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Matrix Revisited: Innovative Approach for Tretinoin

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Tretinoin Formulation: From Microsponges to Polymeric Emulsion

Leon H. Kircik MD

The history of tretinoin and its use in dermatology is a testament both to the drug's well-established efficacy and its potential to cause skin irritation. Over more than four decades, the drug that launched the retinoid class into the market has been used in the topical management of acne, either alone or in combination. In fact, current consensus acne treatment guidelines rely heavily on retinoids, as they address several aspects of acne pathogenesis—they are comedolytic, resolve the precursor microcomedone, and are anti-inflammatory—without posing any risk for antibiotic resistance.[1]

However, topically applied tretinoin has been associated with skin dryness, erythema, and even development of dermatitis. This legacy of irritation may largely derive from the earliest vehicles of the drug, which were formulated with a high concentration of active drug solubilized in solutions that contained several irritating excipients such as alcohol.[2] Innovation led to the formulation of tretinoin in sponge-like, porous, polymeric microspheres that encapsulate the drug and deliver it gradually, in a vehicle where tretinoin has limited solubility.[3] Microsponge delivery of tretinoin was associated with decreased irritation and improved drug stability. Subsequent formulation advancements attempted to further improve the patient experience with tretinoin.

The latest advancement in vehicle formulation for tretinoin has brought prescribers the first topical lotion formulation of tretinoin 0.05% (Altreno, Ortho Dermatologics). The novel lotion formulation incorporates a polymeric honeycomb matrix that helps provide a uniform distribution of both active and moisturizing/hydrating ingredients. Phase 3 data show a 52% percent reduction in inflammatory lesions at week 12 compared to baseline with the use of tretinoin 0.05% lotion; statistically significant reduction in comedonal lesions as early as week 4, and a 46% reduction by week 12.[4] More importantly, the new formulation was very well tolerated in studies.

As discussed ahead, data show specific skin-supporting benefits associated with the novel lotion formulation of tretinoin. Specifically, topical application of the lotion was associated with rapidly increased skin hydration and decreased trans-epidermal water loss (TEWL)—an important measure of barrier function—as measured by Corneometer® and Tewameter®, respectively. The documented barrier-supporting effects of the lotion vehicle are welcomed for acne, as it is well established that a properly functioning barrier is essential to re-establishing healthy skin. A wide range of patients with various skin types may appreciate the hydrating effects of an easily applied topical lotion. Additionally, the lotion formulation may be especially attractive to those women who may wish to apply make-up over their topical medications.

With these thoughts in mind, dermatology providers can see potential benefit in the availability of a topical lotion formulation of tretinoin with proven efficacy and excellent tolerability.

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 ORIGINAL ARTICLE

Polymeric Emulsion Technology Applied to Tretinoin

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The Microsponge Delivery System (MDS) for Tretinoin: A First Attempt at Reducing Irritation

The Microsponge Delivery System (MDS) is a controlled drug delivery system that encapsulates the active drug, releasing it over time; and in response to a trigger such as rubbing, changes in pH, or increased temperature. The technology was developed over 30 years ago,[1] and is widely used in cosmetics, skin care products available over-the-counter or through prescription, and sunscreens.[2]

It consists of porous, polymeric microspheres (polyol-prepolymer-2) forming multiple interconnecting spaces that serve as a drug reservoir and mimicking a rigid sponge. Microspheres vary in size from 5-300µm and the sizes of these porous structures determine the amount and rate of drug release. For example, a typical 25µm sphere can have as many as 250,000 pores. Microspheres do not penetrate the skin; they sit on top of the skin and slowly release tretinoin to potentially reduce any irritation. The empty spheres may stay on the skin and collect lipophilic materials such as sebum and be washed away when the skin is cleansed.

Microspheres delay the onset of irritation, but do not reduce the cumulative irritation when compared with other tretinoin formulations.[3] Another safety concern is the potential bacterial contamination of materials entrapped in the microsponge. Bacteria cannot penetrate into the tunnel structure of the microsphere because the pore diameter, which ranges from 0.007 to 0.2µm, is smaller than bacteria. In addition to any drug delivery benefits, they are capable of absorbing skin secretions, reducing oiliness and shine from the skin. In the case of tretinoin microsphere formulations, the drug is encapsulated in copolymer particles measuring 17-27µm and released gradually into the skin.

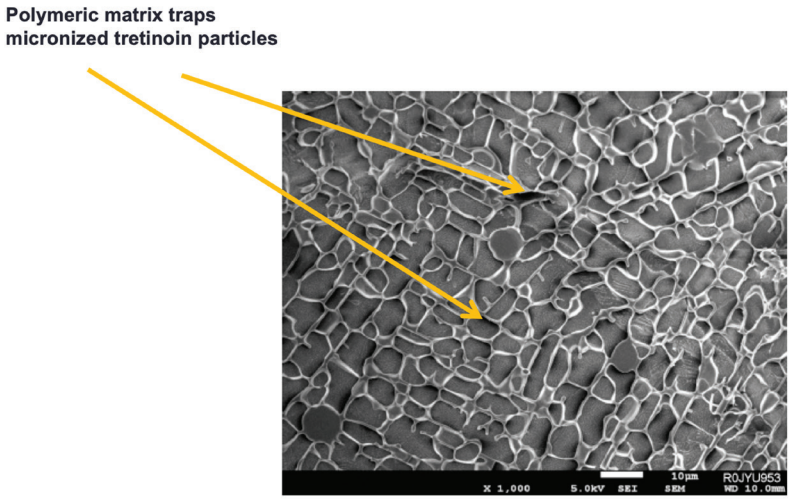
Additional benefits of the MDS include improved photostability, improved compatibility with benzoyl peroxide (BP), and reduced irritation potential. Tretinoin formulations (ie, gels, creams, and lotions) have been reported to be unstable on the skin under bright artificial light or sunlight. When combined with a strong oxidizing agent such as BP and antibiotic such as erythromycin, and subjected to fluorescent light for 24 hours, tretinoin photodegradation in tretinoin 0.025% gel increased to 89% and 95%.[4,5] Tretinoin in a microsphere formulation did not undergo such degradation; 98% of tretinoin tested remained stable after 24 hours exposure to fluorescent light, incandescent light, or darkness.[5] A similar protective effect was seen after exposure to simulated solar UV irradiation for 6 hours; 84% of the initial tretinoin remained stable in the microsphere formulation, compared with only 10% in tretinoin 0.025% gel.[6] Irradiation of a tretinoin microsphere-BP-erythromycin combination resulted in a 94% to 95% tretinoin recovery rate after 8 hours and 86% to 87% recovery rate after 24 hours of exposure to incandescent or fluorescent light.[5] After 6 hours of simulated solar light, 81% of the combination remained stable compared with 0% in tretinoin 0.025% gel.[6] The practical benefits of these findings were demonstrated in a phase 4 study of tretinoin microsphere 0.04% plus BP 5% wash, where patients who cleansed their face with BP 5% wash followed by tretinoin each morning and those who cleansed in the morning and applied tretinoin microsphere 0.04% gel each evening had a similar response.[7]

Application of the MDS to the skin has demonstrated the ability to reduce the irritancy of tretinoin. However, one disadvantage of tretinoin microsphere 0.1% gel is its rough or 'gritty' texture when spread onto the skin, due to the nature of the microsponges and some patients find this unpleasant. Also, a 'burst effect' can occur as tretinoin is released from microspheres attributed to the deposition of drug at or close to the outermost parts of the microsphere walls.[8] This burst delivery of tretinoin may cause drying and peeling that could progress to uncomfortable scaling and redness of the skin and impact adherence. This new technology may be able to improve on the advances already made with the MDS system.

Micronization of Tretinoin

The role of particle size reduction and particle engineering is another important aspect of formulation development in acne. Micronization is a valuable technique for products with poor water solubility and bioavailability. It increases the dissolution rate of drugs through an increased surface area. However, as compared to the effect on dissolution properties, decrease in particle size has comparatively little effect on the solubility of the drug substance as it does not alter the solid-state properties. Tretinoin has a very low water solubility (<0.2µg/ml) which can limit its utility without formulation technology.[9] In addition, the

FIGURE 1. Cryo scanning electron microscopy (SEM) imaging of polymeric matrix.



more lipophilic the vehicle used to suspend the tretinoin is, the greater the concentration of tretinoin at the surface of the skin and higher the risk of potential irritation. A novel formulation of micronized tretinoin 0.05% gel has been developed that potentially enables more efficient penetration into the crevasses and follicular openings of the skin because of its optimal particle size.

The development of this novel aqueous gel formulation that incorporates micronized active drug, suspended in a moisturizing hydrogel vehicle provides a number of advantages; limiting the concentration of tretinoin in solution and by limited solubility-controlled release at the surface of the skin and improving delivery to the pilosebaceous units. In such a hydrogel, hydrophobic drugs like tretinoin are not in solution but a solid state, dispersed and suspended by a polymeric gelling agent. The gel is alcohol-free, contains humectants and moisturizers (soluble collagen, sodium hyaluronate, and glycerin), and produces very little or no additional skin barrier disruption. The sustained delivery of tretinoin, which can eliminate the burst-release characteristics of some tretinoin formulations, and the humectants/moisturizers used in the formulation allow for controlled release over time and should help minimize tretinoin-associated irritation, dryness, scaling, and redness.

Tretinoin particles normally range in size from 200 to 300µm in more traditional formulations. In this formulation of tretinoin 0.05% aqueous gel, at least 85% of the micronized particles are smaller than 10µm. Having such a small particle size could allow for easier penetration into the follicular openings, which are typically 11 to 77µm, with resultant direct uptake into the sebum.[10,11] A more efficient penetration of micronized tretinoin particles into the epidermis/dermis has been reported when compared to tretinoin microsphere 0.1% gel. Micronized tretinoin in this aqueous gel had a three-fold greater efficiency for epidermal and dermal deposition of tretinoin (21% and 3% of the applied dose, respectively, with tretinoin 0.05% aqueous gel, compared with 7% and 1% with tretinoin microsphere 0.1% gel).[12] The total amount of tretinoin delivered is depending upon the concentration of tretinoin as well as the efficiency of its delivery. In this in vitro 24-hour percutaneous absorption study, the epidermal deposition with micronized tretinoin 0.05% aqueous gel was 0.526 µg/cm^2 compared with 0.336 µg/cm^2 with tretinoin microsphere 0.1% gel.[12]

In addition, photodegradation of micronized tretinoin 0.05% aqueous gel is reduced, and the lowest seen with tretinoin formulations so far, and there is no apparent degradation when used with BP. Photodegradation of tretinoin appears to correlate with specific light conditions and formulations used. This phenomenon may also be clinically relevant.[13-15] Photodegradation of micronized tretinoin 0.05% aqueous gel was minimal after eight hours exposure to UVA light, the major contributor to tretinoin photodegradation. The 9% degradation observed (compared with 72% degradation of tretinoin 0.025% gel) was lower than that seen in other studies with tretinoin 0.1% microsphere gel exposed to a stimulated solar UV light source for a shorter period of time.[16]

Polymeric Matrix to Deliver Micronized Tretinoin

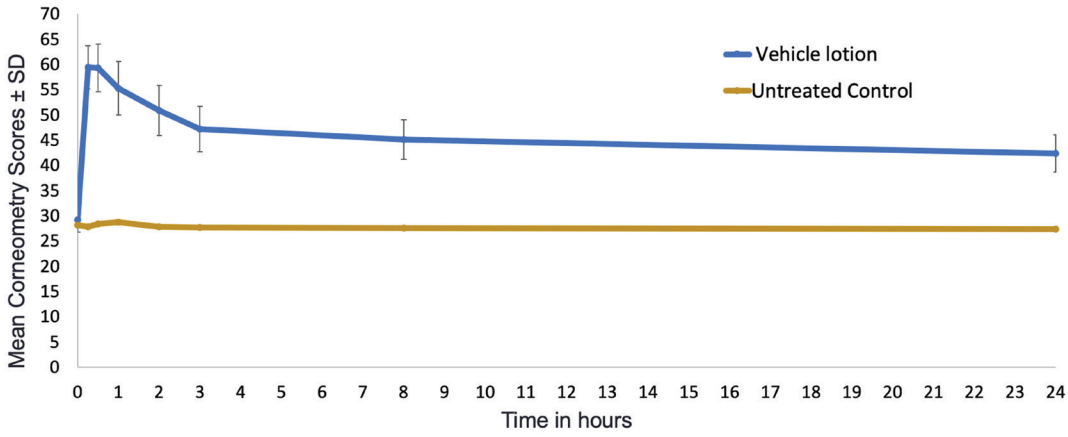
A number of different strategies have been proposed to achieve efficient drug delivery systems. Hydrogels are the latest advance; they are three-dimensional, cross-linked networks of water-soluble polymers commonly used in cosmetic formulations for skin care. Different polymers can be selected to formulate these hydrogels; some of the most commonly used gelling agents are carbomers, high molecular weight polymer of acrylic acid. In formulating these hydrogels product spreadability for correct dosage transfer to the target site, ease of application, extrudability from the proposed packaging, and most importantly consumer preference, must be considered.[17]

The adhesive capacity in dermal administration is important to ensure retention at the site of application, and active ingredient-release key for the product to exert its action either at the skin surface or within deeper layers.[18]

Recently, a polymeric honeycomb matrix (using carbomer cross-linked polymers, carbomer copolymer type B and homopolymer type A), which helps structure the active drug and provide a uniform distribution of both active and moisturizing/hydrating ingredients (sodium hyaluronate, soluble collagen, glycerin) at the surface of the skin, has been deployed for the delivery of micronized tretinoin (Figure 1). The formulation also contains small amounts of mineral oil. Mineral oils are used in skin care products due to their excellent skin tolerance, as well as their antimitotic and cleansing properties and the broad viscosity options they provide. Mineral oils are not percutaneously absorbed and with an absence of dermal uptake do not become systemically available;[19] at low concentrations they exhibit no comedogenicity potential.[20] The concomitant use of moisturizers and humectants can enhance efficacy, alleviate dryness, and improved skin comfort. Sodium hyaluronate is a powerful humectant that attracts and holds onto water, is smaller than hyaluronic acid, and able to penetrate more freely into the deeper layers of the skin. Unlike some moisturizers, sodium hyaluronate doesn't leave a "greasy" feel to the skin. Collagen, too, is an important component for cosmetic formulation, where it is an effective natural humectant with high substantivity. Glycerin has been shown to have a number of additional benefits beyond increasing the hydration of the stratum corneum (SC) structural elements. It prevents SC phase transition, is keratolytic, influences the protective function of the skin against irritation and penetration of substances through the SC, plasticizes the SC, reduces tissue scattering, stabilizes skin collagen, and accelerates the healing process.

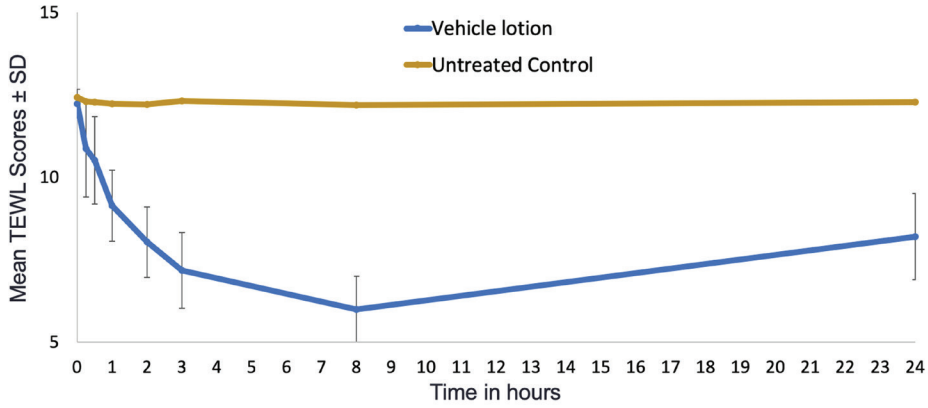
This polymeric matrix and vehicle lotion formulation provide

FIGURE 2. Skin moisturization assessment over 24 hours. (Corneometer method).*



*All time points except baseline P<.001 versus untreated control

FIGURE 3. Skin barrier assessment over 24 hours. Trans epidermal water loss method (TEWL)*



*All time points except baseline P<.001 versus untreated control

an effective skin barrier by reducing epidermal water loss and improving skin hydration. Skin hydration and barrier protection of the lotion were assessed through corneometry and transepidermal water loss (TEWL) in 30 female healthy volunteers (aged 35-65 years) over 24 hours, using the test material applied to the volar forearm, with an untreated site serving as a control. Measurements using Tewameter® and Corneometer® were taken at baseline, 15 and 30 minutes, and 1, 2, 3, 8, and 24 hours post-application. In addition, at the 8-hour study period 15 subjects applied the test material to the right side of their face and completed a customer perception evaluation of the novel formulation. Adverse events (AEs) were noted throughout and irritation assessed at pre- and post-application. There were no AEs or skin irritation reported throughout the study. At baseline, mean corneometry scores were 29.2 ± 2.4 and 28.1 ± 2.7 units (test material and untreated control, respectively). There was an immediate improvement in water content that was maintained throughout the study with the test material. After 15 minutes, the mean score had increased to 59.4 ± 4.3 units (Figure 2). There was no improvement at the control site and

FIGURE 4A. Customer perception results: hydration, moisturization, and absorption properties of vehicle lotion.

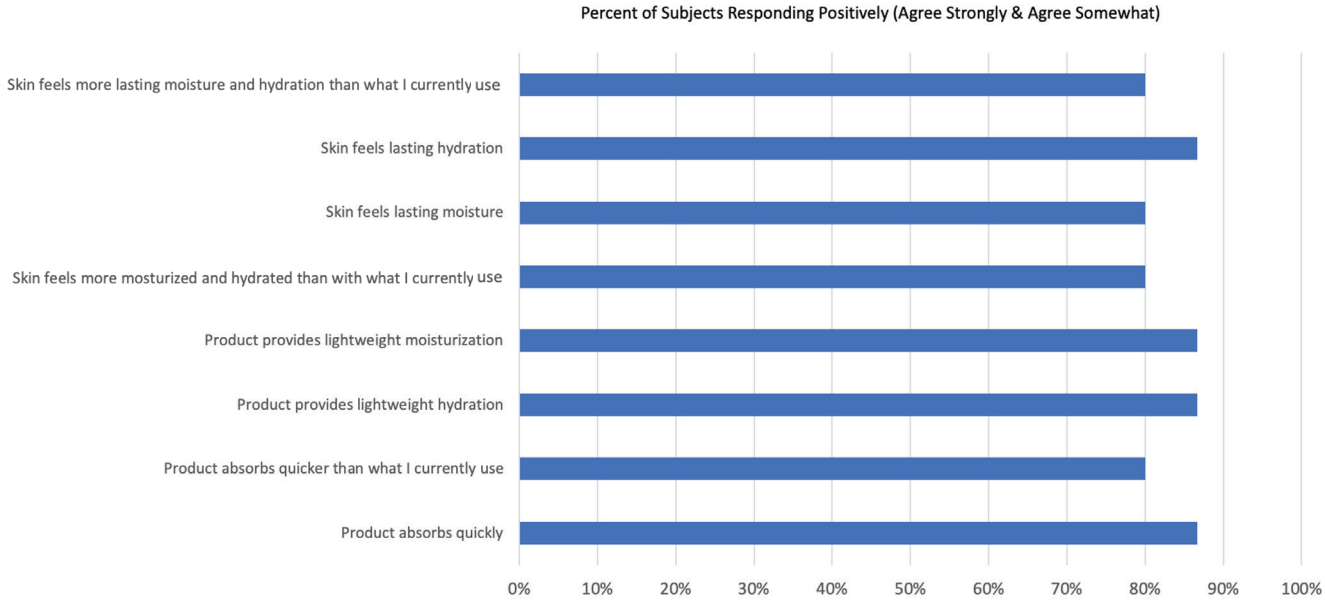


FIGURE 4B. Customer perception results: vehicle lotion properties and attributes.

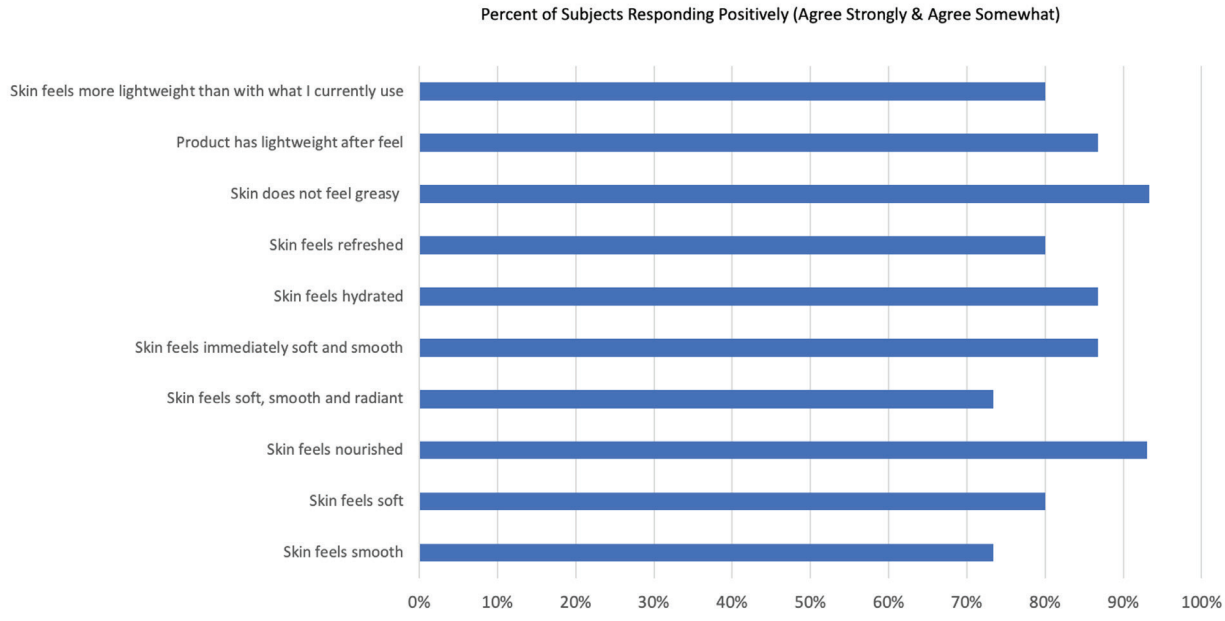


FIGURE 5. Microscopic image and volumetric distribution of tretinoin 0.05% lotion microparticles.

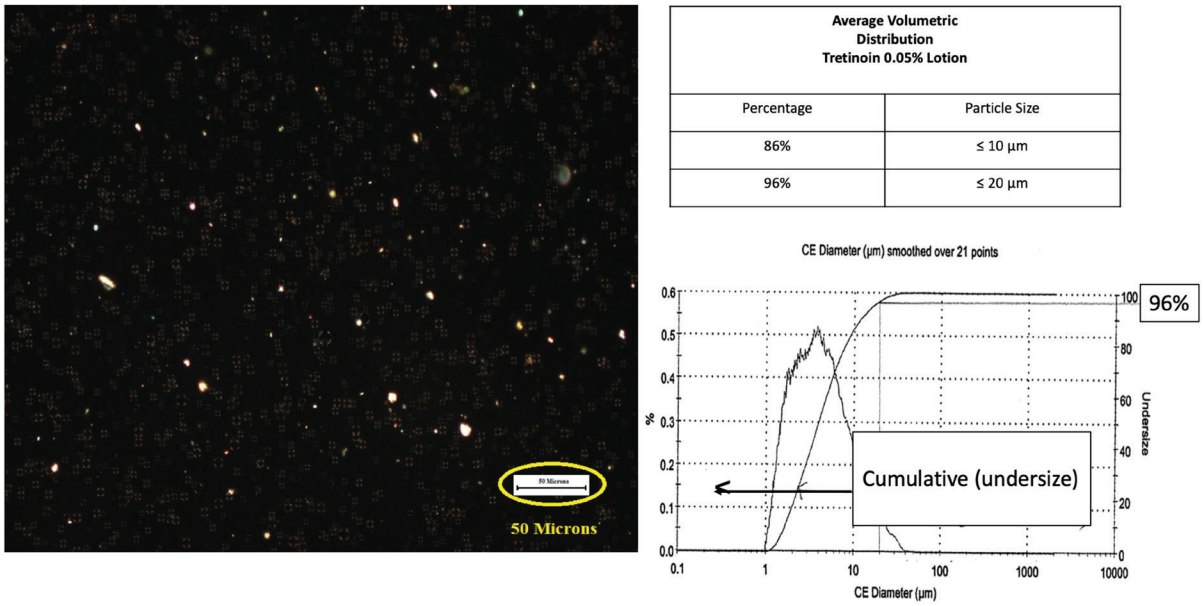
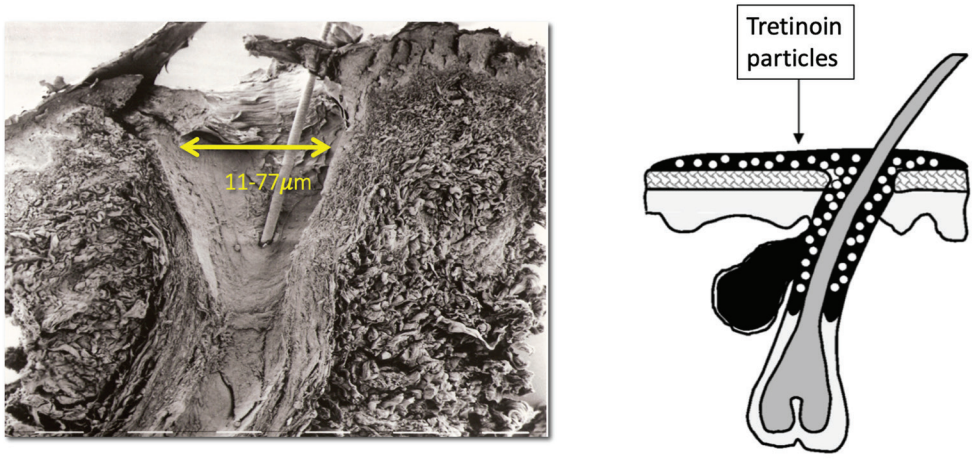


FIGURE 6. Follicular penetration an important aspect of acne treatment: schematic representation of tretinoin 0.05% lotion entering follicles.



differences between the two sites were significant at all post-application assessments (P<0.001). At baseline, mean TEWL scores were 12.32 ± 0.43 and 12.42 ± 0.44 g/hm^2, respectively (Figure 3). There was an immediate improvement in TEWL with test material that continued throughout the study. At 8 hours, the mean score had reduced to 5.98 ± 1.01, a 51.5% change over baseline. There was no improvement at the control site and differences between the two sites were significant at all post-application assessments (P<0.001). Customer perception of the novel lotion formulation was very positive with the majority of subjects responded favorably to all questions relating to the various attributes of the test material (see Figures 4A and 4B).

The main benefits of the polymeric matrix reside in its ability to deliver micronized tretinoin in a more homogenous and highly dispersed form onto the skin to potentially avoid 'hot spots' and help deposition into skin crevasses. The polymeric network will remain at the surface of the skin and only change as a result of variations in pH, temperature, or by the act of rubbing on the skin.

Follicular penetration is also an important aspect. Hair follicles contribute significantly to the penetration of topically applied substances and can serve as an effective reservoir for dermal drug delivery upon the topical application of particulate substances that extends up to 200nm into the underlying tissue. In the past, follicular penetration was ignored because it was assumed that hair follicles covered <0.1% of the total skin area and were therefore not relevant. However, for the scalp and face, the combined areas of follicular openings can be more

FIGURE 7. Percent change in inflammatory lesions from baseline to week 12. Tretinoin 0.05% lotion compared with vehicle (ITT Population pooled data, LS mean).

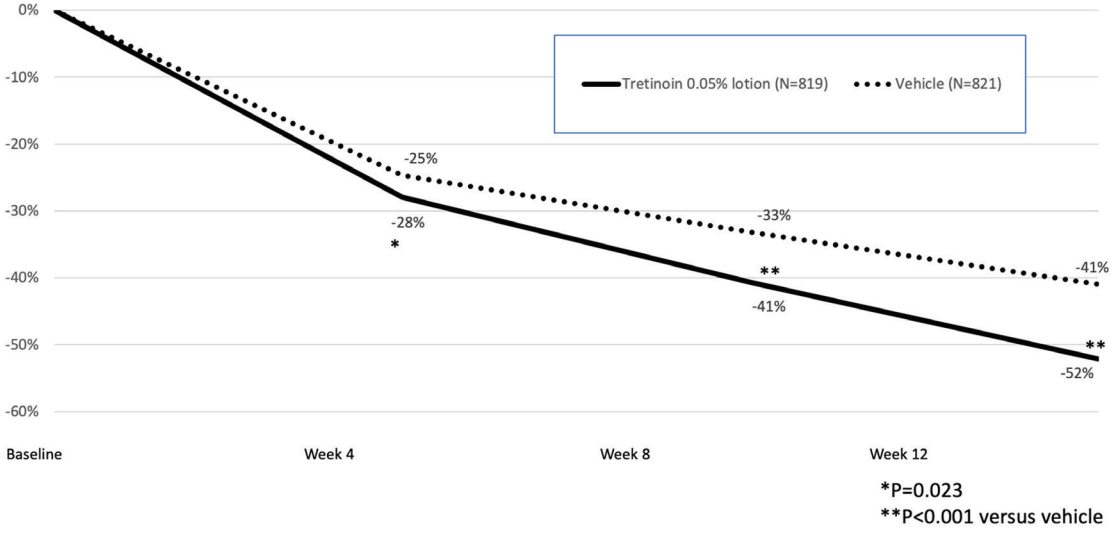
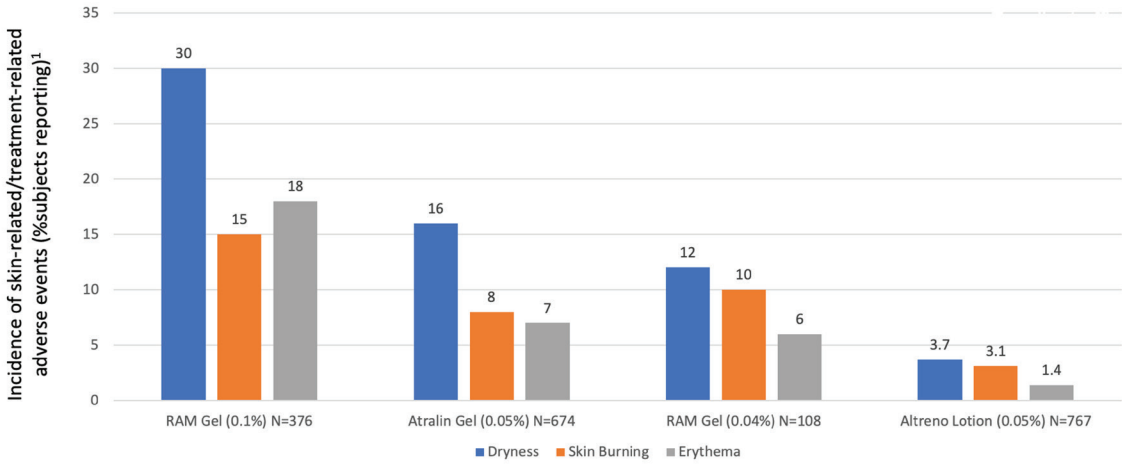


FIGURE 8. Tolerability compared across tretinoin formulations (note different data sources).



RAM 0.1%/Atralin data from Webster G, et al Cutis 2009;83(3):146-154
RAM 0.04% data on file Ortho Dermatologics (CSR NDA-20-475)
Altreno data from Tyring, et al J Drugs Dermatol 2018;17(10);602-609

[1]Reports of application site pain with Altreno (3.1%) included stinging, burning or pain

than 10% of the total skin area.[21] A study of seven different body sites found the average density was highest on the forehead (292 follicles/cm^2), some 10-20 times greater than on the back, thorax, upper arm, forearm, thigh, and calf.[11] Encapsulating compounds within oil-nanoemulsion droplets provides increased transportation via this follicular route.[21] Eighty-six percent of the micronized tretinoin are typically <10µm, an ideal size to penetrate through the follicle openings (Figures 5 and 6).

Clinical Benefits of Micronized Tretinoin Lotion in a Polymeric-Matrix

Efficacy

Retinoids are the foundation of acne treatment because they have been shown to reduce visible lesions and also inhibit the development of microcomedones and new lesions. However, evidence suggests they are under-used in acne. Many physicians believe their utility is primarily restricted to treating comedonal acne; and concerns exist about cutaneous irritation, including peeling, erythema, and dryness that have limited use.[17] A key aspect of acne management has been the ongoing evolution of optimal topical formulations using innovation delivery solutions that help minimize irritation, without compromising efficacy.

Recently, phase 3 data with tretinoin 0.05% lotion encapsulated within a polymeric matrix were published.[22] Tretinoin 0.05% lotion resulted in statistically significant reductions in both inflammatory and noninflammatory lesion reductions compared

to vehicle as early as week 8 and week 4, respectively. Mean percentage change (LS mean) from baseline to week 12 in inflammatory lesion counts was 52.1% versus 41.0% with vehicle (P<.001, Figure 7), and in noninflammatory lesion counts 46.1% versus 29.9% with vehicle (P<.001).

Although there are currently no direct comparative studies with other tretinoin formulations, a phase 3 study with micronized tretinoin 0.05% aqueous gel reported a reduction in inflammatory lesions of 36% by week 12 (P<0.001 versus vehicle).[23] A comparative study of this micronized tretinoin 0.05% gel and tretinoin 0.1% microsphere gel failed to show non-inferiority, although numerically the reduction in inflammatory lesions was greater with the higher concentration formulation of tretinoin.[24]

Safety

The potential to cause irritation has been a major concern with tretinoin, and other retinoids; it appears to be dose-dependent. Micronized tretinoin 0.05% lotion in a novel polymeric matrix was very well tolerated, with a low incidence of dryness, pain (including stinging, burning, or pain), and erythema of 4%, 3%, and 1%, respectively (Figure 8). The same concentration of tretinoin (0.5%) formulated in an aqueous gel, of a similar concentration (0.04%) formulated in a microsphere reported higher incidences of skin irritation (16%, 8% and 7%, and 12%, 10%, and 6%, respectively) in two separate studies.[23] A higher concentration of tretinoin (0.1%) formulated in a microsphere reported dry skin, skin burning, and erythema in 30%, 15%, and 18% of patients.

CONCLUDING REMARKS

The use of retinoids in the treatment of acne is well-established. However, efficacy in inflammatory lesions and local irritation have limited use. A number of formulation advances have been deployed to address these limitations. The most recent is the introduction of a novel polymeric matrix containing micronized tretinoin (tretinoin 0.05% lotion) and a number of formulation advances, including emulsifying agents and mineral oil. Efficacy against inflammatory lesions appears much greater than that reported previously, and tolerability better.

DISCLOSURES

Dr. Kircik has received compensation from JDD for his editorial support and has served either as an investigator, speaker, consultant, or advisory board member for Ortho Dermatologics. Dr. Draelos is a researcher for Ortho Dermatologics. Dr. Berson is consultant/adviser for Allergan, Galderma, Ortho Dermatologics, Almirall, Ferndale, Johnson & Johnson, L'Oreal, Aclaris, P&G, Dermira, Sienna, Revance, and Sonoma.

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