J. Cosmet. Sci., 55, 399–422 (July/August 2004)

Papers Presented at the Annual Scientific Seminar of the Society of Cosmetic Chemists (Friday's Program)

May 7–8, 2004
Mohegan Sun
Uncasville, Connecticut

FORMULATION BASICS

Ken Klein
Cosmetech Laboratories, Inc., Fairfield, NJ

Emulsions are by far the most complicated and difficult of all of the vehicles we cosmetic chemists prepare. We must be concerned with a myriad of issues:

Application qualities
Cost of goods
Delivery of "actives" when applicable
Preservation
Stability (of the emulsion and of the package with the emulsion)
Efficacy

This short talk will discuss formulation strategies and how to address each of the above issues. We will also cover how to intelligently choose raw materials and manufacturing issues. Lastly, we will review commercial products to ascertain their strategies (sometimes good ones and sometimes not so good ones).

EMULSIFIER SELECTION AND USE

Mark Chandler
Uniqema, New Castle, DE

The essence of making a stable emulsion is creating droplets and stabilizing them. Mechanical energy (mixing), thermal energy (heat), and chemical energy (emulsifiers and stabilizers) are employed in various amounts to accomplish this humble task. The job of the creative cosmetic chemist is to use these tools to create the next great cream or lotion. The good cosmetic chemist has to think not only of stability of the product, but the aesthetics and performance of the product as well. Can the approach to stabilizing the emulsion help with these aspects as well?

The cosmetic chemist generally thinks of emollients and actives/functional materials first when asked to design the next great cream or lotion. It is suggested that this habit be broken. With Marketing calling the shots, the selection of actives or functional materials will never leave its place of prominence, but the prominence of emulsion and emulsifier selection should rise higher than its current status. Armed with information on the particular active or functional material to be used and an idea of the needs and desires of the target market (Marketing WILL tell us that, right?), the cosmetic chemist can select the emulsion 'platform' that is right for the job.

There are four primary stabilization mechanisms to choose from:

1) ionic
2) steric
3) polymeric
4) liquid crystalline

Ionic stabilization is the oldest method used. Soap-based emulsions have been produced for centuries and are still in use today. More modern anionic and cationic emulsifiers are finding their way into formulations. These emulsifiers build an ionic double-layer around emulsion droplets leading to electrical repulsion of the droplets. These emulsifiers tend to be efficient but have limitations in terms of pH, salt tolerance, and irritation potential.

The mechanism that is most flexible and most widely used for making oil-in-water emulsions, steric stabilization, requires the most finesse in order to produce a stable, easily manufactured product. Such timesaving tools as the Hydrophile-Lipophile Balance System (HLB), the Lin method of oil phase water solubilization determination, and Phase Inversion Temperature (PIT) have proven to be very useful in the formulation process, especially if steric stabilization is to be used as the primary stabilization mechanism. In many cases ionic and steric stabilization are used together.

The use of polymeric materials as primary emulsion stabilizers has increased in the past few years. These stabilize by building 'zero shear viscosity' in the aqueous phase of an emulsion and have some interaction at the surface of emulsion droplets. Though

straightforward to formulate, these emulsions can be sensitive to extremes in formulation pH and salt content. The rheology and break characteristics of these emulsions can be far different than other emulsions – for better or worse. More often, water-soluble polymers are used to augment a primarily steric stabilized emulsion.

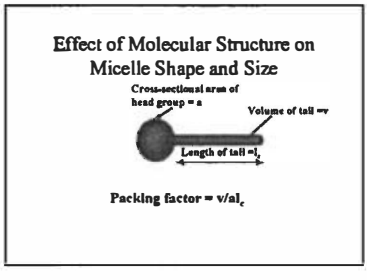
Liquid crystalline phases are two dimensionally organized multilayers of lipophilic emulsifier. Most often used to build viscosity, stability, and pleasing rheology in steric stabilized systems, these phases can be used as the primary emulsion stabilization mechanism with excellent effects. If used as the primary emulsifier, these can stand the help of a small amount of polymer to assist stability. Even with the help, these emulsions are not very tolerant to excesses of salts or low pH.

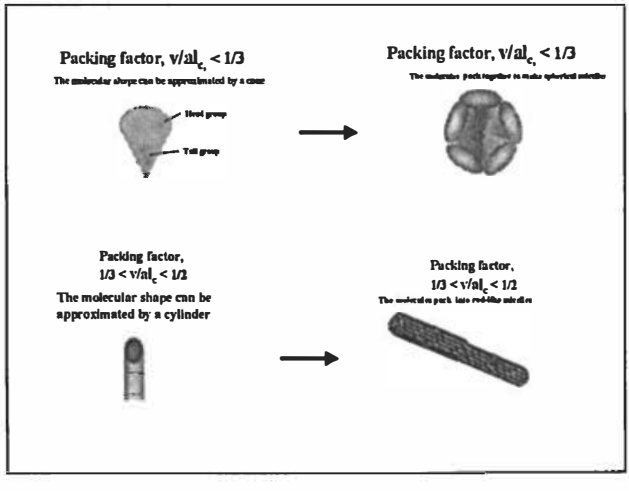
With a better understanding of the emulsion options available including their strengths and limitations, the cosmetic chemist can better serve their target market (and thus rise to fame and fortune.)

LIQUID CRYSTALS: HOW TO USE THEM. WHY THEY ARE OUR FRIENDS.

Robert Lochhead, Ph.D.
The School of Polymers and High Performance Materials
University of Southern Mississippi, Hattiesburg, MS 39406-0076

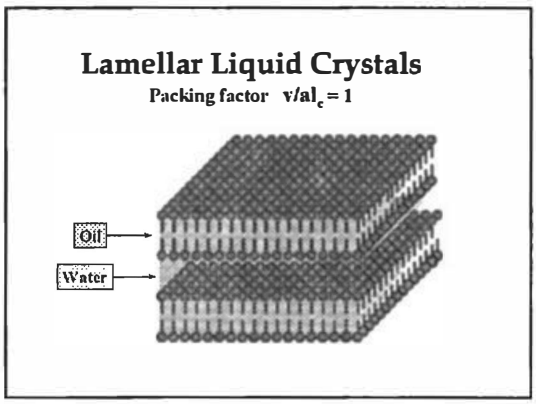
Surfactant aggregation in aqueous solution leads to well-defined nanostructured assemblies that exhibit spherical, rod-like or sheet-like structures[4] and since the discovery of liposomes by Bangham in the 1960's[5], these lyotropic mesomorphic phases have held promise in applications that require precise nanostructured materials. Liquids have no long-range order and perfect solid crystals have three-dimensional order. Liquid crystals are materials that have intermediate order; that is one-dimensional or two-dimensional order. There are two principal classes of liquid crystals: thermotropic and lyotropic. Themotropic liquid crystals are the types commonly found in displays: (watches, calculators) and lyotropic liquid crystals are found in cosmetic, pharmaceutical and household formulations. Lyotropic liquid crystals are formed by self-assembly of amphipathic surfactant molecules. The concept of packing into supramolecular assemblies having precise structure can be understood by consideration of Israelichvili's 'packing factor' definitions.[1] The packing factor is defined as the volume at the hydrophobic tail group divided by the volume of the cylinder subtended from the head group along the entire length of the molecule.

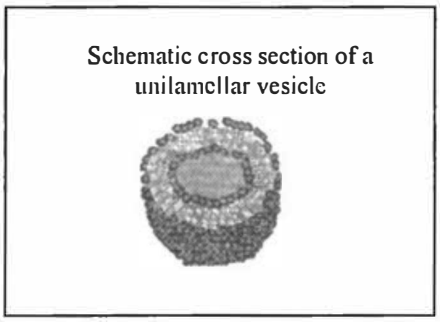




As the packing factor increases the curvature of the self-assembled micelles decrease and this causes a change in micelle shape from spheres to rods to layers to inverse rods and eventually to inverse spheres.

At appropriate concentrations, the cylindrical micelles pack into hexagonal array to produce a liquid crystal phase that is a clear ringing gel. This gel formed the basis of brilliantine hairdressing. Increase in the packing factor to values greater than 0.5 causes the molecules to pack into planar arrays - this is lamellar liquid crystal. Lamellar liquid crystal is a lubricant due to the plane of slippage within the layers. The mutual repulsion between the layers confers a shear-thinning rheology with yield stress (Ellis rheology) on this phase. Lamellar liquid crystal is a useful stabilizing phase for oil-in -water emulsions and it has been used for this purpose to stabilize skin lotions against separation. In the liquid crystalline state, the hydrophobic tail groups of the emulsifier molecules display liquid-like mobility. If the temperature is lowered sufficiently, the hydrophobic chains crystallize and the lamellar phase undergoes a liquid crystal to gel transition. Stearate chains are usually gelled at room temperature. The lamellar gel phase displays more solid-like rheology than the lamellar liquid crystalline phase, but once sufficient shear is applied to overcome the yield stress it flows easily parallel to the slip plane. Lamellar gels are common stabilizing phases in cold creams. Lamellar phase also has the capability of binding water and lowering its evaporation rate and it is not a coincidence that 'lamellar' bodies are found between the corneocytes in the stratum corneum. Substances such as lecithin and distearyldimethylammonium chloride have packing factors that favor lamellar phase. Slight curvature on the lamellae causes the layers to fold into spheres and form unilamellar or multilamellar vesicles. Such vesicles are useful as delivery vehicles. Hair conditioners are often formulated as multilamellar vesicles and this is achieved by self-assembly of twin-tailed surfactants or adjusting the packing factor of single tailed surfactants (e.g. acetyl trimethylammonium chloride) by the addition of cosurfactants such as cetyl alcohol. Reverse hexagonal lyotropic liquid crystal phase contains precisely juxtaposed aqueous cylinders embedded precisely in an organic matrix

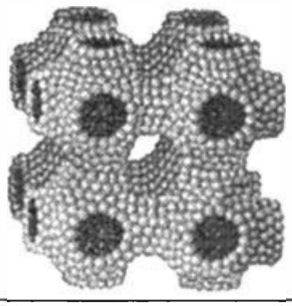




Cubic liquid crystals There are two major classes of cubic liquid crystalline phase. Discontinuous cubic phases are intermediate between spherical micelles and hexagonal phase. Discontinuous cubic phase consists of spherical micelles packed in cubic array and it is exemplified by the Poloxamer gels that are used to thicken hydrogen peroxide. The packed micelle structure confers shear-thinning rheology and a rapid relaxation to the gel structure upon the cessation of shear. The second major class of cubic phase is

bicontinuous cubic liquid crystal. Bicontinuous cubic liquid crystal phase comprises intertwined precisely curved cylinders that pervade the entire material and provide a continuous percolation network. The cubic phase occurs in lipid/water systems as a discontinuous cubic, and a bicontinuous cubic phase. Bicontinuous cubic phase lyotropic liquid crystals are precise periodic, three-dimensional structures in which lipids and water bilayers are twisted into honeycombed nanostructures with continuous domains of water and lipid – like an organic zeolite with uniform aqueous channels having diameters that range from a few nanometers to tens of nanometers. The bicontinuous phase is a thermodynamically stable phase from the condition that the Laplace pressure can be balanced by the positive and negative saddle curvatures of the curved layers of cubic phase. This structure is a member of the family of "infinite periodical minimal surfaces" (IPMS). There are three known types of IPMSs, diamond type (D-surface), primitive type (P-surface) and gyroid type (G-surface) correspond to the cubic phases of CD, CP and CG, and are associated with the space groups P*n3m*, I*m3m* and I*a3d*, respectively. The ability of the monoolein/ water system to form cubic liquid crystalline phase has been well documented and modifications to the phase behavior have been defined.[2] Cubic liquid crystalline phase exhibits advantages over lamellar phase insofar as it shows good temperature stability, high internal surface area, a gel-like viscosity, relative insensitivity to salt and solvent compositions and it can be made from low-cost raw materials that are practical for commercial applications. Cubic Liquid crystal phase has been patented by Unilever, SC Johnson Wax, L'Oreal, Clorox and UCB and has been marketed as glyceryl monooleate and dioleate. Recent L'Oreal patents reveal compositions in which cubosomes are components of skin lotions and are used as emulsifiers to protect the skin against the effects of pollutants. These compositions are being touted as 'surfactant free'. This technology forms part of a trend that was begun in the late 1980's by the introduction of polymeric emulsifiers and is now being pursued via liposomes and Pickering Emulsions stabilized by particles. P&G technology revealed in recent patent applications offers the advantage of easily processed, precise nanostructured cubic phase particles.

Bicontinuous Cubic Phase



References

[1] Israelichvili, J.N.; "*Intermolecular and Surface Forces*", Academic Press, New York. 1992, p 380

[2] Qiu. H., Caffrey, M., "The Phase Behavior of the monoolein/water system", *Biomaterials*, 1999, 21(3), 223-234.

PRINCIPLES OF EMULSION STABILIZATION WITH SPECIAL REFERENCE TO POLYMERIC SURFACTANTS

Tharwat Tadros, Ph.D.
Consultant: 89 Nash Grove Lane, Wokingham, Berkshire, RG40 4HE, UK
tharwat@tadros.fsnet.co.uk

This overview summarises the basic principles of emulsion stabilization, with special reference to polymeric surfactants. The main breakdown processes in emulsions are briefly described : (I) Creaming or sedimentation that is due to the gravity force . (ii) Flocculation that occurs due to van der Waals attraction, when there is not sufficient repulsion between the droplets. (iii) Ostwald ripening that arises from the higher solubility of the smaller droplets when compared to the larger ones. (iv) Coalescence that arises from the thinning and disruption of the liquid film between the droplets. (v) Phase inversion that may occur as a result of the increase in the volume fraction of the disperse phase or due to change in the conditions, e.g. increase of temperature. Many of these breakdown processes, e.g. flocculation, Ostwald ripening and coalescence can be overcome by the use of polymeric surfactants. Particular attention is given to two polymeric surfactants for stabilization of oil-in-water (O/W) and water-in-oil (W/O) emulsions. For O/W emulsions, a hydrophobically modified inulin (HMI) was obtained by grafting several alkyl groups on the backbone of the inulin (polyfructose) chain. This is a graft copolymer AB_n, where A is the stabilizing chain (consisting of strongly hydrated linear polyfructose chain) and B is the "anchor" chain (that is strongly adsorbed at the O/W interface or soluble in the oil droplets). For W/O emulsions an A-B-A block copolymer consisting of oil soluble A chains of polyhydroxystearic acid (PHS) and B chain of poly(ethyleneoxide) (PEO), i.e. PHS-PEO-PHS, is the most suitable. The conformation of both polymeric surfactants at the O/W interface is described. With HMI, the alkyl groups form "multi-point" anchors, leaving "loops" of polyfructose dangling in solution. This configuration produces enhanced steric stabilization. With PHS-PEO-PHS, the PEO forms the "anchor" part (being soluble in the water droplets and the two PHS chains that are soluble in the oil form the stabilizing chains. A section is devoted to the interaction between emulsion droplets containing these adsorbed polymer surfactants. This interaction is referred to as steric stabilization and it is the combination of two main effects : (I) Unfavourable mixing of the A chains when these are in good solvent conditions; this is referred to as the mixing interaction, G_{mix}. (ii) Loss of configurational entropy on significant overlap of the A chains; this is referred to as the entropic or elastic interaction, G_{el}. Combination of G_{mix} and G_{el} with the van der Waals interaction, G_A gives the total energy distance curve for these sterically stabilized emulsions. This energy-distance curve shows only one shallow minimum at a distance of separation comparable to twice the adsorbed layer thickness, after which the total energy increases very sharply with further decrease of the separation distance. The main criteria for effective steric stabilization are summarized : (I) Complete coverage of the droplets by the adsorbed polymer. (ii) Strong "anchor" of the polymer chains to the droplet surfaces to prevent any displacement of the polymer on close approach. (iii) The A chains should

remain in good solvent conditions under all conditions of storage. (iv) Reasonably thick adsorbed layers of the order of 5 – 10 nm..

O/W emulsions based on HMI were prepared and their stability in water and in electrolyte solutions was investigated using optical microscopy. Very stable emulsions were produced both at room temperature and 50°C. The reason for this high stability was attributed to the multipoint anchoring of the polymeric surfactant by several alkyl groups and the strong hydration of the polyfructose loops in water and high electrolyte concentrations and at high temperature. The hydration of the polyfructose chains was confirmed by cloud point measurements in water and high electrolyte concentrations.

W/O emulsions prepared using PHS-PEO-PHS block copolymer could be prepared at high water volume fraction (> 0.6). These emulsions were fluid as confirmed by viscosity measurements. They also remained stable both at room temperature and 50°C.

The last two sections in this overview are concerned with the problems of creaming or sedimentation and phase inversion. Creaming or sedimentation could be prevented by the use of "thickeners" in the continuous phase, e.g. hydroxethylcellulose or xanthan gum. These molecules produce non-Newtonian systems that will have a very high residual or zero shear viscosity. The latter which may exceed 1000 Pas could prevent any creaming or sedimentation of the emulsion. Syneresis of the emulsion could be prevented by control of the bulk (or elastic) modulus of the system. Phase inversion of O/W emulsions could be prevented using HMI, since the polymeric surfactant is insoluble in the oil phase. As long as coalescence and Ostwald ripening are prevented the emulsion could remain stable for very long periods of time at room temperature and 50°C.

DISPERSION OF PARTICULATES

David Schlossman and Yun Shao, Ph.D.
Kobo Products, Inc., South Plainfield, NJ

Introduction

The popularity of personal care formulations containing particulates with consumers depends on sensory characteristics such as their color, gloss, wear, wrinkle hiding power, transparency, softness, spreadability, blendability, and smoothness, in addition to stability in the finished product. Thus, dispersions of particulates are important to cosmetic chemists, because the desirable properties of the particulates are likely to be influenced by the degree of their dispersion in the formulation. Terms such as dispersions, slurries, grinds, pastes, suspensions and gels are all used by cosmetic chemists to describe mixing particles in a liquid medium.

The elements of particulate dispersion technology, wetting, stabilizing, and grinding are frequently cited in patents. Horne, et al. claimed a novel silicone elastomer gel processed from the flow induced shearing through an orifice of a cross linked particulate to create a unique multiple particle size distribution with improved spreadability and substance (1). Gardlik, et al. patented a low residue antiperspirant gel-solid stick comprised of a particulate dispersion of antiperspirant actives held within a non-polymeric crystalline gel-solid matrix (2). Skin care compositions to improve skin appearance containing a charged particulate material dispersed in a thickened hydrophilic carrier were disclosed by Ha, et al. (3) Numerous references can be found describing methods to disperse and emulsify inorganic ultraviolet filters to enhance their SPF and **efficacy** in formulations (4,5,6,7).

Dispersions of particulates have been extensively studied and numerous mathematical models have been proposed to describe their behavior. In practice, however, the formulation and testing of a particulate dispersion is still considered to be much of an art. In this presentation, both science and art will be acknowledged.

Principles of Dispersions

Volumes of articles, chapters and textbooks have been published on the science of dispersions. Dispersion is a stepwise process. The objective is to produce in an application medium a stable and uniform milling of finely-divided particles, i.e. aggregates and primary particles.

- **Mechanical Breakdown**

In order to achieve mechanical breakdown it is necessary to use energy to break down the cohesive forces, the intermolecular forces of attraction that hold the solid particles together. The primary particles always aggregate to form secondary particles due to their high surface energy such as Van der Waal's forces, electrostatic force, hydrogen bonding of surface hydroxyl groups and water bridging between the primary particles (8) The hardness and morphology of the particulate, its percent solids in the carrier and the viscosity of the pre-mix are all likely to influence the mechanical process. High pressure homogenizers, sonolators, and bead mills are all well suited to disperse particulates.

- **Wetting**

The oil absorption value of a particulate will give an indication about its wetting. Theoretically, the wetting of a solid by a liquid is often described in terms of the equilibrium contact angle formed at the solid-liquid-vapor (air) triple interface or the spreading coefficient. Both are functions of the three paired interfaces as shown in Figure 1. The maximum wetting occurs when the contact angle is zero or when the spreading coefficient has a large positive value (9).

Besides surface treatment, dispersing aids are frequently added to increase wetting and stabilization. They also reduce the amount of mixing and milling time, which may prevent the over milling and fracturing of the particles. The finesses of the pigment grind will be determined by the wetting of the particles in the carrier. (9).

- **Stabilization**

Unless the particulates are immobilized by the high viscosity of the slurry, after the mechanical forces that accompany the dispersion process are removed, the forces between the particles will start to come into effect that will lead to sedimentation and flocculation or stabilization. The close approach of particles can be repelled by Coulombic interactions between similarly charged particles in polar media or through steric interactions between long-chain molecules adsorbed on the particulate surfaces. These interactions are shown as Figures 2 and 3, respectively. Steric stabilization can operate in both aqueous and non-aqueous media (9).

The ideal stabilizing molecule must be capable of being absorbed on the particles surface (and swollen around each particle) and being solvated and extended into the carrier. Particles possess potential attractive and repulsive energies whose actions are strongly determined by their distance of separation. As the distance between particles is increased the interaction energy is

diminished. The attractive energy arises from Van der Waal's forces. Thus, the thickness of the adsorbed layer necessary for the effective stabilization of the dispersed particles increases with increasing particle sizes as shown in Figure 4 (8,9). According to theoretical calculations, dispersions of micronized pigments with particle sizes under 0.2 microns should require a thinner layer than dispersions of pigmentary grades or other filler particles greater than 1 micron.

Applications of Dispersion Technology

In practice, most of the inorganic particulates contained in cosmetic formulations have highly polar surfaces that are hydrophilic, and are poorly wetted by organic carriers with low to medium polarity such as cyclopentasiloxanes, hydrocarbons and esters. Organic surface treatments like alkoxy titanates, silanes, methyl polysiloxanes, and alkoxy dimethicones are all known to react with and displace the air and water of hydration absorbed on a pigment surface, rendering it from hydrophilic to hydrophobic or lipophilic. We compared the importance of the surface treatment to the dispersant to pre-wet a 15 nanometer micronized titanium in cyclopentasiloxane in Figure 5. (10) Further, we developed a novel crosspolymer surface treatment to promote the wetting of pigments in multimedia. Figure 6 shows the viscosity of treated iron oxide pre-mixes in mineral oil and cyclopentasiloxane. Figure 7 shows the viscosity of a treated rutile titanium dioxide pre-mix in an ester. (11). Cosmetic dispersions are also made in hydrous (water, polyhydric alcohol) systems. Ammonium and sodium polyacrylates have been found to be important dispersing aids, acting to swell the particles water layer and put a stabilizing charge on their surface. According to our study, reactive polyether silanes may also be employed to enhance wetting in aqueous systems. Viscosity data for iron oxide and titanium dioxide premixes can be found in Figure 8 (11). Lastly, we compared the wetting of branched dimethicone treated rutile titanium dioxide in cyclopentasiloxane to popular hydrophobic treatments in Figure 9 by measuring their pre-mix viscosities. (11).

Table 1 lists the viscosity and particles sizes of four dispersions containing a 14 nm. methicone treated micro titanium dioxide that we compared (12). The wetting was best when polyhydroxystearic acid was used as the dispersant in isododecane. All the dispersions were stable at 50°C for one week. Experiments were made dispersing inorganic ultraviolet filters with primary particle sizes ranging from 10 to 200 nm. in silicone fluids, hydrocarbons and esters with various surface treatments and dispersants. The dispersion particle sizes were recorded and compared to their primary particle size. An index of agglomeration was calculated as the ratio of the dispersion particle size over the primary particle size (12). The data presented in Table 2 is representative of the samples prepared and shows that pigments having a smaller primary particle size contain larger indices of agglomeration. Thus, smaller primary particles are harder to disperse.

We have found that adding bentonite clays, fumed silica, synthetic waxes, and polysaccharides can thicken dispersions to reduce syneresis and improve suspension of pigments and actives.

Evaluation of Pigment Dispersions

Both science and art play a role in dispersion testing. Twenty-five years ago the plant manager could approve a batch of nail laquer by observing the way it ran off his blade. Nowadays, viscosity samples are mixed with a mechanical mixer and incubated before testing on an instrument such as a Brookfield RVT. Draw downs are still compared by operators at various stages during processing on cards or glass plates to study transparency, color, drying time and gloss, however, greater reliance is placed on instruments. An example is the particle size which is often measured by using a light scattering size analyzer. Nevertheless, it is an art to measure the size correctly, as the powder or dispersion sample must be diluted and sonicated to a usually low concentration in an appropriate solvent.

Imaging technologies will play a greater role in evaluating dispersions in the future. Ono, et al measured particle sizes of novel dispersions of cellulose particulates with both a light scattering size analyzer and an electron microscope and calculated a coefficient of aggregation of 1.0 to 3.0 (13). Williams, et al. patented a microelectrical resistance tomography system comprising one or more sensors to characterize flowing dispersions including particle shape and size.

Summary

The conditions to wet pigments were shown to influence their pre-mix viscosity and the dispersion particle size. Silicone/copolymers and polyhydroxystearic acid are effective stabilizers for pigment dispersions. The stability of dispersions could be improved by decreasing their particle size as the theoretical models predict. More work needs to be done to quantify the differences between the dispersions in order to learn more about their behavior and to predict their performance in finished products.

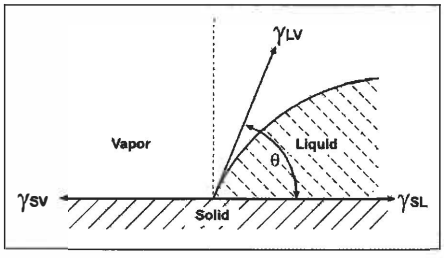


Figure 1. The Equilibrium Contact Angle

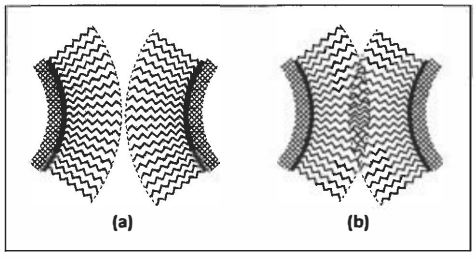


Figure 2. Steric Interactions

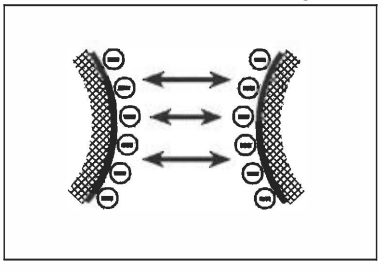


Figure 3. Coulombic Interactions

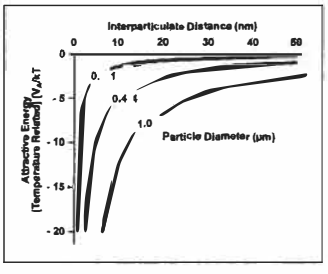


Figure 4. Forces of Attractive Energy

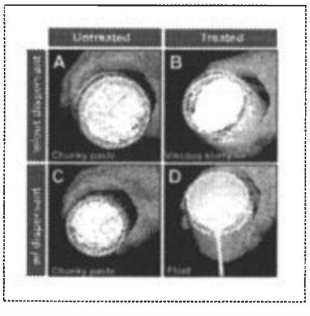


Figure 5. Wetting of 15 nm. TiO_2 Dispersed in Cyclopentasiloxane

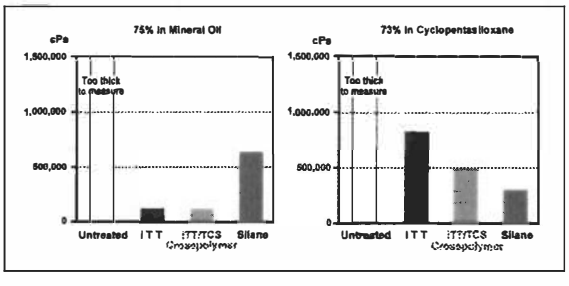


Figure 6. Treated Iron Oxides Pre-mixes with Silicone/Copolymer Dispersant

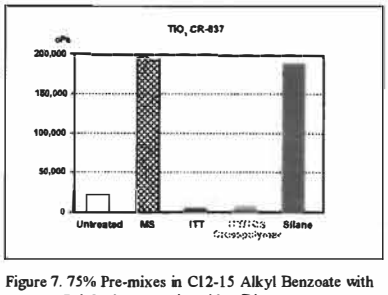


Figure 7. 75% Pre-mixes in C12-15 Alkyl Benzoate with Polyhydroxystearic acid as Dispersant.

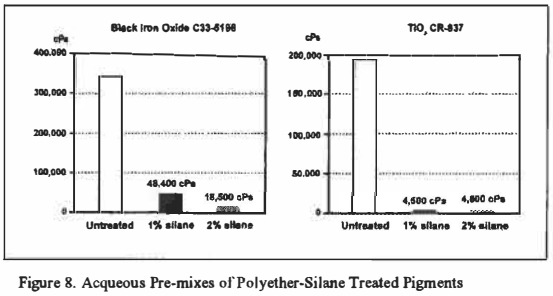


Figure 8. Acqueous Pre-mixes of Polyether-Silane Treated Pigments

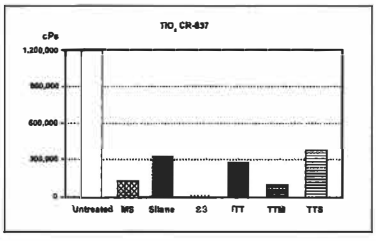


Figure 9. 75% Branched Dimethicone Treated TiO_2 in Cyclopentasiloxane with a Silicone/Copolymer Dispersant

Dispersion Formulation	Percent Solids	P.S. (nm)	Viscosity (cPs)	Index of Agglomeration
Isododecane & Polyhydroxystearic acid	60%	172	180	12.3
Isododecane & Polyhydroxystearic acid	50%	110	20	7.9
C12-15 Alkyl Benzoate & Polyhydroxystearic acid	50%	165	600	11.8
Cyclopentasiloxane & PEG-10 Dimethicone	40%	165	275	11.8

Table 1. Influence of Carrier and Dispersant on Dispersion of 14 nm. Methicone Treated TiO_2

P.P.S. (nm)	Type	P.S. (nm)	Index of Agglomeration
10	TiO_2	110	11
15	TiO_2	143	9.5
20	TiO_2	143	7.2
20-30	ZnO	145	5.8
35	TiO_2	179	5.1
120	ZnO	250	1.3

Table 2. Influence of Particle Size on Agglomeration

References

1. AJ Horne, DS Johnson, JA Kilgour, RD Wang (General Electric Company), US Patent 5,998,542 (1999).
2. JM Gardlik, GJ Guskey, B Curtis (Procter & Gamble), US Patent 6,171,601 (2001).
3. RBK Ha, TJ Fowler (Procter & Gamble), US Patent 5,997,887 (1999).
4. ER Lukenbach, C Cole, P Naik-Satam, R Stutzman (Johnson and Johnson Consumer Products, Inc), US Patent 6,540,986 (2003).
5. MR Nearn, SJ Redshaw, G Burgess, Titanium Dioxide Based Sunscreen Compositions, US Patent 5,498,406, (1996).
6. I Walele, SA Syed,(Finetex, Inc.) US Patent 6,261,713 (2000).
7. C Corcoran, J Zecchino, S Mesin, K Chung (Estee Lauder, Inc.), US Patent 5,468,471, 1994.
8. JM Oyarzún, Pigment Processing, Physico-chemical Principles: 4, 2000. pp 117-166.
9. DH Solomon and DG Hawthorne, Chemistry of Pigments and Fillers: 2, 51-57, 1991
10. D Schlossman and Y Shao (Kobo Products, Inc.), Silicone Dispersants and Physical Sunscreen Dispersions, Recent Developments, SCC Florida Chapter Sun Screen Symposium September 12, 2003.
11. D Schlossman and Y Shao (Kobo Products, Inc.), Super Dispersible Pigments for Color Cosmetics, Color Cosmetics Summit 2003, Montréal, Québec, October 20-22, 2003.
12. D Schlossman and Y Shao (Kobo Products, Inc.), Silicone Dispersants and Physical Sunscreen Dispersions, Recent Developments, The European Sunfilters Conference – Paris October 14-15, 2003.
13. H Ono, T Matsui, I Miyamoto (Asahi Kasei KK), US Patent 6,541,627 (2003)
14. RA Williams, FJ Dickin (Disperse Technologies Limited), US Patent 6,210,972 (2001).

A Family of Emollient Esters Exhibits Anti-Microbial Properties of Practical Use to Formulators Seeking to Reduce or Eliminate the Use of Preservatives

Monna Manning and Philip Orawski
Abitec Corporation, Columbus, OH

Introduction

Kabara and others found that certain fatty acids and esters were useful as antimicrobial agents. [1, 2, 3] Based upon these findings, high purity monoesters of glycerin or propylene glycol were synthesized and assayed for their efficacy against traditional preservatives. Three emollient esters were selected for their anti-microbial properties. This range of high purity short-chain monoglyceride esters have been shown to offer performance comparable to "conventional" anti-microbial agents or preservatives, without the need to register as preservatives.

Experimental

MIC Test and selection of three monoglycerides

Eleven (11) structures were evaluated in a Minimum Inhibitory Concentration test (USP <61> "Microbial Limit Tests"), which tests the efficacy of antimicrobial agents versus concentration. Based upon performance in this test, three structures were chosen to pursue as commercially viable products. In all, eleven (11) organisms were used in MIC testing. The following tables indicate the results for four (4) of the most common organisms: *Candida albicans* (a yeast), *Aspergillus niger* (a mold), *Staphylococcus aureus* (a gram positive bacterium), and *Eschirichia. coli* (a gram negative bacterium). The legend is "+" to indicate growth, and "-" to indicate microbiological kill.

% Dilution	0.010	0.025	0.050	0.075	0.100	0.175	0.250	0.500	0.750	1.000
Candida albicans										
Propylene Glycol Heptanoate	+	+	+	-	-	-	-	-	-	-
Propylene Glycol Heptanoate	+	+	-	-	-	-	-	-	-	-
Glyceryl Caprylate	+	+	+	-	-	-	-	-	-	-
Aspergillus niger										
Propylene Glycol Heptanoate	+	+	-	-	-	-	-	-	-	-
Propylene Glycol Heptanoate	+	-	-	-	-	-	-	-	-	-
Glyceryl Caprylate	+	+	+	+	+	-	-	-	-	-
Staphylococcus aureus										
Propylene Glycol Heptanoate	+	+	+	+	+	-	-	-	-	-
Propylene Glycol Heptanoate	+	+	+	-	-	-	-	-	-	-
Glyceryl Caprylate	+	+	+	-	-	-	-	-	-	-
Escherichia coli										
Propylene Glycol Heptanoate	+	+	+	+	+	-	-	-	-	-
Propylene Glycol Heptanoate	+	+	+	+	+	+	+	+	+	+
Glyceryl Caprylate	+	+	+	+	+	+	+	-	-	-

Challenge Test comparison to DMDM Hydantoin and parabens

In a typical TEA Stearate Lotion formulation, three anti-microbial monoglycerides were evaluated in a challenge test (USP <51> "Antimicrobial Effectiveness Testing") against a blend of 0.2% Methylparaben and 0.1% Propylparaben or against 0.4% DMDM Hydantoin. The individual esters were tested at 0.5%, which is the recommended minimum usage level.

	E. coli	S. aureus	A. niger	C. albicans
Propylene Glycol Heptanoate @ 0.5 % in lotion	√ Outperformed Parabens @ 0.3%	√ Outperformed parabens @ 0.3% or DMDM Hydantoin @ 0.4%	√ Zero Growth. Equal to 0.3% parabens or DMDM Hydantoin @ 0.4%	√ Outperformed 0.4% DMDM Hydantoin
Propylene Glycol Caprylate @ 0.5 % in lotion	√ Outperformed Parabens @ 0.3%	√ Outperformed Parabens @ 0.3%	< Performance marginally inferior	< Performance marginally inferior
Glycerol Caprylate @ 0.5 % in lotion	√ Outperformed 0.3% parabens	√ Outperformed 0.3% parabens or 0.4% DMDM Hydantoin	√ Zero Growth. Equal to 0.3% parabens or 0.4% DMDM Hydantoin	√ Outperformed 0.4% DMDM Hydantoin

Discussion

Additional MIC and Challenge test data will be presented and results and implications discussed.

References

1. US Pat 4,002,775 Fatty acids and Derivatives of Antimicrobial Agents, Jon Kabara, (January 11, 1977)

2. A Branan and P Davison, *Anti-microbials in Foods*, Marcel Dekker, ed., New York, (1986) pp 109-140

3. J Kabara, and M Ohkawa, et al., Examination on Antitumor, Immunological, and Plant-Growth Inhibitory Effects on Monoglycerides of Caprylic Capric and Lauric Acids and Related Compounds; *Pharmacological Effects of Lipids*, Volume II, (1985) pp 263-272

INORGANIC SUNSCREEN DISPERSIONS: EXPERIENCE WITH DEVELOPMENT AND EVALUATION FOR EFFICACY AND AESTHETICS

Art Georgalas[1], Elizabeth Kasprzyk[1], and Andreas Jung[2], Ph.D.
[1]TRI-K Industries, Inc, New Paradigm Technologies, Northvale, NJ
[2]IFAC GmbH, Duisburg, Germany

Formulators must take into consideration multiple factors working with inorganic sunscreens. Because the UV radiation attenuation grade particles of Titanium Dioxide are in the nanometer range, the state of their dispersion in the product film on the skin governs their efficacy and aesthetics.Properties of the particles themselves, including size and coating, the media they are dispersed in and the efficiency and stability of those dispersions impact their performance on the skin. In the final formulation even the same dispersion can give different results depending on the formulation and process. Agglomeration state of particles on the skin film gives variable ratios of UVR and visible light absorption resulting in differences in transparency and sun protection efficacy. Inorganic particles interact with light both optically as inert reflectors and diffractors and as electromagnetic absorbers. They must be effectively dispersed in the finished product and delivered to the skin in a continuous film to work well. An iterative process of experiments using particle size analysis, rheology and suspension properties evaluation to optimize them formulates dispersions. Finally, by looking at *in vitro* instrumental measurements, *in vivo* clinical results for efficacy, product draw down films and skin application a full picture of performance emerges.The chronic effects of long-term UVR exposure display as visible signs of aging and increased incidence of some skin cancers. A reproducible bioassay to give immediate assessment of UVR attenuation can only be made with effects that are acute or instrumental methods that simply measure the light flux effects. Acceptable *in vivo* methods include sun protection factors (SPF) for UVB radiation generated erythema and the measurement of the effects on persistent pigment darkening (PPD) compared to untreated skin for UVA radiation. *In vitro* broad-spectrum capability is demonstrated by identification of the critical wavelength of subject product. This is the wavelength at which the area under the absorbance curve beginning at 290 nm up to that wavelength is 90% of the total solar UV radiation absorbed as measured instrumentally from 290-400 nm, so that, the higher that wavelength the more absorption occurs within the UVA range (320-400 nm). Additionally, instrumental measurement can estimate a UVA protective factor and a ratio of UVA to UVB attenuation. These are measures accepted or being considered by dermatologists, industry formulators and regulatory agencies worldwide. Premade dispersions of the UVR attenuation pigments make formulation easier but also improve efficacy and aesthetics in some formulations, so that these were under evaluation. Preliminary results with some dispersions indicate more UVB versus UVA attenuation with smaller particles and as less and less agglomerates form. This drives the critical wavelength lower but these formulations still show significant UVA effect along with good sunscreen efficacy by SPF measures.

Different grades of titanium dioxide were chosen to represent a full range of varieties available. These included ultra small particle, 10 nm &15 nm, hydrophobically and hydrophilically coated particles, microtitanium dioxide, 35 nm particle size, both uncoated and 20 & 21 nm hydrophilic and hydrophobically coated particles and a larger pigmentary grade of 180 nm plus a new ultra large (1 micron) particle designed to attenuate IR radiation. A variety of Zinc Oxides were also

tested. To test variability in different types of formulas, both two oil-in-water creams and a water-in-oil silicone formulation were evaluated. Tests performed *in vitro* were via the Optometrics 290 SPF Analyzer utilizing IMS Vitro Skin ™ as substrate to better mimic skin application. Clinical studies performed at AMA labs used FDA protocol for SPF and JCIA protocol for PPD assessment of UVA protection. Overall the experiments demonstrated that Titanium Dioxide and Zinc Oxide had advantages when preformulated into dispersions depending also on particular varieties and formulations. When the critical wavelength is compared to the ultimate particle size there appears to be a relationship that graphically suggests that critical wavelength will always be above 370 nm. However, some dispersions in which particles are better dispersed and agglomerates are minimal yield critical wavelengths below 370 nm.

Materials and Methods:
Sunscreen formulations were prepared with the following general compositions that were altered individually to accommodate the different grades of Titanium dioxide used:

10 nm Aluminum Stearate Hydrophobic
15 nm Aluminum Stearate coated Hydrophobic20nm Alumina Glycerin Hydrophilic
21nm Trimethoxycaprylylsilane Hydrophobic
35 nm uncoated Hydrophilic
Pigmentary grade 180 nm Rutile Hydrophilic
One micron (1,000nm) silicone coated Hydrophobic

Formula A. Oil-in-Water Emulsion Formulation nonionic/anionic

- **Water**
- **Magnesium Aluminum Silicate**
- **Glycerin**
- **Xanthan Gum**
- **Butylene Glycol**
- **Phenoxyethanol/Parabens**
- **Glyceryl Stearate and PEG-100 Stearate**
- **Brassica Campestris / Aleurites Fordii Oil Copolymer**
- **Sorbitan Sesquioleate**
- **DEA-Cetyl Phosphate**
- **C12-15 Alkyl Benzoate**
- **Octyl Palmitate**
- **Cetyl Alcohol**
- **Titanium Dioxide (+Coatings) 5.0-10.0%**

Formula B. Oil-in-Water Emulsion Formulation liquid crystal gel network

- **Purified water**
- **Glyceryl stearate, Cetearyl Alcohol, Stearoyl Lactylate**
- **Glycerin**
- **Dimethicone**
- **Caprylyl Methicone**
- **Brassica Campestris / Aleurites Fordi Oil Copolymer**
- **Decyl Shea Butter Esters**
- **Polysorbate 20**
- **Phenoxyethanol/Parabens**
- **Xanthan Gum**
- **Titanium Dioxide (+Coatings) 5.0-10.0%**

Formula C. Water-in-Oil Emulsion Formulation

- **Cyclomethicone and Dimethicone Copolyol**
- **Cyclomethicone**
- **Cyclomethicone and Dimethicone**
- **Methyl Glucose Dioleate**
- **Dimethicone Copolyol**
- **Brassica Campestris / Aleurites Fordii Oil Copolymer**
- **C12-15 Alkyl Benzoate**
- **Lanolin Alcohol**
- **Water**
- **Sodium Chloride**
- **Titanium Dioxide (+Coatings) 5.0-10.0%**

Four distinct dispersions were made and evaluated. See Table 1 below.

DISPERSION (1)	DISPERSION (2)	DISPERSION (3)	DISPERSION (4)
C12-15 Alkyl Benzoate	C12-15 Alkyl Benzoate	PEG-7 Methyl Ether	C12-15 Alkyl Benzoate
Titanium Dioxide (10 nm) (and) aluminum hydroxide (and) stearic acid	Titanium Dioxide (15 nm) (and) aluminum hydroxide (and) stearic acid	Titanium Dioxide (20 nm) (and) glycerin (and) alumina	Titanium Dioxide (21 nm) (and) Trimethoxycaprylylsilane
		Mono-and dibutyl phosphate	Polyglyceryl 3-Diisostearate
Lecithin	Lecithin		Lecithin
Polyglyceryl 3-Diisostearate	Polyglyceryl 3-Diisostearate		Cetyl Dimethicone Copolyol
Cetyl Dimethicone Copolyol	Cetyl Dimethicone Copolyol		

Table 1. Dispersion compositions by INCI name designations.

In vitro sunscreen analysis:

- **Optometrics 290** *In vitro* SPF analyzer (Optometrics, Ayer, MA, USA)
- **Vitro Skin™** - IMS (Innovative Measurement Systems, CT, USA) VITRO-SKIN ™ is an advanced testing substrate that effectively mimics the surface properties of human skin. It contains both optimized protein and lipid components and is designed to have topography, pH, critical surface tension and ionic strength similar to human skin. ***2 μL/ cm2*** product application per FDA OTC Monograph. Each sample result is the average of twelve (12) runs made at preset positions on the X-Y stage of the SPF Analyzer.

In vivo sunscreen analysis:

SPF: FDA Protocol per OTC Final Monograph: 64 Fed. Reg. 27666 May 21,1999:
Twenty (n=20) subjects of skin types I--Always burns easily; never tans (sensitive).
II—Always burns easily; tans minimally (sensitive).
III--Burns moderately; tans gradually (light brown) (normal). **2 μL/ cm2** application

dosage. Calculate SPF value = the ratio of erythema effective exposure for protected skin (Joules per square meter) (MED (PS)) to the erythema effective exposure for unprotected skin (Joules per square meter) (MED (US)) per the Final Monograph. UVA: JCIA protocol PPD (persistent pigment darkening): Ten (n=10) subjects ofskin types II, III, and/or IV. 2③L/ cm2 application dosage. Irradiation with UVA (320-400 nm) by filtered solar simulator radiation with ratio of UVA I (340-400) to UVA II (320-340 nm) close to that of natural sunlight. UVA Protection Factor (PFA) calculated as ratio of the minimal persistent pigment darkening dose (read at 2-4 hours) required to elicit darkening at the product treated site versus the untreated site. Results: Smaller particle size generally yields higher SPF efficacy but with less UVA absorption hence lower critical wavelength at lower particle size. See Table 2 below

Particle size / Properties	10 nm	15 nm	20 nm	21 nm	35 nm	180 nm	1000 nm
Formulation (A)							
SPF / % TiO_2	2.19	2.3	0.91	1.83	1.44	0.76	N/A
Critical Lambda	369.4	374	382.4	375.35	381.6	384.15	N/A
UVA / UVB	0.419	0.509	0.752	0.533	0.726	0.811	N/A
Formulation (B)							
SPF / % TiO_2	1.64	N/A	2.03	1.42	N/A	N/A	N/A
Critical Lambda	370.85	N/A	379.45	374.7	N/A	N/A	N/A
UVA / UVB	0.422	N/A	0.662	0.491	N/A	N/A	N/A
Formulation (C)							
SPF / % TiO_2	2.34	1.89	3.56	1.73	N/A	N/A	0.37
Critical Lambda	367.35	373	380	376.6	N/A	N/A	385.25
UVA / UVB	0.394	0.494	0.701	0.546	N/A	N/A	0.652

Table 2. Particle size of Titanium Dioxides and sunscreen performance properties

In comparing results with powders used as is and dispersed during processing of the emulsion, equivalent dispersions formulated and made prior to batch preparation give higher SPF values and slightly lower critical wavelengths. This would suggest better dispersion in the skin film with higher UVB attenuation and better transparency. Draw down films demonstrate the increased transparency. Some anomalous results suggest that the dispersions are not optimized for that type emulsion and do not promote even distribution in the skin film. Creams made with optimized liquid crystalline lamellar gel networks seem to be shifted out of balance when either the combination of dispersing agents interacts wit the gel network or the surface area of the inorganic sunscreen adsorbs hydrophilic surfactant from the gel network. See Table 3 below.

TiO_2 as powder vs Dispersion	TiO2 (1)	Dispersion (1)	TiO2 (2)	Dispersion (2)	TiO2 (3)	Dispersion (3)	TiO_2 (4)	Dispersion (4)
Formulation (A)								

SPF / % TiO_2	2.19	2.19	2.3	3.36	0.91	2.21	1.83	2.06
Critical Lambda	369.4	370.75	374	370	382.4	381.6	375.35	374.6
UVA / UVB	0.419	0.458	0.509	0.454	0.752	0.751	0.533	0.518
SPF Change		0%		(+) 46%		(+) 142%		(+) 12%
Formulation (B)								
SPF / % TiO_2	1.64	2.19	N/A	N/A	2.03	1.26	1.42	1.7
Critical Lambda	370.85	369.1	N/A	N/A	379.45	381.2	374.7	373.0.5
UVA / UVB	0.422	0.419	N/A	N/A	0.662	0.701	0.491	0.47
SPF Change		(+) 33.5%				(-) 38%		(+) 19.7%
Formulation (C)								
SPF / % TiO_2	2.34	2.89	1.89	2.75	3.56	3.17	1.73	1.05
Critical Lambda	367.35	369.8	373	372	380	379.55	376.8	376.8
UVA / UVB	0.394	0.45	0.494	0.484	0.701	0.703	0.546	0.524
SPF Change		(+) 23.5%		(+) 45.5%		(-) 11%		(-) 39.3%

Table 3. Sunscreen performance properties using powders versus formulated dispersions

Formulation processing also has effects on the final efficacy of product films. In some cases the location of the particles is governed by order of addition so that a hydrophilic dispersion for example (3) easily disperses in a high surfactant O/W but is not homogeneous in an inverse emulsion or a less hydrophilic system as the gel network. Best results in these systems are achieved with direct addition to the oil phase of hydrophobic dispersions. See Table 4 below.

TiO_2 as powder vs Dispersion	TiO2 (1)	Dispersion (1) in oil phase	Dispersion (1) added last	TiO2 (3)	Dispersion (3) in oil phase	Dispersion (3) added last	TiO_2 (4)	Dispersion (4) in oil phase	Dispersion (4) added last
Formulation (A)									
SPF / % TiO_2	2.19	2.19	Not tested	0.91	2.21	2.64	1.83	2.05	1.59
Critical Lambda	369.4	370.75	Product not	382.4	381.6	381.65	375.35	374.6	376.1
UVA / UVB	0.419	0.458	homogenous	0.752	0.751	0.757	0.533	0.518	0.544
SPF Change		0%			(+) 142%	(+) 190%		(+) 12%	(-) 13.2%
Formulation (B)									
SPF / % TiO_2	1.64	2.19	2.13	2.03	1.26	1.51	1.42	1.7	1.74
Critical Lambda	370.85	369.1	371.5	379.45	381.2	381.2	374.7	373.0.5	373.35
UVA / UVB	0.422	0.419	0.451	0.662	0.701	0.705	0.491	0.47	0.468
SPF Change		(+) 33.5%	(+) 29.8%		(-) 38%	(-) 25.7%		(+) 19.7%	(+) 22.5%
Formulation (C)									

SPF / % TiO_2	2.34	2.89	2.33	3.56	3.17	3.08	1.73	1.05	0.71
Critical Lambda	367.35	369.8	370.2	380	379.55	380.2	376.6	376.8	376.05
UVA / UVB	0.394	0.45	0.437	0.701	0.703	0.709	0.546	0.524	0.538
SPF Change		(+) 23.5%	(-) 0.5%		(-) 11%	(-) 13.5%		(-) 39.3%	(-) 59%

Table 4. Comparison of powder performance versus addition of dispersions to oil phase or final emulsion

Looking more closely at the amphiphilic dispersion of the hydrophilic Titanium Dioxide in the amphisoluble polyether, PEG 7 Methyl Ether, optimal performance occurs with addition to the emulsion continuous phase favoring effective dispersion in the outer phase with less dependence on emulsion breakdown on skin and coalescence of sunscreen micropigment laden droplets. See Table 5.below.

Properties	Dispersion in water phase	Dispersion in oil phase	Dispersion added last
Formulation (A)			
SPF / % TiO_2	3.79	2.21	2.64
Critical Lambda	380.47	381.6	381.65
UVA / UVB	0.73	0.751	0.757
Formulation (B)			
SPF / % TiO_2	1.6	1.26	1.51
Critical Lambda	380.8	381.2	381.2
UVA / UVB	0.702	0.701	0.705
Formulation (C)			
SPF / % TiO_2	2.93	3.17	3.08
Critical Lambda	379.7	379.55	380.2
UVA / UVB	0.714	0.703	0.709

Table 5. Dispersion of Hydrophilic Titanium Dioxide in Polyether (PEG 7 Methyl Ether)

Performance of polyether dispersion is significantly better in hydrophilic O/W emulsion but not in gel network or inverse water-in-silicone emulsion. See Table 6. below

Properties Dispersion (3) in PEG7 Methyl Ether	TiO2 and solvent in water phase	Dispersion in water phase	TiO2 and solvent in oil phase	Dispersion in oil phase	TiO2 in oil phase, solvent in water phase	Dispersion added last
Formulation (A)						
SPF / % TiO_2	1.57	3.75	0.91	2.21	1.39	2.64
Critical Lambda	380.9	380.47	382.4	381.6	381.5	381.65
UVA / UVB	0.731	0.73	0.752	0.751	0.717	0.757
SPF Change		(+) 141%		(+) 142%		
Formulation (B)						
SPF / % TiO_2	N/A	1.6	2.03	1.26	N/A	1.51
Critical Lambda	N/A	380.8	379.45	381.2	N/A	381.2
UVA / UVB	N/A	0.702	0.662	0.701	N/A	0.705
SPF Change				(-) 38%		
Formulation (C)						
SPF / % TiO_2	N/A	2.93	3.56	3.17	N/A	3.08
Critical Lambda	N/A	379.7	380	379.55	N/A	380.2
UVA / UVB	N/A	0.714	0.701	0.703	N/A	0.709
SPF Change				(-) 11%		

Table 6. Polyether (PEG 7 Methyl Ether) dispersion versus controls added to water phase, oil phase or final emulsion.

Overall, both performance and aesthetic aspects, especially transparency as demonstrated by draw down films and skin application, point to control by parameters of the initial inorganic pigment chosen for UVR attenuation and the way it is dispersed in the skin film. Methods need to advance to the stage where skin film particle size and SPF can be determined simultaneously site by site for more accurate assessment of film differences. Even within the scope of current technology, additional experiments need to be conducted to support the hypothesis that optimal performance occurs with optimal dispersion in the product film after rub in and dry down on the skin. Directionally, these preliminary results point to getting the active particles well dispersed in the continuous phase that lays down on the skin. But this is also linked to the nature of the emulsion as it breaks down on the skin and where those particles eventually go to effectively absorb, reflect and diffract UVR with limited effect on visible light to make their efficacy invisible.

THE STUDY FOR RETINOL STABILITY USING 3-DIMENSION

Jung Sik Choi and Hong Geun Ji
Department of R&D Center, H & A Pharma Chem., Bucheon-si, 421-080, Korea

Introduction

In these several years, the functional materials have attracted many people being engaged in cosmetics and pharmaceutics because of their infinite application. Retinol is one of those kinds of materials owing to a wide variety of biological functions such as palpating embryonic growth and development, vertebrate vision, immune reactions and epidermal differentiation. It is also a prime candidate for cancer prevention.[1-3], However its efficaciousness is falling down as time is going by, because vitamin activity is decreased by isomerization, photochemical oxidation and thermal oxidation. Such degradation reactions can also reduce vitamin activity of stored and processed foods. In general, the stability of retinol and its relatives is gently declined in condition of high humidity, low pH and high temperature.[4]

Retinol is a fat-soluble material and abundant in fish and mammalian liver, milk fat and egg yolks. Due to its hydrophobic character, it is usually found in a complex with lipid droplets or micelles. If this system, liposome, could be applied, we could expect to protect retinol from degradative reactions.[5-6] Liposome is spherical closed vesicles of phospholipid bilayers with an entrapped aqueous phase. The lipid layers are mainly made up phospholipids that are amphophilic. In aqueous solution, they are arranged in bilayers, which form closed vesicles like artificial cells.

In the cosmetic area, liposome is used to stabilize the unstable materials against exterior condition (air, light, oxygen, etc), maximize their efficacy and enhance skin absorption by phospholipid having the great affinity for skin. The stability and delivery of liposome-incorporated retinol has been studied in several articles. However, the stability of retinol in liposome has not been sufficiently studied. [7]

Materials and Experimental

Materials

In this experiment, Retinol 50C (1.58 Million I.U./g, BASF), Lipoid S 100-3 and S 75-3 (Lipoid) are used as received. Other material also are commercial available. Purified water passed through an anion-cation exchange resin column is employed.

Experimental

The stability and skin penetration of retinol are improved by 3-dimensional method. As 1-dimension, porous silica is prepared using sol-gel method, and then retinol is entrapped into mesoporous silica. As 2-dimension, solid lipid nanoparticles (SLN) containing retinol and silica are obtained by high pressure

homogenizer (M110F, Microfluidics, USA). Finally 3-dimension is completion through lamellar phase self-organization that combines SLN-retinol with skin lipid matrix (SLM).

We used laser light scattering system (Zetasizer 3000H, Malvern, UK), cyro-SEM, chromameter (Color JS 555, Color techno system, Japan), HPLC(model510, Waters, USA) and image analyzer to analyze our 3-dimentional systems.

Conclusions

The skin adsorption and bio-availability can be improved by the general liposome, which is composed of phospholipid etc. But the general liposome is relatively unstable. In order to better this unstability, we used 3-dimensional system that doubly capsulated retinol. That formed multi lamellar structure, after formation of primary liposome.

According to chromameter date, the color stability of 3-dimensional retinol is enhanced by 5~10 times compared with general liposome systems. We also confirmed through HPLC analysis that 3-dimensional retinol is more long lasting. The effect of skin penetration and wrinkle reduction are improved, too.

References

[1] C M. Lee, A C. Boileau et al, *Review of Animal Models in Carotenoid Research, J. Nutr.*, **129**, 2271-2277, *1999.*

[2] Willhite, C.C., *Structure-activity relationships of retinoids in developmental toxicology. II. Influence of the polyene chain of the vitamin A molecule. Toxicol. Appl. Pharmacol.*, **83**, 563-575, *1986.*

[3] H Oikarinen, A. I. Oikarinen et al, *Modulation of procollagen Gene Expression by Retinoids. J. Clin. Inves,t* **75**, 1545~1553, *1985.*

[4] H. B. Sauberlich, *Bioavailability of vitamins. Prog. Food Nutr. Sci.*, **9**, 1-33, *1985.*

[5] C. J. Kirby, *Controlled delivery of functional food ingredients: Opportunities for liposomes in the food industry; in Liposome Technology II, Gregoriadis, G. (Eds.) CRC Press, Boca Raton*, 215-232, *1984*

[6] H. H Kim, I. C Baianu., *Novel liposome microencapsulation techniques for food applications. Trends Food Sci. Technol.*, **2**, 55-61, *1991.*

[7] A M. Young and G Gregoriadis, *Photolysis of retinal in Liposomes and its protection with Tocopherol and Oxybenone, Photochem & Photobiol.*, **63**, 344~352, *1996*