzone, octinoxate, oxybenzone, octisalate, and homosalate. Each BP 5%/clindamycin 1% tube gel combination was held at 35ºC, and assays of all active ingredients were performed by using stability-indicating high-performance liquid chromatography to determine drug concentrations at baseline (immediately after admixture) and at 1, 2, 4, 6, and 24 hours after admixture. Triplicate assays were performed at each time point. The results were reported as a percentage of theoretical (actual measurement at time point/baseline stated concentration), allowing for accepted minor differences in drug concentration that occur during FDA-approved product manufacturing and accepted variability ranges related to laboratory measurement (assay techniques). The results of 24-hour stability testing with each admixture are listed in Tables 2, 3, and 4.

TABLE 2

**Benzoyl Peroxide 5%/Clindamycin 1% Tube Gel Plus Adapalene 0.1% Gel: 24-Hour Stability Data**

| | Theoretical | | |
|---|---|---|---|
| Time Point (h) | Adapalene | Benzoyl Peroxide | Clindamycin |
| 0 | 101% | 102% | 100% |
| 1 | 101% | 99% | 102% |
| 2 | 102% | 101% | 102% |
| 4 | 102% | 102% | 103% |
| 6 | 101% | 105% | 102% |
| 24 | 106% | 104% | 102% |

TABLE 3

**Benzoyl Peroxide 5%/Clindamycin 1% Tube Gel Plus Tretinoin Microsphere 0.1% Gel: 24-Hour Stability Data**

| | Theoretical | | |
|---|---|---|---|
| Time Point (h) | Tretinoin | Benzoyl Peroxide | Clindamycin |
| 0 | 96% | 99% | 101% |
| 1 | 95% | 100% | 102% |
| 2 | 92% | 100% | 105% |
| 4 | 87% | 104% | 104% |
| 6 | 84% | 105% | 103% |
| 24 | 56% | 102% | 106% |

## Conclusion

BP, clindamycin, and adapalene were stable at each tested time point up to 24 hours (final assay) in the mixture of the 2 products (ie, BP 5%/clindamycin 1% gel and adapalene 0.1% gel).

BP and clindamycin were stable up to 24 hours in the admixture with tretinoin microsphere 0.1% gel. Tretinoin remained 92% stable at 2 hours and 84% stable at 6 hours. Tretinoin content decreased to 56% of its original concentration at 24 hours.

BP, clindamycin, and the sunscreen ingredients avobenzone, octinoxate, oxybenzone, octisalate, and homosalate were stable for up to 24 hours (final assay) in the mixture of the 2 products (ie, BP 5%/clindamycin 1% gel and sunscreen).

TABLE 4

## Benzoyl Peroxide 5%/Clindamycin 1% Tube Gel Plus Multiple Sunscreens: 24-Hour Stability Data

| | Theoretical | | | | | | |
|---|---|---|---|---|---|---|---|
| Time Point (h) | Avobenzone | Oxybenzone | Octinoxate | Octisalate | Homosalate | Benzoyl Peroxide | Clindamycin |
| 0 | 101% | 100% | 100% | 100% | 100% | 98% | 100% |
| 1 | 100% | 99% | 100% | 100% | 99% | 102% | 100% |
| 2 | 100% | 100% | 100% | 100% | 100% | 99% | 100% |
| 4 | 98% | 98% | 98% | 98% | 98% | 99% | 101% |
| 6 | 98% | 98% | 98% | 98% | 98% | 102% | 101% |
| 24 | 100% | 97% | 103% | 103% | 103% | 104% | 103% |

Results of this study suggest that sequential application of the tested products in clinical practice would not result in the chemical incompatibility of active ingredients. This approach would allow for single-application use, which would likely enhance patient compliance. Clinical studies to evaluate efficacy and skin tolerability with this approach are warranted.

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