by Charles Fox

From Tranexamic Acid on Freckles to Nonanimal Fillers: Patent, Literature Findings

Skin and Skin Care

Tranexamic acid (TA) on pigmentation: Kondou et al. have published results from a clinical study examining the effects of a tranexamic acid (TA) emulsion applied topically to melasma and freckles.[1] The study involved 33 subjects, 25 with melasma and 8 with freckles, who applied the TA emulsion for five to eighteen weeks, after which their skin pigmentation was visually assessed by a dermatologist.

Researchers found that the TA emulsion had improved the pigmentation in 20 subjects with melasma (80%) and 6 subjects (75%) with freckles. No side effect was recognized and thus the TA emulsion was deemed safe. In regard to changes over the course of the study, marked improvement was observed within eight weeks for melasma but within 12 weeks for freckles; therefore, improvement was considered to require at least two months of topical application. The authors concluded the TA emulsion was an effective cosmeceutical that provided a whitening effect on melasma and freckles through inhibition of melanin synthesis. It also prevented the appearance of new pigment spots and freckles.

Trans-retinol and skin: Pudney et al. have published an in vivo confocal Raman study examining the delivery of trans-retinol into human skin.[2] Delivery to real living systems such as skin can be difficult to execute and is problematic to confirm and measure. So far, methods for studying the delivery of compounds through the skin are mostly ex vivo; thus they inherently influence the skin and may not translate directly to an in vivo situation. Raman spectroscopy is unique in its ability to measure biological processes in vivo.

This study showed that trans-retinol penetration into the skin could successfully be measured in vivo using this technique. The test measured the volar forearm of volunteers treated with 0.3% trans-retinol in both a propylene glycol ethanol vehicle and in caprylic/capric acid triglyceride. The sample solutions were applied and confocal Raman depth profiles of the stratum corneum (SC) and viable epidermis (VE) were then obtained up to 10 hr after treatment.

Raman spectroscopy is unique in its ability to measure biological processes in vivo.

Remarkable differences between the penetrating and nonpenetrating solutions could be clearly observed. Treating skin with trans-retinol in the propylene glycol ethanol vehicle resulted in trans-retinol penetration through the SC and into the VE. Its penetration was also observed to be highly correlated with the depth of penetration of the propylene glycol, which is well-known as an efficient penetration enhancer.

In contrast, treatment with trans-retinol in caprylic/capric acid triglyceride hardly penetrated at all. For the first time, according to the authors, the penetration of trans-retinol has been monitored directly after application of solutions in vivo without skin excision and very effectively by Raman spectroscopy.

Hyaluronic acid fillers: Rohrich et al. review the role of hyaluronic acid fillers in facial cosmetic surgery.[3] Bioengineered hyaluronic acid derivatives are currently available that provide safe and effective soft tissue augmentation in a comprehensive approach to nonsurgical facial rejuvenation. Current hyaluronic acid fillers do not require pre-injection skin testing and produce reproducible, longer-lasting, nonpermanent results compared with other fillers such as collagen.

The authors add that bioengineered hyaluronic acid fillers can be combined with botulinum toxin type A treatments to enhance both effect and longevity by as much as 50% when properly administered.

A review of the authors' extensive experience at the University of Texas Southwestern Medical Center was conducted to formulate the salient requirements for successful utilization of hyaluronic acid fillers. Technical refinements and key components for optimized product administration categorized by anatomical location are described. The efficacy and longevity of results are also discussed.

Key components to optimize the administration of fillers include proper anatomical evaluation, changing or combining various fillers based on particle size, altering the depth of injection, using different injection techniques, and co-administering botulinum toxin type A. Concomitant administration of hyaluronic acid fillers, along with surgical methods of facial rejuvenation, can serve as a powerful tool in maximizing a comprehensive treatment plan.

Lip plumping: Bottiglieri et al. disclose methods and products for the plumping of human lips.[4] The described invention comprises first topically applying a composition that includes

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one or more blood circulation-enhancing substances, followed by a lip gloss that also includes one or more of such substances. An example of such a lip composition is shown in **Formula 1**.

Evening out skin tone: Kosei Co., Ltd., discloses cosmetics for covering uneven skin tone.[5] The disclosed composition contains: 1,1,3,5,5-pentaphenyl-1,3,5-trimethyltrisiloxane; a spherical powder having a refractive index of 1.35–1.5; polyglyceryl triisostearate and/or polyglyceryl diisostearate; and an oily paste component. The invention provides flexibility and attaches well to skin. An example is shown in **Formula 2**.

Kosei Co., Ltd., discloses another cosmetic composition for covering uneven skin color, such as dark circles.[6] The invention contains titanium oxide particles having an average particle diameter of 0.5–2.0 µm and photoluminescent powders having purple interference reflection color. Preferably, the glittering powders have specified reflection rates and light permeability. An example is shown in **Formula 3**.

Skin Pigmentation

Hyperpigmentation and skin lightening: Aoki has published a review on hyperpigmentation mechanisms and skin whitening agents.[7] Hyperpigmentation, the author reports, is caused mainly by accumulation of melanin in the skin. Solar or senile lentigo appears as dark brown spots that occur on sun-exposed areas and is considered to be a common hyperpigmented lesion of aged skin. The histopathology features of solar lentigo have been reported, including a hyperpigmented basal layer, elongation of the rete ridges and large melanosomal complexes.

To further clarify the mechanisms underlying solar lentigo, the author examined gene expression in solar lentigines using DNA microarray analysis. In comparison with sun-protected skin, many inflammation-related genes were up-regulated in solar lentigo, whereas in comparison with sun-exposed control skin, up-regulation of genes related to fatty acid metabolism was apparent in solar lentigo. Moreover, the author found down-regulation of cornified envelope-related genes, which suggests suppression of cornification in the epidermis in solar lentigo.

Immunohistochemical expression of filaggrin and involucrin was decreased in the lesional skin, where the number of cell layers of the SC was significantly higher than in normal skin. The results of the microarray analysis of solar lentigo, demonstrating up-regulation of genes related to inflammation, fatty acid metabolism and melanocytes, and down-regulation of cornified envelope-related genes, suggest that solar lentigo is induced by the mutagenic effect of repeated UV light exposures over time, leading to the characteristic enhancement of melanin formation together with decreased proliferation and differentiation of lesional keratinocytes.

Actives for skin whitening: Sato et al. have published on the development of active ingredients for skin whitening.[8] The skin whitening boom in Japan sparked around 1990, according to the authors. Since then, the demand for skin whitening products by Japanese women has been a major trend, thus expanding Japan's skin whitening market.

According to the authors, the Japanese word representing skin *whitening* projects a different sense of beauty than words representing skin *bleaching* or *fair* skin. In recent years, whitened skin has been established as the ideal look for Japanese women.

Skin whitening products are categorized as quasi-drugs in Japan.

Formula 1. Lip-plumping composition[4]

Cyclomethicone	8.80% w/w
Butylene glycol	5.50
Glycerin	5.50
Glyceryl stearate SE	4.50
Stearyl alcohol (and) ceteareth-20	2.20
Sorbitan stearate	1.30
Polysorbate 20	1.10
Palmitoyl oligopeptide	1.00
Xanthan gum	0.40
Tocopheryl acetate	0.05
Allantoin	0.01
Benzyl nicotinate	0.80
Phenoxyethanol	0.75
Methylparaben	0.20
Propylparaben	0.10
Flavor	1.00
Water (*aqua*)	66.79
	100.00

Formula 2. Cream to even out skin tone[5]

Beheneth-30 (Emalex BHA-30, Nihon)	1.00% w/w
PEG-60 hydrogenated castor oil (Nikkol HCO-60, Nikko)	0.50
Hydrogenated soybean phospholipid (Lecinol S-10, Nikko)	0.50
Methylparaben	0.15
1,3-Butylene glycol	12.00
Behenyl alcohol	0.70
Dipentaerythrityl hexahydroxystearate/hexastearate/hexarosinate (Cosmol 168ARNV, Nisshin Oillio)	2.50
Paraffinum liquidum (mineral) oil	2.50
Dimethicone	1.50
Trimethyl pentaphenyl trisiloxane	9.00
Polyglyceryl-2 triisostearate	1.00
Carbomer	0.40
Sodium hydroxide	0.12
1,3-Butylene glycol	1.20
Silica	3.00
Methyl polymethacrylate	3.00
Ethanol	5.00
Water (*aqua*)	qs to 100.00

Products that claim a skin whitening function contain skin whitening actives that must be approved by the Japanese Ministry of Health, Labor and Welfare. Four active ingredients have been developed: arbutin, ascorbic acid 2-glucoside, tranexamic acid and 4-methoxy salicylic acid. In this report, the authors describe a process for the development of a skin whitening active ingredient and a formulation containing the ingredient.

Adenosines for skin depigmentation: L'Oréal discloses cosmetic compositions comprising substituted adenosines for depigmentation of skin.[9] The invention disclosed relates to the procedure of depigmentation and/or bleaching of human skin by applying a cosmetic composition containing an adenosine; e.g., 2',3'-isopropylidene-5'-butanoyladenosine or 2',3'-isopropylidene-5'-ethyladenosine. An example is shown in **Formula 4**.

Makeup

Organic silicone resins for lips: Shiseido Co., Ltd., discloses o/w-type base cosmetics containing organic silicone resins for lips, and a makeup method and cosmetic products using them.[10] The o/w bases are liquids or pastes containing: organic 0.1–8.0 parts silicone resins; 1.0–30.0 parts pigments; 0.1–10.0 parts water-swellable thickeners; and an aqueous media including water ≥ 40.0% w/w.

Lipsticks, lip glosses or lip creams are used after application of the base cosmetic for makeup. These bases are placed in containers with applicators. An example of such a base is shown in **Formula 5**. The product disclosed reportedly exhibited rapid-drying properties and good covering effects without affecting the color or moist feeling of a lipstick applied over it.

Preservatives

Parabens in skin: El Hussein et al. have published an ex vivo study on the assessment of principal parabens used in cosmetics after their passage through human epidermal and dermal layers.[11] Concern is continuously raised about the safety of parabens that are present in most cosmetic preparations. In the described investigation, methyl-, ethyl-, propyl- and butylparaben (MP, EP, PP, BP), in a commercial cosmetic lotion, were deposited on human skin fragments collected after surgical operations. Permeated parabens were determined after their passage through human epidermal and dermal layers, fixed on Franz diffusion cells. A 3% bovine serum albumin was employed as receptor fluid and parabens were assessed by liquid chromatography.

The objective of the research was to determine the permeation of these molecules through human epidermis and dermis, and their possible passage

Formula 3. Cosmetic composition for uneven skin color[6]

Titanium dioxide (with an average diameter 0.7 µm)	1.00% w/w
Titanium dioxide (and) mica (and) silica (Timiron Splendid Violet, EMD Chemicals Inc.)	3.00
Stearic acid	1.20
Cetyl alcohol	0.40
Glyceryl stearate	0.80
PEG-50 hydrogenated castor oil	0.80
Squalane	5.00
Octinoxate	5.00
Cyclopentasiloxane	3.00
Dipropylene glycol	15.00
Triethanolamine	0.70
Methylparaben	0.20
Carbomer	0.15
Water (*aqua*)	qs to 100.00

Formula 4. Adenosine composition for depigmentation of skin[9]

2',3'-isopropylidene-5'-butanoyladenosine	0.005% w/w
Glyceryl stearate	2.000
Polysorbate-60	1.000
Stearic acid	1.400
Triethanolamine	0.700
Carbomer	0.400
Butyrospermum parkii (shea) butter	12.000
Squalane	12.000
Antioxidant	0.050
Fragrance (*parfum*)	qs
Water (*aqua*)	qs to 100.000

Formula 5. Lip base[10]

Bentonite	1.00% w/w
Xanthan gum	0.10
Cellulose gum	0.10
Butylene glycol	5.00
Titanium dioxide	3.50
Iron oxide	1.00
Talc	3.50
Triethanolamine	0.50
Palmitic acid	1.00
Stearic acid	1.00
Glyceryl stearate	1.00
Propylene glycol stearate	1.00
Decamethylcyclopentasiloxane solution of trimethylsiloxy silicate, 50%	5.00
Water (*aqua*)	65.00
Fragrance (*parfum*)	qs to 100.00
Emollient oils	qs to 100.00
Antioxidant	qs to 100.00
Preservatives	qs to 100.00

to body tissues and/or accumulation in skin layers. Two groups of experiments were performed. In the first experimental group (G1), unique doses of the test cosmetic were deposited on skin fragments fixed on Franz cells (n = 6) at time 0 hr, followed by receptor fluid withdrawals at 12, 24 and 36 hr. G1 results demonstrated that paraben penetration was influenced by lipophilicity: the more lipophilic the parabens (BP > PP > EP > MP), the less they crossed the skin layers (BP < PP < EP < MP).

The second experimental group (G2) constituted three equal deposits on each Franz cell (n = 6) at different times—0, 12 and 24 hr, followed with three withdrawals of the receptor fluid at 12, 24 and 36 hr. The G2 results indicated a significant increase of paraben permeation into skin layers. The test situation provoked the accumulation of these molecules, which were considered by some authors as the cause of skin toxicities and carcinogenicity.

Antiperspirants

Fast-drying roll-ons: Henkel KGaA discloses fast-drying cosmetic emulsions for roll-on applications.[12] The invention concerns cosmetic o/w emulsions that contain: 0.5–6.5% w/w oil; a minimum of 60% w/w water; 0.00001–38.0% w/w of a cosmetic substance such as antiperspirant; and at least one polysaccharide. The compositions exhibit good storage stability, are fast-drying and leave no oily after feel. An example of an o/w antiperspirant is shown in **Formula 6**.

Sunscreens

Nonirritant UV protection: Cosmetechno K.K. discloses nonirritating cosmetics comprising octyl p-methoxycinnamate and dimethicone crosspolymer, at the ratio of 6–50:1, that are protective against UV rays.[13] The described sunscreen invention is reported to inhibit eye irritation and dry skin caused by octyl p-methoxycinnamate. The sunscreens may further contain microparticles of titanium dioxide and/or zinc oxide. An example is shown in **Formula 7**.

Transparent w/o sunscreen emulsions: Kosei Co., Ltd., discloses w/o-type sunscreen cosmetic compositions that are excellent in transparency and UV-blocking effects and that remain on the skin with a fresh feeling.[14] The composition is characterized by containing: a volatile organopolysiloxane; metal oxide fine particles; a siloxane compound having an organopolysiloxane group and long-chain alkyl group in the branched polymer; and ethanol. An example is shown in **Formula 8**.

Formula 6. Fast-drying roll-on antiperspirant[12]

Water (*aqua*)	81.00% w/w
Aluminum chlorohydrate	13.00
Steareth-2	2.50
Steareth-21	1.50
Fragrance (*parfum*)	1.10
PPG-15 stearyl ether	0.50
Bisabolol	0.10
Aluminum starch octenyl succinate	0.10
Bis-PEG-18 methyl eher di-methylsilane	0.10
Tocopheryl acetate	0.10
	100.00

Formula 7. Sunscreen that inhibits eye irritation[13]

Ethylhexyl methoxycinnamate	10.00% w/w
Dimethicone crosspolymer/decamethylcyclopentasiloxane (DC 9045, Dow Corning)	3.00
Cyclotetrasiloxane	5.00
Trimethylsiloxysilicate	1.00
Titanium dioxide (microparticle slurry)	1.00
Zinc oxide (microparticle slurry)	32.00
1,3-Butylene glycol	3.00
Ethanol	5.00
Methylparaben	0.10
Water (*aqua*)	22.50
Cyclopentasiloxane	qs to 100.00

Formula 8. W/O sunscreen[14]

ZnO dispersion (*see below*)	50.00% w/w
Octinoxate	10.00
Glyceryl triisooctanoate	5.00
Dimethicone, 10cs	5.00
PEG-9 dimethicone	1.00
1,3-Butylene glycol	7.00
Ethanol	5.00
Sodium chloride	0.50
Preservative	qs
Water (*aqua*)	qs to 100.00
ZnO dispersion	
ZnO	40.00% w/w
Lauryl-PEG-9-polydimethylsiloxyethyldimethicone	10.00
Cyclopentasiloxane	50.00
	100.00

O/W, stable sunscreen with good skin feel: Shiseido Co. Ltd. discloses an o/w emulsion sunscreen preparation.[15] The invention is reported to provide excellent stability and skin feel by meeting the following requirements: a) containing the three following surfactants at 1.0% to 6.0% by mass, based on the whole preparation: polyoxyethylene (20–120) stearate, sorbitan tristearate and glyceryl stearate having an HLB of 5 to 8; b) containing the following oil-soluble UV absorber, solid at room temperature, used in an amount of 0.01% to 5.0% by mass, based on the whole preparation: bis-ethylhexyloxyphenol methoxyphenyltriazine and/or tert-butylmethoxybenzoylmethane; c) containing the following oil-soluble UV absorber, liquid at room temperature, at 1.0% to 14.0% by mass, based on the whole preparation: ethylhexyl methoxycinnamate and/or octocrylene; d) containing the following water-soluble UV absorber at 0.1% to 5.0% by mass, based on the whole preparation: phenylbenzimidazolesulfonic acid; and e) containing a higher alcohol having 14 to 24 carbon atoms. An example is shown in **Formula 9**.

Interesting New Vehicles

Untreated elastomers, pigments in cosmetics: L'Oréal discloses cosmetic emulsions containing uncoated silicone elastomers and nonsilicone treated pigments.[16] The disclosed compositions are in the form of emulsions and contain an uncoated silicone elastomer, a solvent for the elastomer, a nonsilicone treated pigment and an emulsifier, methods of making the compositions and methods to apply the composition to a keratinous substrate or tissue. An example of a cosmetic foundation is shown in **Formula 10**.

Interesting Raw Materials

Nonanimal hyaluronic acid fillers: Carruthers reviews scientific and technical considerations of nonanimal-based hyaluronic acid fillers.[17] Recent advances in the technology and biocompatibility of the hyaluronans in all skin types have made them the temporary facial filling agents of choice for many esthetic physicians and surgeons. Hyaluronan products that have been approved for clinical use by the US Food and Drug Administration (FDA) and Health Canada were reviewed in this paper with respect to their composition, clinical effects and safety profiles, and potential complications.

The author reports the current approved standard for the hyaluronan family of fillers of nonanimal bacterial origin includes brands such as Restylane and Perlane in the United States, and Perlane, Restylane Touch and SubQ in Canada, all of which are products of Q-Med. Also of nonanimal origin, the Juvederm 24HV, 30 and 30HV products, developed by Allergan Inc., were approved by the FDA in June 2006. Another brand of bacteria-derived

hyaluronan filler is Captique by Inamed Corp. and Genzyme Corp., that seems to be similar in effect and longevity to the Hylaform brand group of hyaluronan fillers of animal origin by McGhan Medical Canada Ltd.

Formula 9. O/W sunscreen emulsion[15]

PEG-100 stearate	1.100% w/w
Sorbitan tristearate	1.000
Glyceryl stearate	2.500
Butyl methoxydibenzoylmethane	2.000
Bis-Ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S, Ciba)	0.500
Octocrylene	5.000
Phenylbenzimidazole sulfonic acid	2.000
Stearyl alcohol	0.500
Behenyl alcohol	2.000
Glycerin	7.000
Dipropylene glycol	5.000
Butylene glycol	8.000
Xanthan gum	0.150
Myristyl myristate	2.000
Microcrystalline wax	1.000
Dimethicone	3.000
Squalane	5.000
Triethanolamine	1.200
Titanium dioxide	1.000
Cellulose	0.500
Edetate	0.100
Phenoxyethanol	0.500
Sodium pyrosulfite	0.003
Sodium hexametaphosphate	0.100
Red Iron Oxide	0.0003
Yellow Iron Oxide	0.006
Water (*aqua*)	qs to 100.000

Formula 10. Cosmetic foundation[16]

Cyclopentasiloxane	15.00% w/w
Isotridecyl isonanonate	7.50
Disteardimonium hectorite	1.00
PEG-9 polydimethylsiloxyethyl dimethicone	2.00
Dimethicone crosspolymer (and) cyclopentasiloxane	44.50
Titanium dioxide (and) disodium stearoyl glutamate (and) aluminum hydroxide	8.55
Yellow Iron Oxides (and) disodium stearoyl glutamate (and) aluminum hydroxide	1.00
Red Iron Oxide (and) disodium stearoyl glutamate (and) aluminum hydroxide	0.37
Black Iron Oxides (and) disodium stearoyl glutamate (and) aluminum hydroxide	0.08
Water (*aqua*)	14.00
Sodium citrate	0.20
Phenoxyethanol (and) methylparaben (and) ethylparaben (and) butylparaben (and) propylparaben (and) isobutylparaben (Phenonip, Clariant)	0.80
Glycerin	5.00

The remarkable biocompatibility of the hyaluronan group of agents in individuals of all skin types, allied with the superior aesthetic result and outstanding longevity of response, promises that patients will continue to demand these recent advances in safe filler technology.

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