Irritation Profile of Benzoyl Peroxide Acne Washes: Impact of Formulation

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Benzoyl peroxide (BPO) is highly effective against acne and a mainstay of acne treatment. It also has the potential to irritate the skin, a risk that is generally considered dose dependent. Because compliance is poor with skin products found to be irritating, there is a need for gentle BPO products. Microsponge formulations which provide a gradual release of the active ingredient over time and thus may be less irritating could be a potential solution to this problem. The purpose of this study was to assess the irritancy of a prescription BPO wash 7% with microsponge delivery system relative to 3 other prescription washes—branded BPO creamy wash 4%, generic BPO creamy wash 4%, and BPO foaming cloths 3%—and 1 over-the-counter (OTC) product, OTC branded BPO wash 2.5%, as well as a negative control (no product) using a standard 21-day patch test protocol. Thirty-two participants were enrolled. Branded BPO creamy wash 4% was found to be the most irritating of the washes tested. Benzoyl peroxide wash 7% with microsponge delivery system—the prescription wash with the highest BPO concentration—and OTC branded BPO wash 2.5% were proven the least irritating. This study suggests that microsponge technology is effective in reducing the skin irritation associated with BPO.

Benzoyl peroxide (BPO) is a mainstay of topical acne treatment in dermatology. Acne treatment guidelines put forth by the Global Alliance to Improve Outcomes in Acne position BPO as an essential part of the acne treatment armamentarium, both for its anti-acne activity and its ability to reduce the risk of the bacterial resistance that arises when antibiotics are used over the long term. The guidelines recommend BPO for treatment of moderate acne and as a combination therapy whenever an antibiotic is used to treat acne.[1]

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Although highly effective, BPO also can irritate the skin surface. A member of the organic peroxide family, BPO consists of 2 benzoyl groups joined by a peroxide group. It is prepared by reacting sodium peroxide with benzoyl chloride to yield BPO and sodium chloride. Originally developed in 1917 as an ingredient to bleach flour, BPO was first used medically in the 1960s to treat leg ulcers and adapted for the treatment of acne in the 1970s.

Benzoyl peroxide is effective in the treatment of acne due to its antibacterial, anti-inflammatory, and comedolytic effects.[2] On contact with skin, BPO breaks down into benzoic acid and oxygen, neither of which is problematic. Its antimicrobial properties against *Propionibacterium acnes* are demonstrated by a 2-$\log_{10}$ decrease in *P acnes* concentration after 2 days of topical BPO 5% application.[3] This same mean 2-$\log_{10}$ decrease in organisms also was

observed after applying BPO cream 10% for 3 days; however, after 7 days, no further decline in *P acnes* level was observed.[4] Benzoyl peroxide demonstrates better *P acnes* killing than any topical antibiotic alone, including erythromycin and clindamycin, and use of BPO does not result in resistant organisms.[5] These positive attributes of BPO are the rationale for the currently popular combination of BPO and clindamycin in cream or gel prescription formulations,[6] as well as the Global Alliance's guideline recommendation that BPO be used whenever an antibiotic is used in patients with acne.[1] Of note, BPO cleansers also can suppress the development of resistant organisms, which is important in topical prescription treatments in which topical clindamycin alone or in combination with a retinoid is employed.[7] Thus, BPO is found in many acne treatment regimens as a rinse-off or leave-on product.

In addition to its antimicrobial activity, BPO acts as an anti-inflammatory agent by reducing oxygen radicals. Further, its ability to lower the *P acnes* population also reduces inflammation by diminishing bacteria-induced cytokines, including tumor necrosis factor-α, IL-1β, and IL-8 produced by monocytes.[8] This anti-inflammatory effect lessens acne lesion redness and pain, which are further decreased by the comedolytic effect of BPO. Benzoyl peroxide is capable of producing a 10% reduction in comedones.[3]

Current trends in BPO formulation have focused on the use of novel irritation-reducing delivery systems.[9] This is a particular challenge in BPO cleansers, because BPO is an unstable particulate that must be suspended in solution and thoroughly rinsed from the skin. Currently marketed BPO cleansers come in a variety of forms, including microsponge, creamy wash, foaming wash, bar, and woven pad formulations, and a range of BPO concentrations.[10]

Microsponges are porous microspheres 10 to 25 µm in diameter that are formed by the polymerization of methyl methacrylate and capable of delivering an active agent to the skin surface over an extended period.[11] The drug is placed in the monomer to be incorporated into the polymer sponge. The active agents that can be trapped in a microsphere must be fully miscible in the monomers that link to form the microsponge. An active agent must be water-miscible, inert to the monomer, and stable when in contact with the polymer and during the polymerization process. Benzoyl peroxide is an ingredient that meets all of these requirements.[12]

Once the BPO is incorporated into the sponge, the pressure of rubbing and an increase in skin temperature can release it. Polymer design is crucial in determining the rate of release of the active agent over the specified release period. The time-release characteristics are ensured by maintaining equilibrium between, in this case, the BPO in the product vehicle and the amount present in the microsponge. When the drug concentration is depleted in the vehicle through absorption into the skin, more drug is released from the microsponge, creating a reservoir effect. Typically, no more than 10% to 12% w/w of the microsponge is used in topical formulations, because a higher concentration can produce skin whitening.

Since product mildness is key to fostering patient compliance, it is important to develop BPO cleansers with enhanced tolerability profiles. Because the microsponge formulation provides gradual release of BPO over time, this technology would be expected to fill the need for a mild, gentle cleanser.

The industry standard for measuring tolerability is the 21-day cumulative irritancy test. This test protocol involves the placing of patches containing the study products on the backs of healthy volunteers for 21 continuous days. The patches are replaced daily, Monday through Friday, with the same patch worn over the weekend (Saturday and Sunday). Such exaggerated exposure can be used to quantify the irritancy of a given formulation. This trial employed the 21-day cumulative irritancy test protocol to assess the relative irritancy of 5 BPO washes of different strengths and formulations and a control patch with no product. The 4 prescription and 1 over-the-counter (OTC) BPO washes tested were as follows: BPO wash 7% with microsponge delivery system (NeoBenz Micro Wash 7%; Intendis); branded BPO creamy wash 4% (Brevoxyl-4 Creamy Wash; Stiefel Laboratories, Inc); generic BPO creamy wash 4% (Benzoyl Peroxide Creamy Wash 4%; Glenmark Generics Inc., USA,); BPO foaming cloths 3% (Triaz Foaming Cloths 3%; Medicis, The Dermatology Company,); and OTC branded BPO wash 2.5% (Proactiv Solution Renewing Cleanser 2.5%; Rodan & Fields, LLC).

METHODS

This 21-day cumulative irritancy test to evaluate the mildness and tolerability of a variety of BPO cleansers enrolled 32 healthy men and women without skin disease. All oral medications and skin care products remained unchanged during the study. Topical medications were forbidden, as were oral medications that might decrease the irritation response, including corticosteroids, immunosuppressives, antineoplastics, antihistamines, and nonsteroidal anti-inflammatory drugs. Participants reported to the research center Monday through Friday for 3 consecutive weeks for a total of 15 days of active product application under a semi-occlusive adhesive patch on the upper back. Participants wore the patches for 24 hours during the weekdays and for 72 hours over the weekend and

avoided any activities that might result in removal of the patch. Bathing practices were modified to allow the patches to remain in place. All cleansing products were diluted to 10% of their former strength prior to patch application. Patches were administered until severe irritation in the form of vesiculation was observed at the patch site.

Blinded investigator irritation and tolerability assessments were made daily Monday through Friday by a dermatologist; subject tolerability assessments were performed on the same schedule. Six patches were applied, including a control patch with no product, and 5 patches with 10% aqueous product dilution of the following 5 test products: BPO wash 7% with microsponge delivery system; branded BPO creamy wash 4%; generic BPO creamy wash 4%; BPO foaming cloths 3%; and OTC branded BPO wash 2.5%.

Irritation was evaluated separately for each patch using several different parameters. The blinded investigator assessed erythema, edema, vesiculation, bullae, ulceration, dryness, and peeling. The investigator also queried the subjects for stinging, tingling, itching, and burning at each site. All ratings were made on a 5-point ordinal scale (0=none, 1=slight, 2=mild, 3=moderate, 4=severe), including the subject assessments and the investigator assessments of global irritation at each patch site. This is the same scale used for the evaluation of irritant contact dermatitis when reading traditional patch tests.

The data were analyzed using the direct comparison technique for a Mann-Whitney 2-tailed paired *t* test. A response distribution also was tabulated. Significance was defined as $P<.05$, based on a 2-sided test.

RESULTS

All (32/32) participants successfully completed the 21-day cumulative irritancy test, with none of them missing patch replacement visits. Although a traditional 21-day cumulative irritancy test is run continuously for 21 days, the study protocol had to be modified at day 10, because all study products reached the maximum irritancy rating (4) and were discontinued. As a result, the study was completed in 2 discontinuous phases. All 5 study product patches and the control were applied daily during the weekdays from day 1 until day 10 with a 10% dilution of the study products. Participants were then given a 5-day rest period and 3 of the study products (BPO wash 7% with microsponge delivery system, generic BPO creamy wash 4%, and OTC branded BPO wash 2.5%) and control were repatched at a lower aqueous dilution of 5%. The first reading was taken at day 15, continuing until day 20 when the readings for irritation had again reached 4 at all of the study sites.

The investigator irritancy ratings are presented in Figure 1 for each of the study products through day 10. Higher ratings indicate increased irritancy, which can be assessed according to the absolute numeric rating and the rapidity with which a rating of 4, indicating skin vesiculation, occurred. Once the patched product reached a rating of 4, it was discontinued and the rating of 4 carried forward for all evaluations. All product-containing patches were compared to the control patch to assess irritation.

Figure 1 shows the relative irritancy of each BPO wash. Steeper slopes indicate a more rapid induction of irritation, and thus a more irritating product. The branded BPO creamy wash 4% was the most irritating, followed by the generic BPO creamy wash 4% on day 3 (significant difference in irritancy from branded BPO creamy wash 4% on days 2−4). The third most irritating product was the BPO foaming cloths 3% (significantly different from generic BPO creamy wash 4% on day 4, but no other days). Finally, BPO wash 7% with microsponge delivery system and OTC branded BPO wash 2.5% were the least irritating. The BPO wash 7% with microsponge delivery system was significantly less irritating than the BPO foaming cloths 3% on days 2 through 5, whereas the OTC branded BPO wash 2.5% was significantly less irritating on days 2 through 9. The BPO wash 7% with microsponge delivery system and the OTC branded BPO wash 2.5% exhibited no significant differences in irritancy until days 8 and 9.

The data are examined from a different standpoint in Figure 2, which shows the proportion of patients with a maximal irritancy score for each product on each day. This analysis reaffirms the data presented in Figure 1. No irritation was seen at any time, as expected, for the control patch, and the tested products ranked the same in irritancy as in the first analysis, as follows: branded BPO creamy wash 4% > generic BPO creamy wash 4% > BPO foaming cloths 3% > BPO wash 7% with microsponge delivery system > OTC branded BPO wash 2.5%.

These ratings were again confirmed by the second phase of the study, the rechallenge, which began on day 15 with the reduced 5% dilution of the 3 selected BPO washes: generic BPO creamy wash 4%, BPO wash 7% with microsponge delivery system, and OTC branded BPO wash 2.5% (Figure 3). Again, the generic BPO creamy wash 4% was the most irritating, followed by the BPO wash 7% with microsponge delivery system and the OTC branded BPO wash 2.5%, which were equally irritating.

The formulations tested varied in proportion of BPO, from 2.5% to 7%. The irritancy scores were adjusted

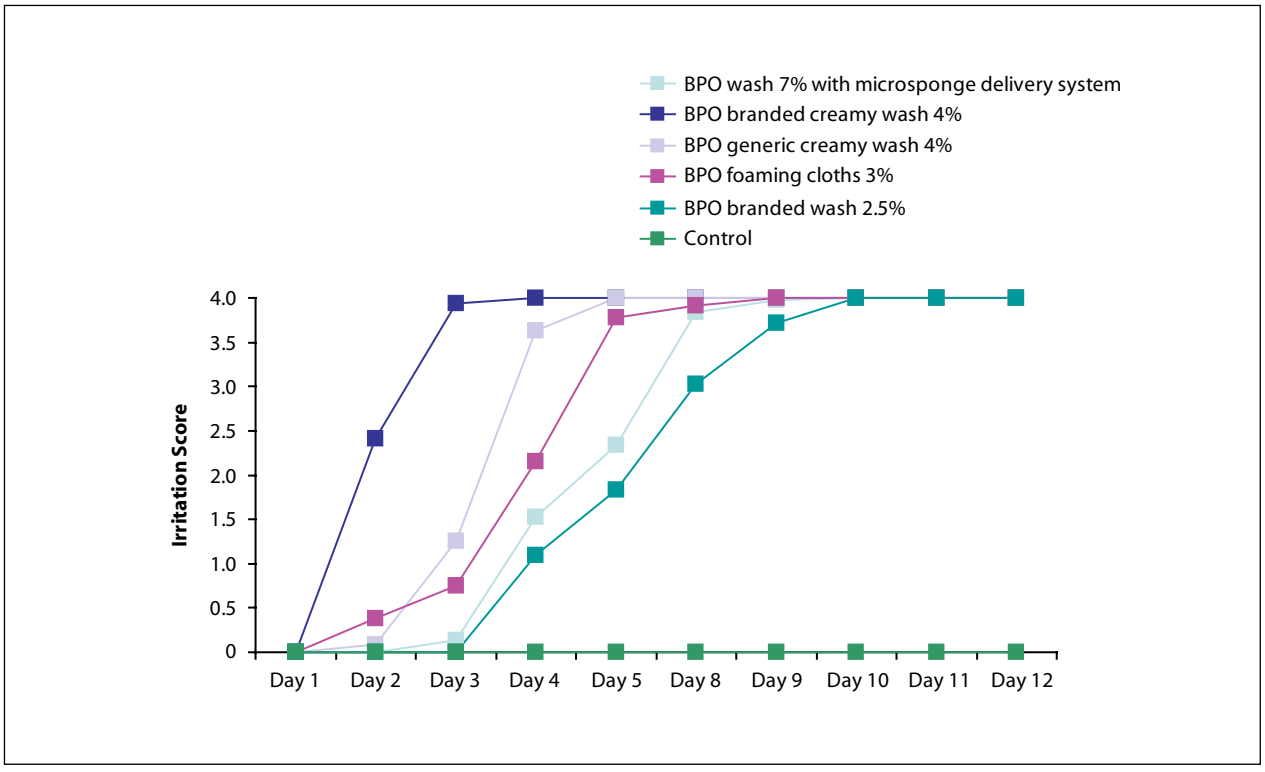

Figure 1. Average irritancy over time of BPO wash 7% with microsponge delivery system, branded BPO creamy wash 4%, generic BPO creamy wash 4%, BPO foaming cloths 3%, branded BPO wash 2.5%, and control.

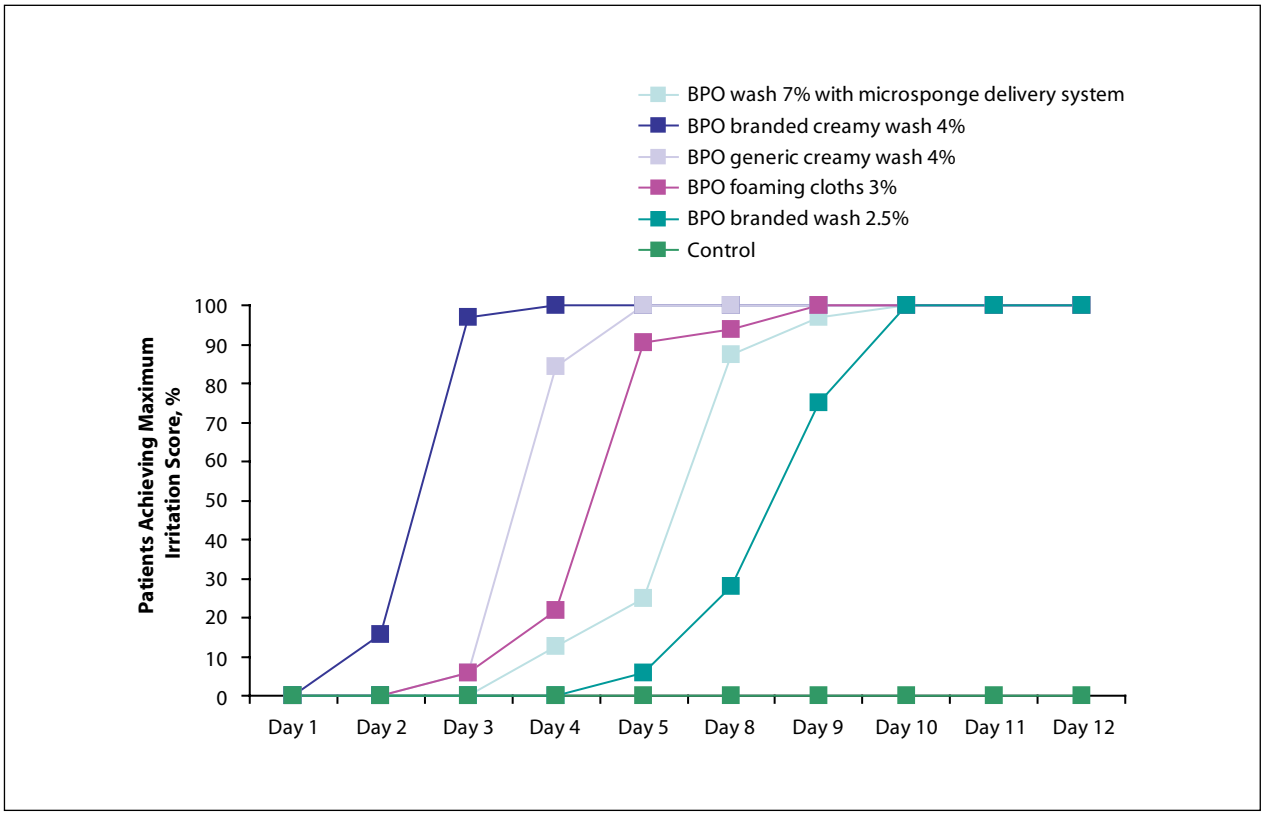

Figure 2. Proportion of patients achieving maximum irritation score over time.

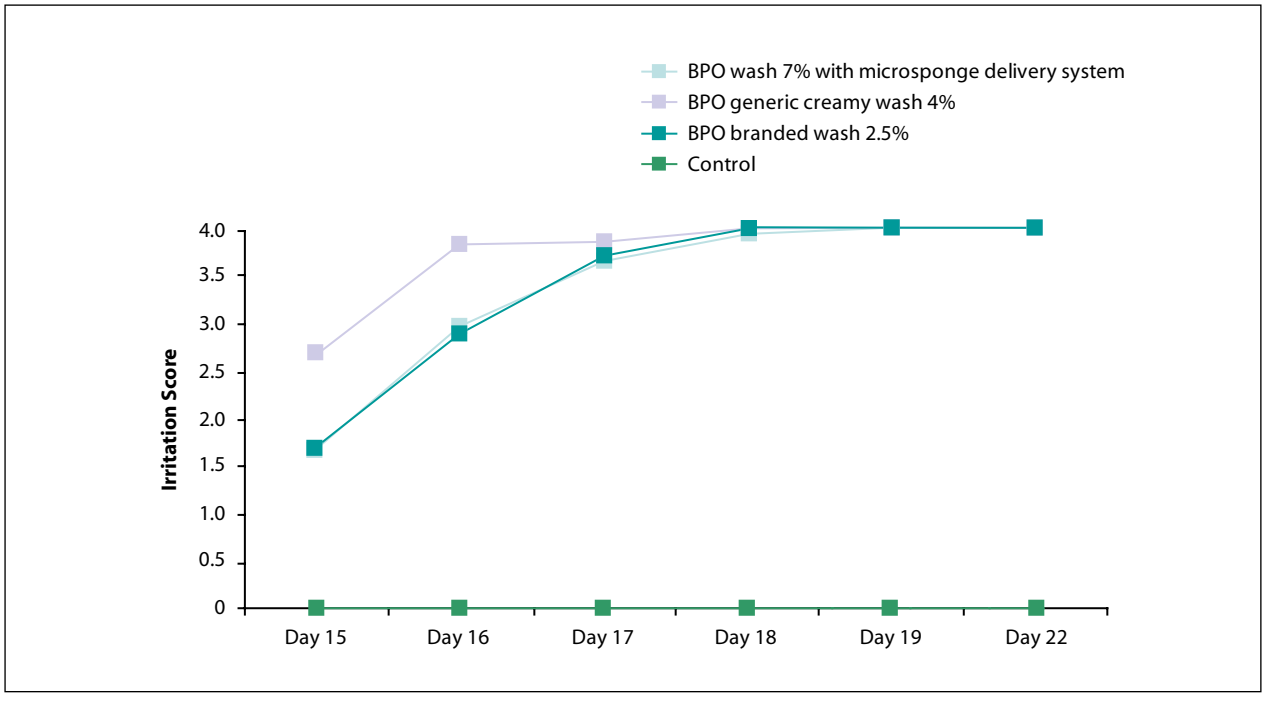

Figure 3. Average irritancy during the rechallenge phase of the study.

per BPO content by dividing each irritancy score from part 1 of the study by the percentage of BPO (ie, for 7%, divide by 7) to yield an irritancy score normalized for the amount of active ingredient (Table). When irritancy scores are adjusted for BPO strength, the hierarchy of irritancy changes: BPO foaming cloths 3% are the most irritating per unit BPO, followed by branded BPO creamy wash 4%, generic BPO creamy wash 4%, and OTC branded BPO wash 2.5%. The least irritating product tested per BPO strength is the BPO wash 7% with microsponge delivery system.

COMMENT

This research evaluated the irritancy of a variety of BPO wash formulations that featured different delivery systems and concentrations of BPO. Based on the standard patch test irritancy protocol, branded BPO creamy wash 4% was the most irritating, followed by the generic BPO creamy wash 4% and BPO foaming cloths 3%. The BPO wash 7% with microsponge delivery system and OTC branded BPO wash 2.5% were the least irritating.

It is not surprising that the study did not allow continuous patch application for the entire 21 days, even with the milder BPO formulations, because this irritancy testing protocol is usually performed for products designed to be left on the skin, rather than rinse-off products. However, achieving maximum irritancy by day 10 of the 21-day test period permitted the introduction of a rechallenge phase of 3 washes. Conducted following a 5-day rest period, the rechallenge was interesting in that it mimicked the condition of a damaged skin barrier in disease states that may be found concomitantly with acne, because a full 2-week recovery period following skin vesiculation was not completed. Irritancy scores rose more rapidly in the rechallenge phase, but the relative irritancy of the different BPO washes remained the same: generic BPO creamy wash 4% was the most irritating, and the BPO wash 7% with microsponge delivery system and the OTC branded BPO wash 2.5% were equally irritating.

The irritancy of BPO is concentration dependent.[13] In this study, however, the BPO wash 7% with microsponge delivery system was found to be less irritating than 2 different BPO creamy wash 4% formulations and a BPO foaming cloth 3%. Further, the BPO wash 7% with microsponge delivery system was comparably mild to the tested OTC branded BPO wash 2.5%. This disconnect between formulation strength and irritancy is even more clear when irritancy scores are adjusted for BPO strength, an adjustment that revealed BPO foaming cloths 3% to be the most irritating of the BPO washes tested, and BPO wash 7% with microsponge delivery system the least.

These findings demonstrate the ability of the vehicle in a BPO wash formulation to alter irritancy. In the case of

Average Irritancy Scores Adjusted for BPO Strength

	D1	D2	D3	D4	D5	D8	D9	D10
BPO wash 7% with microsponge delivery system	0	0	0.018571	0.218571	0.334286	0.548571	0.567143	0.571429
Branded BPO creamy wash 4%	0	0.6025	0.985	1.0	1.0	1.0	1.0	1.0
OTC branded BPO wash 2.5%	0	0	0	0.436	0.736	1.212	1.488	1.6
Generic BPO creamy wash 4%	0	0.0225	0.3125	0.9075	1.0	1.0	1.0	1.0
BPO foaming cloths 3%	0	0.126667	0.25	0.72	1.26	1.303333	1.333333	1.333333

Abbreviations: BPO, benzoyl peroxide; D, day.

the products tested, the microsponge technology utilized in the BPO wash 7% with microsponge delivery system seems to have reduced the irritancy of the wash such that it was less irritating than formulations with much lower concentrations of BPO. Of note, irritancy may vary among even ostensibly similar formulations. In this study, 2 BPO creamy washes 4%—one branded and one generic—were found to differ significantly ($P<.05$) in their irritancy effect.

At both dilutions 10% and 5%, the BPO wash 7% with microsponge delivery system was found to be mild relative to the other BPO washes tested. A previous study found that this BPO wash 7% is as mild as an OTC gentle facial cleanser.[14] In this study, conducted by Trookman et al,[14] patients with acne were randomly assigned to use either BPO wash 7% with microsponge delivery system or a mild cleanser (Purpose Gentle Cleansing Wash; Johnson & Johnson Consumer Companies Inc.) daily for 21 days. These patients found the BPO wash 7% with microsponge delivery system to be as well-tolerated as the mild unmedicated cleanser.[14] Taken together, these findings suggest that the BPO wash 7% with microsponge delivery system is a mild BPO cleanser that will be acceptable to a range of patients.

Delivery systems are uniquely important in dermatology, where the manner in which the drug is presented to the skin can affect tolerability and exposure. The ultimate goal is to provide the most efficacious dose in a manner that reduces skin barrier breakdown. High drug doses are most expeditiously delivered to a degraded barrier; however, repeated topical application of such a formulation is not tolerable, and patients will discontinue use owing to discomfort. The microsponge formulation is well suited to delivery of a cutaneous irritant, such as BPO. The continuous reservoir release of BPO may expose the skin to lower actual concentrations over an extended period, which would likely reduce skin levels of *P acnes* and yield better acne control.

CONCLUSION

This study demonstrated that a prescription acne BPO wash 7% applied via a microsponge formulation was as

mild as an OTC acne BPO wash 2.5% in a standard lotion formulation. The microsponge technology is effective in reducing the skin irritation associated with BPO. This suggests that newer BPO wash formulations with reduced irritancy may offer important benefits to the patient relative to more traditional BPO wash formulations, including the potential for improved treatment adherence.

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