Original Contribution

Novel interpenetrating polymer network provides significant and long-lasting improvements in hydration to the skin from different body areas

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Abstract
Background: Hydration and moisturization both impact skin quality, directly reflecting its appearance. Signs and onset of dehydration-related skin aging are region-specific and require tailored treatment to be effective.

Aims: To test the hydrating effects of formulas containing a novel 3-dimensional 3-polymer interpenetrating network (3D3P-IPN) to deliver humectants and actives to specific body sites.

Methods: Two clinical studies were conducted focused on the skin under eyes and body (arms/legs). Healthy women ages 25-65 (eyes) or 35-65 (body) with mild to moderate dry and aged skin were enrolled. Study product containing the 3D3P-IPN and tailored actives was applied twice daily for 8 weeks on the periorbital area and for 4 weeks on the body. Changes in skin attributes were measured by biophysical instrumentation for hydration, dark circles, skin color, elasticity and transepidermal water loss, and by clinical grading and subject self-assessment.

Results: Significant improvements in hydration and skin smoothing were demonstrated in both studies. In the periorbital region, actives and humectants delivered by the 3D3P-IPN also led to significant improvements in dark circles, fine lines/crow’s feet, puffiness, restoring radiance, and overall younger-looking appearance. On the arms and legs, there were significant reductions in crepiness and dullness. The arms and legs also had improvements in tactile and visual skin texture, radiance, and general healthy look. Improvements were immediate and persisted through the end of both studies.

Conclusion: The 3D3P-IPN provides immediate and long-lasting improvements in skin hydration and overall healthy appearance regardless of the targeted application site.

Keywords
interpenetrating polymer network, skin hydration, TIVI, under-eye circles

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1 | INTRODUCTION

Skin hydration is affected by both intrinsic and extrinsic factors. Genetic predisposition, active medical conditions (eg, atopic dermatitis, psoriasis, endocrine disorders), and psychological stress can alter water and sebaceous gland secretions, resulting in rough, itchy, and dry skin.\(^1\)\(^2\) Noxious extrinsic factors such as ultraviolet radiation, pollution, and harsh weather may further alter cornode-mosomes function, slowing epidermal turnover and leading to thick-ening, sensitivity and inflammation of the skin.\(^1\)\(^4\)\(^6\) Dry, irritated, and inflamed skin is prone to premature aging, arising from a combina-
tion of physiologic processes (eg, vasodilation, increased transepi-
dermal water loss [TEWL], and slower lipid formation) that together manifest as a deepening of fine lines, dullness, crepiness, and loss of elasticity.\(^1\)\(^5\)\(^7\)\(^8\)

In skincare, different approaches have been taken to improve the penetration of hydrophilic compounds that combat skin dry-
ness. One of them, a novel 3-dimensional 3-polymer (3D3P) inter-
novating polymer network (IPN) 3D3P-IPN has been shown to improve hydration with concomitant enhanced delivery of actives to deeper layers of the skin.\(^9\) The 3D3P-IPN was created by interlacing calcium PCA-activated gellan gels with branched and hydropho-
bically modified cellulose, linear sodium hyaluronate, and glycerin (Figure 1). This unique technology, in addition to acting as a super humectant, allows for the incorporation of actives exclusively tai-
lored to target the needs of skin in specific areas.\(^9\)

Signs and onset of dehydration-related skin aging are specific to different parts of the body.\(^9\) Skin in the periorbital area, which is thinner and has stagnant circulation and less subcutaneous fat, is the first to show signs of aging in the form of fine lines, dullness, and dark circles.\(^7\) These areas are targeted for the treatment by the addition of caffeine and micro-algae extracted from Chlorella vulgaris in addition to the humectants carried by the polymer network.\(^7\)\(^10\)\(^12\) Micro-algae extract, along with the polyphenols and flavonoids from Passiflora tarminiana fruit, provides additional anti-aging benefits by boosting collagen and elastin, producing firm periorbital skin with less visible dark circles and improved barrier function.\(^11\)\(^13\) Other actives targeting the periorbital area (eg, ceramides, anti-oxidative vitamins C and E, and the energy-booster adenosine) regulate kerati

In contrast, the skin on the arms and legs, which is thicker, con-
tains fewer sebaceous glands and has slower epidermal turnover than the face and is therefore prone to dryness, scaling, and crepi-
ness.\(^17\)\(^18\) Consequently, skin on the limbs benefits from ceramides, oil-rich occlusion, and small peptides that restore barrier function and boost collagen production.\(^16\)\(^19\) For perceived clinical and visual improvement, the bio-functional ingredients must be delivered to the deeper epidermal layers and form an evenly distributed layer for better light reflection.\(^16\)

Toward this end, we tested the clinical changes in hydration pro-
vided by two 3D3P-based products, each fortified with tailored ac-
tives that targeted either the delicate skin under the eyes or the dry, crepy skin on the body.

2 | METHODS

All subjects in both studies gave their written informed consent be-
fore enrollment, and both studies were adherent to Good Clinical Practice and the International Conference on Harmonization standards.

2.1 | Eye study

Efficacy of the eye product was tested on periorbital skin based on twice-daily application for 8 weeks in younger (25-39) and older (40-65) female subjects with the following signs of aging: xero-
sis-related fines lines and wrinkles, under-eye dark circles, and hollowness. Biophysical measurements were obtained using the cor-
neometer (CM 825, Courage + Kazaka Electronic GmbH), PRIMOS\(^\circ\)\(^3\)D Lite (Primos), Spectrophotometer (Konica Minolta CM700d), and TIVI-700 (Tissue Viability Imaging from Wheels Bridge AB) to as-

dess hydration, fine lines/wrinkles, pigmentation/redness, and dark circles, respectively. PRIMOS\(^\circ\)\(^3\)D Lite is a unique technique that measures (in \(\mu\text{m}\)) fine line/wrinkle depth by analyzing the micro-
topography of the skin while probing three parameters \(R_a\) (rough-
ness), \(R_z\) (average relief), and \(R_t\) (maximum relief amplitude), where a decrease indicates smoother and less wrinkled skin.\(^1\)\(^20\) TIVI-700 evaluates dark circles by measuring in real time the sub-epider-
mal concentration of red blood cells in the microcirculation, using a special algorithm to distinguish differences in the absorption of

FIGURE 1 Modified from published in Skin Res Technol.\(^23\)
Theoretical image of the 3D3P-IPN. The blue network fibers represent gellan gum fortified with purple calcium cross-linked bridges. The red and darker blue represent hyaluronic acid and hydrophobically modified cellulose polymers interlaced and entrapped inside the gellan structures. The orange represents the hydrophobic modifications of cellulose, and the smaller yellow are ceramides.
red, green, and blue light.\cite{21} Nine attributes were assessed by clinical grading: lines/wrinkles and dark circles under the eye (6-point), crow’s feet and under-eye puffiness (8-point), and radiance/vibrancy, softness, smoothness, dryness, and younger-looking skin around the eye area (10-point) scales. Improvement on the attributes is indicated by an increased score for radiance, softness, smoothness, and younger-looking skin and a decreased score for dryness, crow’s feet wrinkles, and under-eye bags/puffiness and wrinkles.\cite{22} Standardized pictures were obtained with the Visia® CR (Canfield Scientific, Inc) using three lighting modes for visual documentation, and by subject self-assessed questionnaire to evaluate consumer satisfaction on skin condition and study product. Measurements at each time point (15 minutes postbaseline, week 4, and week 8) were compared with baseline.

2.2 | Body study

The single-center clinical study was designed to assess skin hydration on the outer upper arm and outer calf over 4 weeks, based on twice-daily application of study product, and compared measurements at each time point (30 minutes postbaseline, week 1, and week 4) to baseline. Eligible female participants, aged 35-65, had all skin types with moderate dryness, tactile roughness, and dullness on the calves, and moderate crepiness and uneven skin tone on the upper arms. Study product efficacy was assessed by live clinical grading for tactile and visual skin texture, softness, dullness, and crepiness (8-point scale). At the conclusion of the study, the expert grader also compared (on a −4- to +4-point scale) photos of the upper arm at each time point with those at baseline for changes in crepiness, overall healthy skin appearance, skin radiance/luminosity/glow, and skin tone evenness (blotchiness/redness). Bioinstrument measurements of the leg included assessment of hydration by capacitance with the corneometer, and assessment of barrier function (TEWL) with the evaporimeter RG-1 (CyberDERM) using TEWL probes (Cortex Technology). Subjects completed a self-assessment questionnaire at each time point and a daily diary to monitor their study compliance, use of test materials, and adverse events (AEs).

2.3 | Safety

Adverse events (AEs) and local intolerances (LIs) were monitored by physical examination, direct questioning of the subject, and review of completed diary entries, and their relation to study product was determined.

2.4 | Statistical analysis

For continuous variables, descriptive statistics including number of subjects (N), mean, and standard deviation (SD) values were calculated; for categorical variables, the frequency and percentage of each category were calculated. For the eye study, a mixed analysis of variance (ANOVA) model fitted to the raw data was used to calculate repeat measurements. The Wilcoxon rank-sum test was used for clinical grading (and rating of skin attributes) to compare ratings at each time point with baseline. For the body study, comparisons within treatment groups were presented with respect to changes from baseline. For all analyses, \( P \leq .05 \) was taken as the level of significance. Statistical calculations utilized SAS 9.4 and EXCEL software.

3 | RESULTS

Overall, the results indicate the beneficial effects of the 3D3P interpenetrating molecular matrix on hydration and skin surface smoothing based on both instrumental, clinical, and self-perceived assessments.

3.1 | Eye study

Forty-four subjects completed the study, 21 in the young (mean 34 ± 1 years) and 23 in the older (mean 55 ± 2 years) subgroups. The Fitzpatrick skin type ranged from II to IV, on average, and most subjects had dry or combination skin.

A significant (\( P < .001 \)) improvement of 23% in hydration over baseline was measured by corneometer, as observed immediately (15 minutes postbaseline) after product application and maintained through week 8 (21% improvement) for the vast majority (85%) of subjects in both subgroups (Figure 2A).

Improvements in cutaneous smoothing (\( R_9 \) parameter) and anti-wrinkle effects (\( R_p \) parameter) were observed at week 4 compared with baseline in the older subgroup, as measured by the PRIMOS® 3D Lite (Figure 2B,B').

Periorbital hyperchromia was significantly diminished from baseline in both subgroups, as assessed by Spectrophotometer and TIVI-700®. A significant (\( P < .001 \)) improvement in the \( L^* \) (lightness, increase of 8%) and \( a^* \) (redness, decrease of 23%) values and worsening of the \( b^* \) (yellowness, decrease of 30%) value in 90% of subjects from both subgroups was observed (Figure 2C,C',C''). However, only the younger subgroup experienced significant (\( P < .02 \)) diminishing of dark circles, as demonstrated by the 4% decrease in red blood cell concentration in the vessels of 60% of subjects at week 8 measured by TIVI-700® (Figure 2D).

All nine skin attributes assessed by clinical grading significantly improved in all populations at the end of the study compared with baseline. The three attributes representing skin relief/topography each improved significantly (\( P < .001 \)) at all time points compared with baseline, changing progressively throughout the study such that at week 8; crow’s feet/fine lines had decreased by 25%, wrinkles by 15%, and smoothness increased by 31%. Similarly, the three attributes for tired signs and skin quality around the eyes all improved significantly (\( P < .001 \)) by week 8 in the total population, with
**FIGURE 2** The multi-attribute benefits in the under-eye skin quality coming from 3D3P matrix and targeted actives as evaluated with biophysical instrumentation: Hydration with corneometer (A); Smoothness ($R_a$ parameter, B) and Fine lines ($R_z$ parameter, $B'$) with PRIMOS Lite; Luminance ($L^*$ parameter, C), Redness ($a^*$ parameter, $C'$), and Yellowness ($b^*$ parameter, $C''$) with Spectrophotometer; Dark circles with TIVI-700 (D). Improvement is indicated by an increase in values for Hydration (A) and Luminance (C); a decrease in values for Smoothness (B), Fine lines ($B'$), Redness ($C'$), Dark circles (D), and worsening of Yellowness ($C''$). Data presented as Mean ± SEM, % rate improvement from the Baseline (D0, before product application or D0 + 15 min, 15 min after first product application), statistical analysis with t test where $P \leq .05$ was considered significant. AU, arbitrary unit.

**FIGURE 3** Perceived improvement (percentage variations, ∆%) of selected under-eye skin attributes evaluated by clinical grading (A) and improvement in under-eye skin quality (lightening, diminishing of dark circles and fine lines) by representative standardized pictures over time from cross-polarized lightening mood taken with Visia® CR (B). A significant ($P \leq .01$) improvement was observed for all attributes tested for immediate (D0 + 15 min) and over time (D28, D56) endpoints, except for puffiness at D0 + 15 (not significant).
dark circles and puffiness decreasing by 27% and 18%, respectively, and younger-looking skin increasing by 24%. Skin quality improved immediately and progressed through week 8 at which time the mean respective increases in radiance and softness were 44% and 30%, and mean decrease in dryness was 39% (Figure 3A).

Attributes of the skin around the eye were self-assessed as showing the greatest improvement at weeks 4 and 8 in softness (87%, 96%, respectively), dryness (86%, 95%), hydration (86%, 93%), overall appearance (84%, 89%), brightness (71%, 79%), lines/wrinkles (75%, 77%), firmness (75%, 77%), and dark circles (72%, 69%). Dramatic improvements in hydration, softness, and dryness were first noted at 15 minutes after baseline and continued throughout the study. The responses in the younger subgroup were more profound than in the older subgroup and reached 100% improvement in softness, dryness, and hydration at week 8, compared with 82% for softness and dryness at week 8 in the older subgroup and 78% for hydration. The representative visual incremental improvements of the skin quality over 8 weeks of product application are depicted in Figure 3B.

### 3.2 Body study

A total of 36 female subjects, with average age of 56.5 years, completed the study; subjects were from all ethnicities and had dry (52.8%), normal (16.7%), or combination (30.6%) skin types. Two subjects were excluded from statistical analysis due to noncompliance.

Overall, the results indicated a significant increase in hydration as measured by both conductance and capacitance, indicating congruence between these two methodologies. Corneometer measurements of the calf revealed significant ($P < .01$) improvements (increase in value) beginning at 30 minutes postbaseline (38.85 ± 8.68) and continuing through week 4 (39.20 ± 9.94) compared with baseline (22.91 ± 8.00), as shown in Figure 4A. There was also a radical improvement in barrier function (decreased TEWL values) on the calf from week 1 which reached statistical significance at the end of the study (Figure 4B). Firmness and elasticity of the upper arm both improved significantly ($P < .01$) as assessed by the DermaLab® Suction Cup, where values for elasticity decreased from 175.67 ± 61.55 at baseline to 148.82 ± 32.141 at week 4 (Figure 4C).

There was close approximation of clinical grading by live and photographic assessment on both the arms and legs. Live grading of the skin on the arms revealed significant ($P < .001$) and clinically relevant (Δ ≥ 2 grades for all attributes) immediate improvements compared with baseline in tactile skin texture (61.8%), softness (70.5%), and crepiness (55.9%), which continued through week 4. Similarly,
perceptible improvements in tactile (94.0%) and visual (100%) texture, and skin dullness (100%) were detected on the legs in most subjects. Photo grading revealed significant (P < .001) perceptible improvements at week 4 compared with baseline in crepiness, overall healthy appearance, and skin radiance in 94%, 79%, and 64% of subjects, respectively.

Subject self-assessment in the nine skin attributes of firmness, radiance/glow, softness/suppleness, texture, tone/evenness, crepiness, and overall appearance all showed significant (P < .001) improvement by the end of the study in over 90% of subjects. Moreover, significant percentages of subjects also strongly agreed that their skin felt/looked softer/suppler, healthier, smoother and more comfortable/nourished, hydrated, and radiant (Figure 4D).

Both study products were well tolerated, since no AEs nor LIs were reported. There were a few incidences of mild itching, tightness, and erythema on the arms and legs which self-resolved and their relation to study product was excluded.

4 | DISCUSSION

Together, both studies demonstrate the benefits provided by the 3D3P-IPN to skin in different regions of the body, particularly with respect to hydration and younger-looking skin appearance. In addition to the hydration improvements stemming from hyaluronic acid (HA) and glycerol embedded in the molecular network, the IPN facilitated the delivery of other targeted actives to deeper epidermal layers where they could exert their full effects.9

The 3D3P-IPN is a hydrophobically modified super humectant scaffold that delivers entrapped hydrophilic humectants, such as HA and glycerin, as well as other actives, to provide enhanced moisture deposition to dry skin.9 During the manufacturing process of the 3D3P molecular network, cross-linking occurs between network constituents, connecting them by salt bridges. The IPN has been shown to restore and sustain hydration content by attracting and binding water molecules more efficiently than traditional cosmetic-grade forms of HA. Skin that is deeply hydrated by the IPN facilitates the penetration of other actives deeper into the skin and prevents from evaporation leading to an additional moisturization effect.9,23 It is also believed that the IPN distributes the delivered actives evenly across the skin surface to enhance light reflection and perceived visual appearance of the skin.24

In the eye study, immediate improvements in hydration were sustained for the full 8 weeks as evaluated by clinical grading and self-assessment and confirmed by corneometer. Improved hydration likely also benefitted skin smoothness and elasticity, measured by the PRIMOS® 3D. The improved hydration of the stratum corneum was aided by the combined effect of the humectant properties of the HA and glycerol in the IPN, and the added ceramides that “filled” the spaces in the lipid bilayer.3,25 Together these improved barrier function, allowing the surface of the delicate skin around the eyes to appear smoother and younger.3,16,25 The ability of the glycerol to facilitate desmosome degradation and subsequent desquamation likely also played a role in improving smoothness by revealing younger, more evenly shaped epidermal cells.3,6

The immediate onset of changes in periorbital hydration, softness, and dryness reported by the study subjects was likely more profound in the younger subgroup because of the ability of younger skin to retain water more efficiently than older skin.3,5,8 The observed improvements in cutaneous smoothing (R_j) and anti-wrinkle effects (R_R), but not in the maximum relief amplitude (R_R) parameter measured by the PRIMOS® 3D Lite, are due to differences in the location of these changes within the skin. R_j and R_R reflect variations occurring in the epidermis and epidermal/dermal junction, which can improve immediately after topical hydration.1,20 However, lack of improvement in R_R, which represents wrinkle depth in the dermis, suggests either that topical treatment may be insufficient to penetrate to that depth or that longer treatment is required to achieve measurable improvement.1,20 Periorbital dyschromia diminished significantly by week 8. The increase in the L* (lightness) parameter and decrease in the a* (redness) parameter measured by spectrophotometer in both subgroups were likely due to the anti-inflammatory and vasoconstrictive properties of the actives, particularly the Chlorella vulgaris extract, vitamin C, and caffeine, as well as the polyphenols and flavonoids in the Passiflora tarminiana.1,2,7,10-12 The worsening of the b* (yellowness) parameter may be the result of neo-melanogenesis that occurred during the study, since it was conducted during the summer and no effective photoprotection was provided. Nevertheless, the diminishment of dark circles was supported by clinical grading and subject self-assessment. The fact that benefits to blood circulation in the periorbital vessels were only evident in the younger subgroup may indicate better blood flow and lower vascular permeability in this subpopulation compared with the older subgroup, which likely also prevented edema associated with under-eye puffiness in the younger subgroup.12

Benefits to skin hydration and smoothness were also evident in the body study, where barrier function of the skin on the calf improved radically, as measured by progressively decreasing TEWL values, and clinical grading on the arm and calf both showed immediate and sustained improvements in visible and tactile skin attributes.3,6,25 These were supported by subject self-assessment of perceived improvements in skin softness and suppleness. Perceptible improvements in skin hydration on the arms and legs were immediate and long-lasting (eg, dryness, roughness, and smoothness). Benefits related to moisturization (eg, crepiness, texture, and overall appearance) required a longer period to manifest due to an accrual of a more robust lipid layer in the stratum corneum preventing from water evaporation.23,25

The skin quality around the eyes and on the arms and legs also showed significant improvements in radiance and brightness (eyes), and in radiance/glow, dullness, and overall appearance (arms/legs), as assessed by clinical grading and subject...
self-assessment. This was achieved by the delivery of tailored actives that independently targeted the under-eye area (eg, ceramides, vitamins C and E, and the energy-booster adenosine) and the body (eg, ceramides, small peptides, and essential fatty acids). A common feature of these actives is their ability to regulate keratinocyte turnover, thereby restoring healthy radiance and glow by increasing desquamation. Ceramides are the major lipid component of the stratum corneum, forming an ordered matrix that contains the embedded keratinized corneocytes. The depletion of ceramides with age and skin conditions interferes with the barrier function of the stratum corneum. Their replenishment by moisturizers softens, smooths, and adds pliability to the skin surface, filling the valleys between partially desquamated skin flakes. Skin that is deeply hydrated, such as by the 3D3P-IPN, facilitates the degradation of corneodesmosomes and enhances desquamation, further contributing to radiance and glow. Small peptides can perform several key functions, including stimulating collagen and endogenous hyaluronic acid production, which substantially contribute to skin health and improve its appearance and radiance.

The results demonstrate the effectiveness of the eye and body products tested, most likely by virtue of their delivery of actives by the IPN to deeper layers of the skin. The excellent tolerability and safety record of both products reflect the careful selection of ingredients and their concentrations, which were formulated into mild products that did not cause irritation.

Limitations of both studies presented herein stem from their open-label design, which did not allow comparison with placebo or a control product.

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CONFLICT OF INTEREST

No conflict of interest. All authors are employees of Rodan + Fields, San Francisco, CA. The clinical studies were performed by the independent Clinical Research Organizations and funded by Rodan + Fields.

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