

# The Effect of Simulated Solar UV Irradiation on Tretinoin in Tretinoin Gel Microsphere 0.1% and Tretinoin Gel 0.025%

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*Topical tretinoin is highly effective and widely used in the treatment of acne vulgaris. Tretinoin gel microsphere 0.1% (TGM)—alone or in combination with erythromycin–benzoyl peroxide (EBP) or clindamycin–benzoyl peroxide (CBP) topical gels—and tretinoin gel 0.025% (TG)—alone or combined with EBP—were exposed to simulated solar UV irradiation to determine the degree of tretinoin photodegradation/isomerization. The investigation revealed that 94% and 84% of the initial tretinoin in the TGM formulation remained stable after 2 and 6 hours, respectively, of simulated solar UV irradiation. When combined with EBP topical gel, 89% and 81% of the initial tretinoin remained stable after 2 and 6 hours, respectively, of exposure to simulated solar UV irradiation; 86% and 80% of the tretinoin remained stable after 2 and 6 hours, respectively, when combined with CBP topical gel. In contrast, only 19% and 10% of the tretinoin remained unchanged after 2 and 6 hours, respectively, of simulated solar UV irradiation of TG. Combined with the EBP topical gel, undegraded tretinoin quantities were further reduced to 7% and 0% at 2 and 6 hours, respectively, with TG. These data suggest that the TGM formulation offers marked*

*protection against tretinoin photodegradation compared with TG, even in the presence of a topical gel containing a potent antibiotic or a strong oxidizing agent. Although simulated solar UV irradiation is not entirely reflective of actual conditions, the results appear to be substantial.*

*Cutis. 2006;77:313-316.*

Tretinoin (all-*trans*-retinoic acid) has wide use in topical formulations for treating skin disorders such as acne vulgaris, psoriasis, and photodamaged skin. When prescribed as an acne vulgaris treatment, tretinoin often is used in combination with a topical antibacterial agent because no single topical therapeutic agent to date has been capable of ameliorating all of the causes of acne vulgaris.<sup>1</sup> The cornerstone of the current treatment is to reverse microcomedone formation by applying tretinoin, often combined with antibacterial agents such as clindamycin, erythromycin, or benzoyl peroxide, to kill the offending bacteria that colonize the follicle.<sup>2,3</sup>

Skin irritation in some patients<sup>4</sup> with acne who were treated with topical tretinoin, as well as tretinoin's susceptibility to degradation under various light conditions,<sup>5,6</sup> have been reported. Photodegradation/photoisomerization was accelerated when tretinoin was exposed to benzoyl peroxide's strong oxidative action.<sup>6,7</sup>

Tretinoin gel microsphere 0.1% (TGM), a microsp sponge formulation, was developed to minimize tretinoin irritation by trapping the active ingredient in a polymeric delivery system of porous microspheres.<sup>8</sup> TGM irritated skin less when compared with other tretinoin formulations in several

Accepted for publication July 26, 2005.

From Johnson & Johnson Consumer and Personal Products Worldwide, Skillman, New Jersey.

This study was supported by a grant from Johnson & Johnson Consumer and Personal Products Worldwide. Ms. Nighland, Mr. Yusuf, Dr. Wisniewski, and Ms. Huddleston are stockholders for Johnson & Johnson Consumer and Personal Products Worldwide. Dr. Nyirady was an employee of Johnson & Johnson Consumer and Personal Products Worldwide.

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clinical trials.<sup>9,10</sup> A recent stability study also demonstrated that the microsphere formulation offers marked protection against tretinoin photodegradation from fluorescent and incandescent light sources.<sup>7</sup> Our study investigated the effect of simulated solar UV irradiation on the degradation of tretinoin in TGM, with and without the addition of erythromycin–benzoyl peroxide (EBP) and clindamycin–benzoyl peroxide (CBP) topical gels, and compared the results with those of tretinoin gel 0.025% (TG).

### Materials and Methods

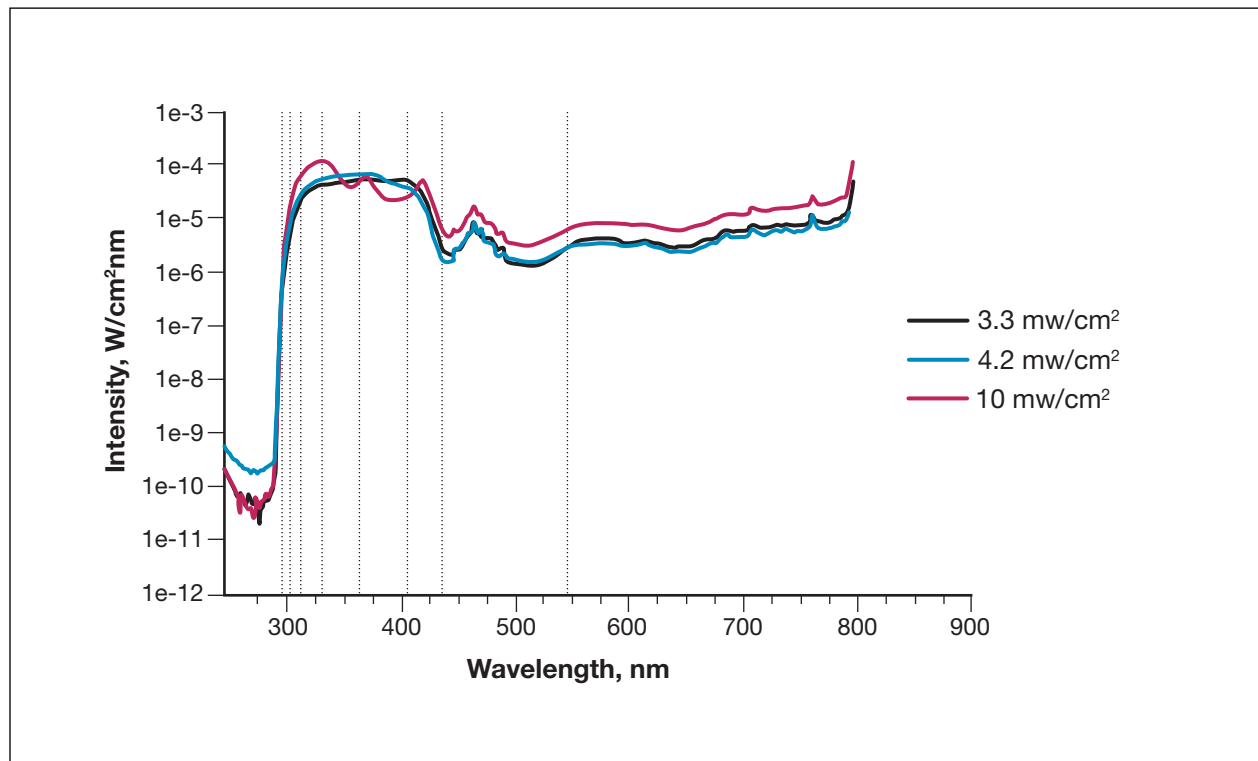
**Materials**—The study used TGM and TG, as well as erythromycin 3%–benzoyl peroxide 5% and clindamycin 1%–benzoyl peroxide 5% topical gels.

**Methods**—TGM and TG were placed into separate beakers and vortexed for 2 to 3 minutes. Approximately 4.0 g of each product then were placed into 5-mL plastic syringes, one for each time point. In a similar manner, 40.5 g of TGM and 40.5 g of TG were mixed with 4.5 g of EBP topical gel in separate beakers for 5 minutes. Approximately 4.0 g of these mixtures were then placed into individual 5-mL plastic syringes, one for each time point. Using the same process, 40.5 g of TGM also were mixed with 4.5 g of CBP topical gel and transferred to individual syringes. All syringes then were positioned under the solar UV

simulator; individual samples were removed at 15 and 30 minutes, and at 1, 2, 3, 4, and 6 hours for analysis of their tretinoin contents.

The solar simulation system included the 1000 W Oriel solar simulator with a 1-mm Schott WG 320 optical glass filter; the fluency rate of the simulator was measured with a radiometer equipped with a colored filter detector (spectral range, 315–390 nm). UV doses varied from 75 to 900 kJ/m<sup>2</sup>. The spectral characteristics of the simulated solar UV light are shown in Figure 1.

After irradiation, test samples were analyzed for tretinoin using high-performance liquid chromatography (HPLC). The instruments used included a Waters® 600E Pump Controller, a 717 Auto Injector, and a 996PDA Detector. The chromatographic data processor was Waters Millennium® Version 3.2. The HPLC assays were conducted using a Supelcosil™ LC-18 five- $\mu$ m, 25-cm  $\times$  4.6-mm column. Separation was achieved with a mobile phase of acetonitrile, water, and glacial acetic acid in a ratio of 800:200:0.2. The wavelength and flow rate were set at 353 nm and 1.8 mL/min, respectively. The column temperature and injection volume were 30°C and 10  $\mu$ L, respectively. All tretinoin analyses were duplicated and results given as a percentage of initial content.

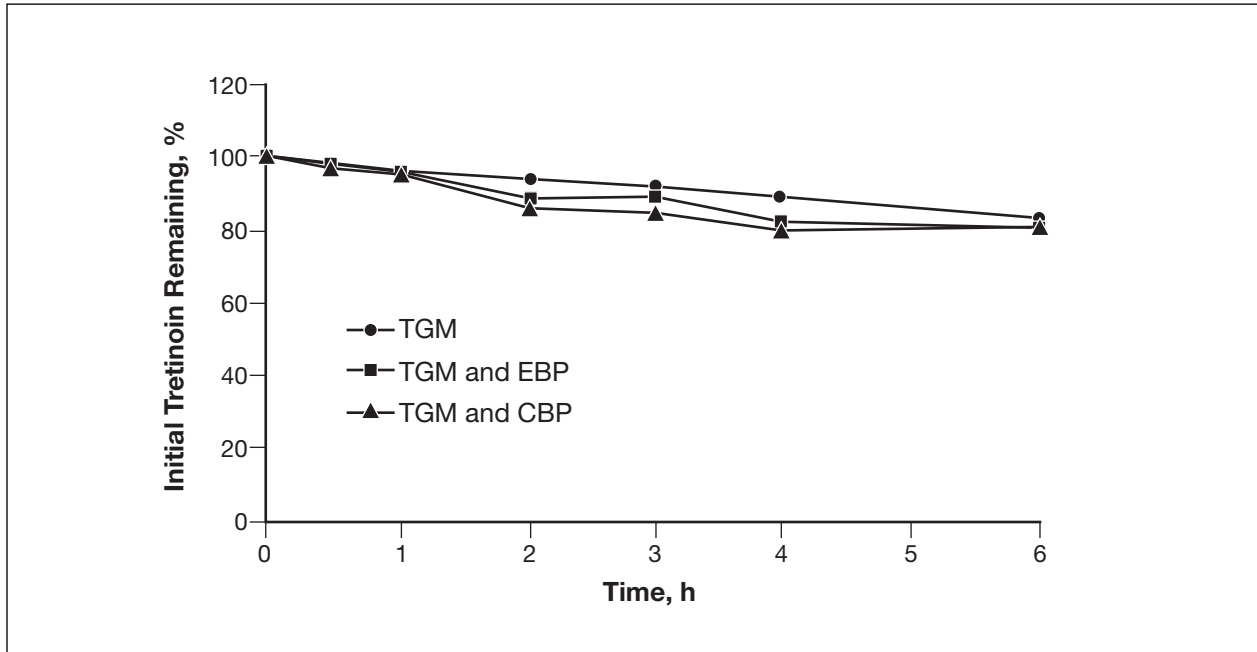


**Figure 1.** Spectral characteristics of solar UV simulator. Vertical dotted lines represent mercury calibration peaks at 296, 303, 313, 333, 365, 405, 436, and 546 nm.

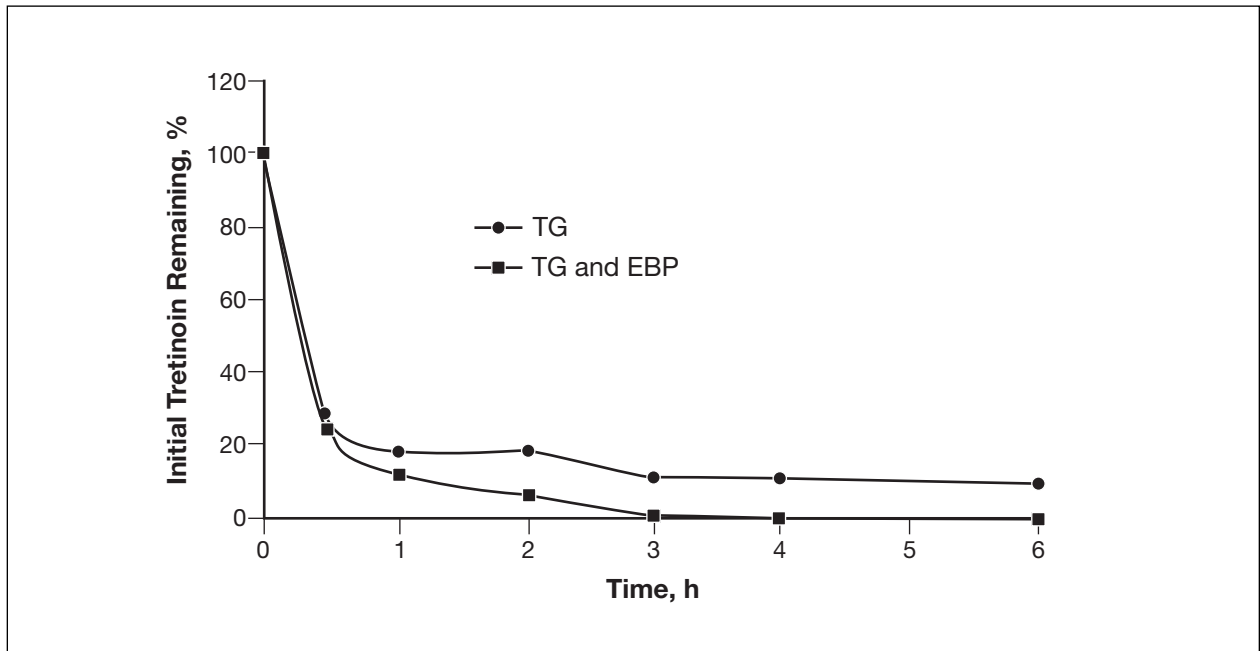
**Results**

HPLC analysis of the initial 2- and 6-hour irradiated TGM samples were evaluated and compared with the equivalent TG analyses. The results obtained from TGM alone and TGM combined with EBP or CBP were similar. Only 3 small discrete degradation peaks

were visible from each sample at 6 hours. The analyses also revealed that after 2 hours of irradiation, 94%, 89%, and 86% of the initial tretinoin was recovered from the samples of TGM, TGM and EBP, and TGM and CBP, respectively. After 6 hours of irradiation, 84%, 81%, and 80% of the initial



**Figure 2.** Percentage of initial tretinoin remaining in tretinoin gel microspheres 0.1% (TGM), TGM and erythromycin-benzoyl peroxide (EBP), or TGM and clindamycin-benzoyl peroxide (CBP) samples over 6 hours during simulated solar UV irradiation.



**Figure 3.** Percentage of initial tretinoin remaining in tretinoin gel 0.025% (TG), and TG and erythromycin-benzoyl peroxide (EBP) samples over 6 hours during simulated solar UV irradiation.

tretinoin was recovered from the samples of TGM, TGM and EBP, and TGM and CBP, respectively (Figure 2). These results indicated that tretinoin in the TGM formulation remained substantially stable over a period of 6 hours under simulated solar UV irradiation.

In sharp contrast to the TGM results, HPLC analysis of the initial and 6-hour irradiated samples of TG alone or in combination with EBP suggested that tretinoin had been substantially degraded by the simulated solar UV irradiation. As depicted graphically in Figure 3, recoverable (undegraded) tretinoin was reduced to 19% and 10% in the TG samples after 2 and 6 hours, respectively, of irradiation; these amounts were further reduced to 7% and 0%, respectively, when combined with EBP. A combination of TG and CBP was not tested.

### Comment

Tretinoin is used extensively in various formulations (ie, gels, creams, and lotions) to modify abnormal follicular keratinization, promote detachment of keratinocytes, and enhance the shedding of corneocytes from the follicle.<sup>3,5</sup> Through these actions, the comedone contents are extruded and the formation of the microcomedone, the initial lesion of acne vulgaris, is reduced. Tretinoin preparations have been reported to be unstable on the skin under bright artificial light or sunlight.<sup>3,5</sup> When combined with a strong oxidizing agent such as benzoyl peroxide and subjected to 24 hours of fluorescent light, tretinoin photodegradation increased to 89% and 95%.<sup>6,7</sup>

Tretinoin in the TGM formulation does not undergo such degradation. As Nyirady et al<sup>7</sup> reported, 98% of tretinoin tested remained stable after 24 hours of exposure to fluorescent light, incandescent light, or darkness. In the same study, irradiation of a TGM-EBP mixture resulted in a 94% to 95% tretinoin recovery rate after 8 hours and an 86% to 87% recovery rate after 24 hours of exposure to incandescent or fluorescent light.<sup>7</sup>

In our study, a similar protective effect by the microsphere formulation was observed after simulated solar UV irradiation for 6 hours, a period that tends to mimic reasonable daily outdoor use. Eighty-four percent of the initial tretinoin remained stable in the TGM formulation, compared to 10% in the TG formulation; 81% of the initial tretinoin in the TGM-EBP combination remained stable versus 0% in the TG-EBP combination. HPLC analyses of the various samples (TGM, TGM and EBP, and TGM and CBP) at 30 minutes and 1, 2, 3, 4, and 6 hours indicated that a limited amount of tretinoin

polymerization did occur with time, but degradation was gradual and linear, whereas in TG and the TG-EBP combination, tretinoin degraded precipitously to less than 20% of the initial amount within the first hour of irradiation.

### Conclusion

The results from this study indicate that tretinoin in the TGM formulation provided a high degree of protection against photodegradation. More than 80% of the tretinoin remained stable when exposed to 6 hours of simulated solar UV irradiation. Under the same light conditions, 0% to 10% of the tretinoin in the TG formulation was left undegraded. These findings should be of critical importance when choosing a tretinoin product for the treatment of acne vulgaris.

*Acknowledgment*—The authors would like to thank Robert Diener, DVM; Peter Lyte, BS; Jeff Pote, MS; and Claude Saliou, PhD for their technical assistance.

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