The Stability of Tretinoin in Tretinoin Gel Microsphere 0.1%

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Topical tretinoin is highly effective and widely used in the treatment of acne vulgaris. In studies to determine the degree of tretinoin photo degradation (isomerization), 2 tretinoin formulations, tretinoin gel microsphere 0.1% and tretinoin gel 0.025%, alone or in combination with erythromycin-benzoyl peroxide topical gel, were exposed to fluorescent light, incandescent light, or darkness for up to 24 hours. Results of the investigations revealed that after 24 hours of exposure to fluorescent light, 98% of the initial tretinoin in the tretinoin gel microsphere 0.1% formulation remained unchanged. When tretinoin gel microsphere 0.1% was combined with erythromycin-benzoyl peroxide topical gel and exposed to fluorescent light, 99% and 87% of the tretinoin was recovered after 4 and 24 hours, respectively, indicating only a limited amount of degradation. In contrast, exposure of tretinoin gel 0.025% to 24 hours of fluorescent light resulted in up to 69% tretinoin degradation and up to 89% degradation when the gel was combined with the erythromycin-benzoyl peroxide topical gel. The data suggest that the tretinoin gel microsphere 0.1% formulation offers marked protection against tretinoin photo degradation, even in the presence of a strong oxidizing agent such as benzoyl peroxide.

Tretinoin (all-*trans*-retinoic acid) is used widely in topical formulations for the treatment of various skin disorders, such as acne vulgaris, psoriasis, and photodamaged skin. When prescribed as a treatment for acne vulgaris, tretinoin often is used in combination with a topical antibacterial agent (ie, clindamycin, erythromycin, benzoyl peroxide) because to date, no single topical therapeutic agent is capable of ameliorating all the etiologic factors of acne vulgaris.[1] Present-day treatment of acne usually centers around the topical application of retinoids to reverse microcomedo formation (hypercornification, hyperkeratinization, and hypodesquamation of the follicular infundibulum), while antibiotics such as erythromycin or a strong oxidizing agent such as benzoyl peroxide is used to kill the *Propionibacterium acnes* that colonize the follicle.[2]

The effectiveness of topical tretinoin is well established,[1,2] though skin irritation in some patients[3] and susceptibility to photo degradation under various light conditions[4,5] in others have been reported. Combinations of tretinoin and benzoyl peroxide were found to degrade more rapidly than the tretinoin itself when exposed to actinic (fluorescent) light because of the strong oxidative action of benzoyl peroxide.[5]

Tretinoin gel microsphere 0.1%, a microsponge formulation, was developed with the goal of minimizing cutaneous irritation.[6] This polymeric delivery system, consisting of porous microspheres that entrap active ingredients, markedly decreased the incidence of noninflammatory lesions in 2 clinical trials[7] and demonstrated a lower irritation profile when compared with tretinoin cream 0.1% in a half-face comparative study and a 21-day cumulative irritation study.[8] However, no literature references could be found that documented the degree of photo degradation (isomerization) of tretinoin in this particular formulation. Therefore, the objectives of the present study were to study the effect of

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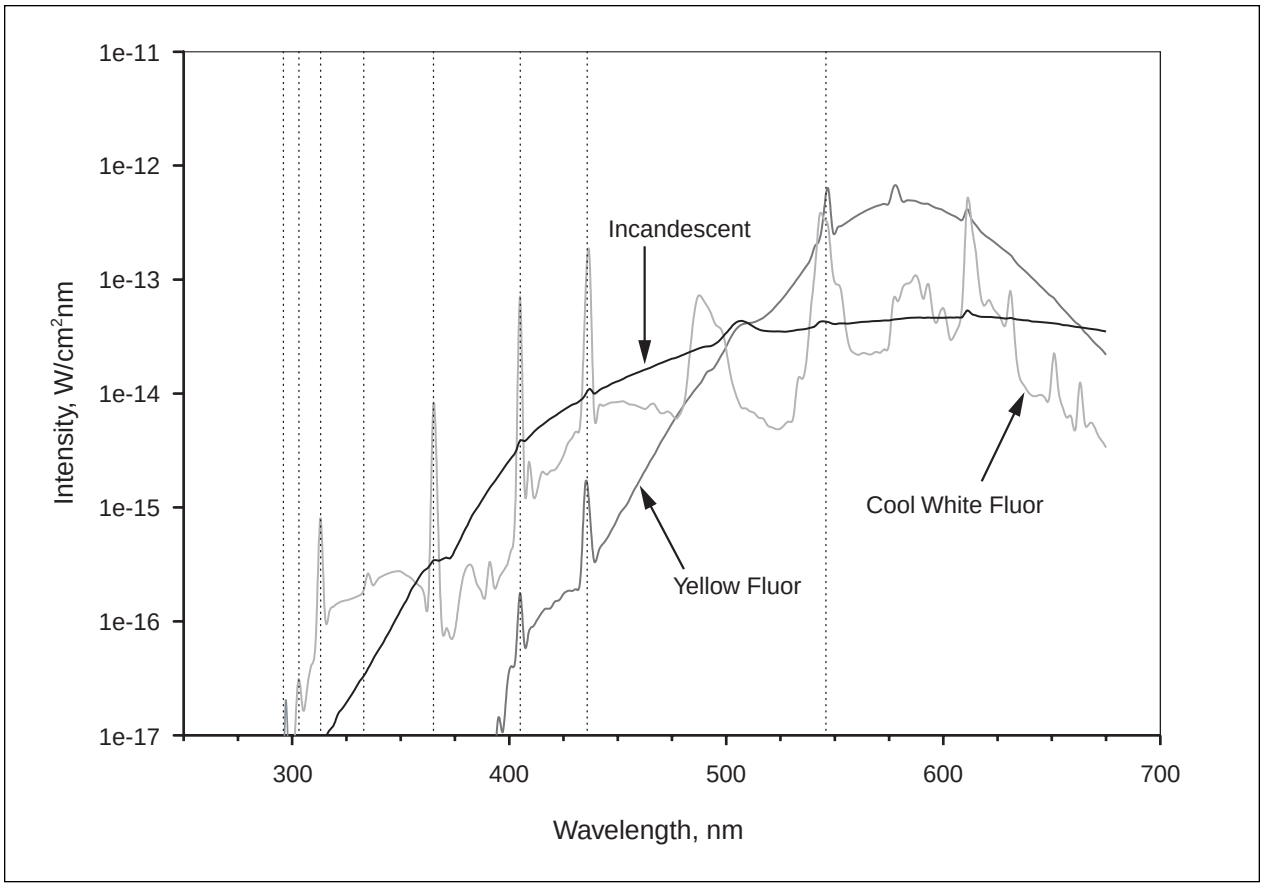

Figure 1. Light spectrum of fluorescent and incandescent lighting. Vertical dotted lines represent mercury calibration peaks at 296, 303, 313, 333, 365, 405, 436, and 546 nm.

different indoor lighting conditions (fluorescent and incandescent lights, as well as darkness) on the degradation of tretinoin in tretinoin gel microsphere 0.1% and tretinoin gel 0.025%, with and without the addition of an erythromycin-benzoyl peroxide topical gel.

Materials and Methods

Materials—Tretinoin gel microsphere 0.1% and tretinoin gel 0.025% were obtained from Ortho Dermatological, Ortho-McNeil Pharmaceutical, Inc. The erythromycin-benzoyl peroxide topical gel was obtained commercially.

Methods—Both tretinoin gel microsphere 0.1% and tretinoin gel 0.025% 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 tretinoin gel microsphere 0.1% and 40.5 g of tretinoin gel 0.025% each were mixed with 4.5 g of the erythromycin-benzoyl peroxide topical gel in a beaker for 5 minutes. Approximately 4.0 g of these mixtures then were placed into individual 5-mL plastic syringes, one for each time point.

The fluorescent light source included eight 32-W tubular lightbulbs; the incandescent light source included four 75-W lightbulbs. Spectral comparison of the illumination from the fluorescent and incandescent lighting is shown in Figure 1. The spectrum encompasses the visible light spectrum and only minimal spectrum from UVA.

Syringes were exposed to specified light conditions (fluorescent, incandescent, or darkness) for 0, 1, 2, 4, 8, 22, or 24 hours, respectively.

After exposure to the various lighting conditions, test samples were analyzed for tretinoin via high-performance liquid chromatography (HPLC). HPLC assays were conducted using a Supelcosil LC-18 (5 µm, 25-cm×4.6-mm column). Separation was achieved with a mobile phase of acetonitrile/water/glacial acetic acid in a ratio of 800/200/0.2. Wavelength and flow rate were set at 353 nm and 1.8 mL/min, respectively. Column temperature and

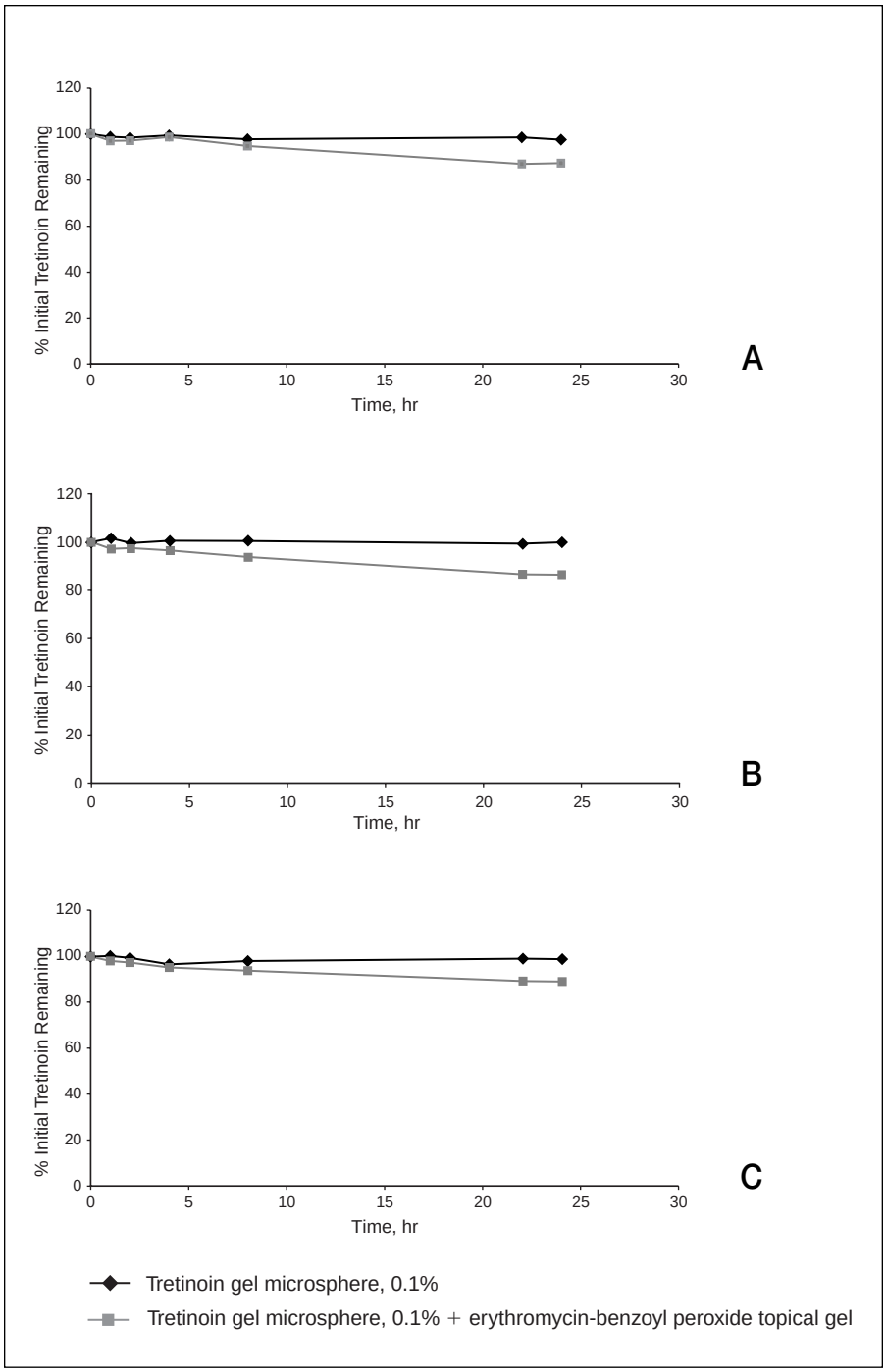

Figure 2. The percentage of initial tretinoin remaining in tretinoin gel microsphere 0.1% alone and when mixed with erythromycin-benzoyl peroxide topical gel when the lighting condition is (A) fluorescent, (B) incandescent, and (C) darkness.

injection volume were 30°C and 10 µL, respectively. All tretinoin analyses were conducted in duplicate and results given as a percentage of initial content.

Results

HPLC analysis of the 24-hour tretinoin gel microsphere 0.1% samples exposed to fluorescent light revealed the presence of only 2 small degradation peaks that were barely detectable. Two similar but slightly larger peaks also were observed after the analysis of the 24-hour samples of tretinoin gel microsphere 0.1% mixed with erythromycin-benzoyl peroxide topical gel and exposed to fluorescent light.

Graphic stability profiles for tretinoin gel microsphere 0.1% and tretinoin gel microsphere 0.1% mixed with erythromycin-benzoyl peroxide topical gel and exposed to the 3 light conditions are

illustrated in Figure 2. The amount of tretinoin recovered from the tretinoin gel microsphere 0.1% samples at each time point was 98% of the initial amount, regardless of the lighting condition (one exception: 97% recovery occurred at 4 hours in the absence of light). Tretinoin in the tretinoin gel microsphere 0.1% mixed with erythromycin-benzoyl peroxide topical gel remained essentially unchanged after 4 hours of exposure to fluorescent light, incandescent light, or darkness (99%, 97%, and 96% of initial values, respectively). After 8 hours of exposure, 94% to 95% of the initial tretinoin was recovered in the samples. After 24 hours of exposure, 87%, 86%, and 90% of tretinoin remained stable in the samples exposed to fluorescent light, incandescent light, or darkness.

HPLC analysis of the 24-hour samples of tretinoin gel 0.025%, either alone or mixed with erythromycin-benzoyl peroxide topical gel and exposed to fluorescent light, revealed the presence of multiple large peaks representing a variety of degradation products. The degradation products were more numerous in the tretinoin gel 0.025% mixed with erythromycin-benzoyl peroxide topical gel. Exposure to fluorescent light for 24 hours resulted in a 69% degradation of tretinoin in tretinoin gel 0.025% and an 89% degradation of tretinoin when combined with erythromycin-benzoyl peroxide topical gel.

Comment and Conclusion

Various formulations of tretinoin (gel, cream, liquid) are used extensively to reduce hyperkeratinization and to unplug pilosebaceous follicles, the initial lesion of acne vulgaris. These preparations have been reported to be unstable on the skin under bright artificial light or sunlight.[1,4] Furthermore, Martin et al[5] have reported that as much as 95% of the initial quantity of tretinoin in tretinoin gel 0.025% degraded when mixed with erythromycin-benzoyl peroxide topical gel and subjected to 24 hours of fluorescent light.

The present investigation examined the stability of tretinoin in the microsponge formulation and compared it with the stability of tretinoin in the tretinoin gel 0.025% formulation under various indoor lighting conditions. The spectrum of indoor lights covered the visible light spectrum and included only minimal UVA radiation. The effect of solar radiation on tretinoin in the tretinoin gel microsphere 0.1% formulation also has been completed recently, and results will be published separately.

Results from the present investigation revealed that under the test conditions of the study, 89% of the tretinoin in the tretinoin gel 0.025% had undergone degradation after 24 hours of exposure to fluorescent light when it was combined with erythromycin-benzoyl peroxide topical gel. Sixty-nine percent of the tretinoin was degraded under the same exposure conditions in tretinoin gel 0.025% alone. These results are similar to those obtained by Martin et al.[5]

Although the findings of Martin et al[5] were confirmed in the present study with the tretinoin gel 0.025%, degradation of tretinoin was limited in the tretinoin gel microsphere 0.1% formulation. In fact, the tretinoin gel microsphere 0.1% formulation itself was completely stable (98% recoverable) when exposed to fluorescent light, incandescent light, or darkness over a period of 24 hours. When combined with erythromycin-benzoyl peroxide topical gel, 87% of the initial tretinoin remained stable.

The tretinoin gel microsphere 0.1% formulation not only demonstrated a lower irritation profile than tretinoin cream 0.1% in clinical studies[8] but also provides a high degree of protection against tretinoin photo degradation, even in the presence of benzoyl peroxide and erythromycin. These important findings should be taken into consideration when tretinoin combination therapy is chosen in the clinics.

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REFERENCES

1. Weiss JS. Current options for the topical treatment of acne vulgaris. *Pediatr Dermatol*. 1997;14:480-488.
2. White GM. Acne therapy. In: James WD, Cockerell CJ, Dzubow LM, et al, eds. *Advances in Dermatology*. Vol 14. St Louis, Mo: Mosby; 1999:29-59.
3. Leyden JJ. Topical treatment of acne vulgaris: retinoids and cutaneous irritation. *J Am Acad Dermatol*. 1998;38:S1-S4.
4. Brisaert M, Plaizier-Vercammen J. Investigation on the photostability of a tretinoin lotion and stabilization with additives. *Int J Pharm*. 2000;199:49-57.
5. Martin B, Meunier C, Montels D, et al. Chemical stability of adapalene and tretinoin when combined with benzoyl peroxide in presence and in absence of visible light and ultraviolet radiation. *Br J Dermatol*. 1998;139(suppl 52):8-11.
6. Nacht S, Katz M. The microsponge: a novel topical programmable delivery system. In: Osborne DW, Amann AH, eds. *Topical Drug Delivery Formulations*. New York, NY: Marcel Dekker Inc; 1990.
7. Webster GF. Topical tretinoin in acne therapy. *J Am Acad Dermatol*. 1998;39:S38-S44.
8. Retin-A Micro [package insert]. Skillman, NJ: Ortho Dermatological, Ortho-McNeil Pharmaceutical, Inc; 1999.