Summary:
A novel silicone-based vesicle delivery system capable of entrapping, delivering and subsequently releasing oil-based substances is presented. Silicone vesicles and vesicular aggregates, neat and vitamin-loaded, are successfully made to a specific size between 30 nm to a few microns – a preferred range for topical applications. A new alcohol enabling method made it possible to prepare simple and complex vesicles from a wide range of selected silicone polyethers, rake type and block copolymer types included. The parameters governing the morphological, physical, and stability properties of these new silicone vesicles are investigated. The suitability for topical delivery of oil-based personal care ingredients, specifically vitamins, is presented. Properties uniquely associated with silicone vesicles are also presented.

Introduction:
Incorporation of water-incompatible substances into aqueous finished products is an important cosmetic formulation need. This need is often met by encapsulating the water-incompatible substances using amphiphilic colloidal systems in microemulsions, or occasionally in liposomes. There are important distinctions between microemulsion and liposome approaches. Microemulsions are thermodynamically stable systems and are relatively easy to prepare, but the microemulsion droplets rapidly change / re-equilibrate their phase once formulated into products and after applications. On the other hand, liposomes are kinetically stabilized systems that the liposome structures may remain stable in formulations, as energy is needed to unlock or break them, though they might exhibit instability over time.

Liposomes are hollow colloidal particles dispersed in aqueous medium with a lipid bilayer membrane capable of encapsulating both lipophilic materials within the bilayers and hydrophilic medium into their interior. The bilayer membrane is most frequently composed of lipid bilayers made from natural or synthetic polar lipids. Natural surface-active lipids found in vesicles include phospholipids (egg or soy lecithins), glycolipids, sphingolipids (ceramides) and even “skin-lipids” (cerebroside, cholesterol, fatty acids, cholesterol sulfate). Additionally, phosphatidylcholine zwitterionic phospholipid is one of the recent lipid variations that increases liposome stability and improves encapsulation efficiency [1].

Synthetic nonionic surfactants like mono- and dialkyl polyglyceryl ethers or polyoxyethylene glycols were also known to form vesicles. Vesicles formed from nonionic surfactants are sometimes referred to as niosomes. Novasomes is a variation of niosomes prepared from the mixture of monoester of polyoxyethylene fatty acids, cholesterol and free fatty acids at 74/22/4 ratio [1].

Silicone polyether was another class of synthetic amphiphilic compounds found to form vesicles [2-4]. The early works were limited to “self-assembly” type vesicles that formed spontaneously on dispersion in water from a very limited number of PEG-12 dimethicones. Use of vesicle-forming silicone polyethers in personal care applications can be found in U.S. patent prior art [5].

One main objective of this project is to develop a better understanding on silicone-based vesicle technology and its utility as delivery system for key personal care actives such as vitamins. Another objective is to develop / identify silicone polyethers useful for vesicle preparation, and potential synergistic benefits for use in skin care applications.

Materials and Methods:
Two classes of silicone polyethers (SPEs) were prepared for the study: PEG-12 dimethicones (formerly known as dimethicone copolyol) and dimethicone PEG-12 copolymers (proposed INCI name; where 12 is the average number of oxyethylene units per PEG block). PEG-12 dimethicones have a rake-type structure of MD$_x$D$(EO)^{y}_2$ where PEG-12 polyether is grafted onto the silicone backbone at selected sites, the D/D’ value is the ratio of x to y, an
indicator for relative PEG-12 polyether content. Dimethicone PEG-12 copolymers are (AB)n alternating block copolymers of PEG-12 polyether block (represented by A) and silicone block (represented by B). Three PEG-12 dimethicones are shown in Table 1. All materials were made by Dow Corning for the study.

<table>
<thead>
<tr>
<th>PEG-12 Dimethicone</th>
<th>MD27D(^{(EO12)})_3M</th>
<th>MD22D(^{(EO12)})_2M</th>
<th>MD70D(^{(EO12)})_3M</th>
</tr>
</thead>
<tbody>
<tr>
<td>D/D’ ratio</td>
<td>9.0</td>
<td>11.0</td>
<td>23.3</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>Soluble</td>
<td>Soluble</td>
<td>Insoluble</td>
</tr>
<tr>
<td>Vesicle type</td>
<td>Self-assembly</td>
<td>Self-assembly</td>
<td>Assembly-required</td>
</tr>
</tbody>
</table>

Cryogenic transmission electron microscopy (Cryo-TEM) was used to characterize the vesicles in both neat and vitamin oil loaded states. Vesicles are unique three-dimensional structures that are only stable in the medium as prepared. Cryo-TEM is a technique that preserves the structures of interest by vitrifying the liquid, and then analyzes the dry specimen at cryogenic temperature. The TEM used is JEOL JEM-2000FX. The microscope is a 200kV TEM capable of obtaining 0.3 nm resolutions. The microscope is equipped with a lanthanum hexaboride filament.

Approximately 2.3 µl of aqueous vesicle dispersion, prediluted to about 5% with de-ionized water, was applied using a micropipette onto a lacey carbon film coated Cu TEM specimen grid. The excess fluid was removed by blotting the grid surface. The specimen grid was then plunged into a liquid ethane vessel contained in a -175 °C liquid nitrogen cryo-plunge system to vitrify the water. The grid was loaded, via a Gatan cryo-transfer system, in a cryo-TEM stage in TEM. The specimen was maintained at below -160 °C. An in-line cold finger trap, maintained at -180 °C, was used to minimize possible contamination on the specimen during analysis.

HPLC was used for simultaneous quantification of vitamin actives and silicone vesicle carriers, and to confirm the payload and the stability of vitamin actives. The HPLC chromatographic equipment consisted of a Waters 2695 Separations Module, a Waters 2487 UV detector and a Polymer Laboratories PL-ELS 1000 Evaporative Light Scattering detector. The separation was made with a 150 mm x 3.9 mm Waters Nova-Pak® C\(_{18}\) 4 um guard column. The analyses were performed with a ten minutes isocratic MeOH/IPA (75/25) run followed by a four minute ramp to THF, and then holding at 100% THF for three minutes before returning to the starting solvent blend. All solvent was run at 1.0 mL/min. The columns were heated to 30 °C and the UV detector was set at 325 nm and 4 AUFS. The PL-ELS 1000 conditions were nitrogen at 1.0 SLPM, nebulizer at 50 °C, and drift tube at 80 °C. The VAP was quantified using the UV response and the SPEs were quantified using the ELSD response. The repeatability for this analysis was estimated to be ±10%.

An NPA 150 Nanotrac particle analyzer (Microtrac Inc., Montgomeryville, PA) was used to quantify the size and distribution of vesicles in dispersion. Particles with size range from 0.0032 to 6.54 um are measured based on dynamic light scattering principle. Vesicles in aqueous dispersion were determined their size and distribution using the technique.

A range of skin care formulations were prepared: hydrogel, cream and lotion. Formulation latitude and compatibility with common cosmetic ingredients were investigated. Cryo-TEM was used together with Nanotrac to verify stability in the formulations, and HPLC was used to verify vitamin stability.

**Results and Discussion:**

Vesicles were formed on dispersing MD\(_{27}\)D\(^{(EO12)}\)_3M and MD\(_{22}\)D\(^{(EO12)}\)_2M PEG-12 dimethicones into water, in excellent agreement with previously findings [2-4]. These vesicles are referred to as “self-assembly” vesicles, to be consistent with the prior art, as no specific energy / effort is required for these PEG-12 dimethicones to assemble into vesicular structure. MD\(_{70}\)D\(^{(EO12)}\)_3M PEG-12 dimethicone, on the other hand, had little solubility in water. No dispersion in water was observed, even after extensive mixing.

We recently discovered a process which effectively dispersed MD\(_{70}\)D\(^{(EO12)}\)_3M PEG-12 dimethicone and enabled it to form vesicles in aqueous media. The vesicle size could be effectively engineered to sizes ranging from 40 nm to submicron in diameter. The vesicles formed via this proprietary, patent-pending process are called “assembly-
required”, as energy / work was required to enable the PEG-12 dimethicone to form vesicles. A comparison between these two vesicle types in terms of structure, proposed features / benefits was recently presented by Lin, et al. [6].

Oil-soluble vitamins can also be effectively entrapped into “assembly-required” vesicles of PEG-12 dimethicone via this proprietary process. The “assembly-required” vesicles are believed to have better stability than the “self-assembling” vesicles, as these vesicular structures are “locked into place” and more energy is required to break them. The vesicle dispersion composition and particle size are shown in Table 2.

Table 2. Composition and property of vitamin-loaded PEG-12 Dimethicone vesicle dispersions

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>2003</th>
<th>2002</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-12 Dimethicone</td>
<td>MD_{27}D_{(EO12)}^{3M}</td>
<td>MD_{22}D_{(EO12)}^{3M}</td>
<td>MD_{70}D_{(EO12)}^{3M}</td>
</tr>
<tr>
<td>Vesicle Type in Dispersion</td>
<td>Self-assembly</td>
<td>Self-assembly</td>
<td>Assembly-required</td>
</tr>
<tr>
<td>Dispersion Composition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% PEG-12 Dimethicone</td>
<td>20.01</td>
<td>20.00</td>
<td>20.61</td>
</tr>
<tr>
<td>% Vitamin A Palmitate</td>
<td>4.11</td>
<td>4.11</td>
<td>4.41</td>
</tr>
<tr>
<td>% Aqueous Phase</td>
<td>75.87</td>
<td>75.90</td>
<td>74.99</td>
</tr>
<tr>
<td>Avg. Vesicle Size (um)</td>
<td>0.525</td>
<td>0.518</td>
<td>0.184</td>
</tr>
<tr>
<td>D(0.5, um)</td>
<td>0.474</td>
<td>0.535</td>
<td>0.156</td>
</tr>
<tr>
<td>D(0.9, um)</td>
<td>1.036</td>
<td>0.949</td>
<td>0.346</td>
</tr>
<tr>
<td>Span</td>
<td>2.03</td>
<td>1.61</td>
<td>1.800</td>
</tr>
</tbody>
</table>

A structure vs. vesicle-forming property and vesicle type was established for PEG-12 dimethicones, shown in Figure 1. As shown, the D/D’ ratio of PEG-12 dimethicone is the most critical parameter which dictates the water miscibility of this type of SPEs. PEG-12 dimethicones with D/D’ significantly higher than 15 do not disperse readily in water, and no vesicles could be observed via direct dispersion. Vesicles of desirable size could be prepared conveniently via the patent-pending process from PEG dimethicones with high D/D’ values.

![Figure 1. PEG-12 dimethicone structure and vesicle formation property.](image)

The lipophilic substances such as vitamin A palmitate (VAP) can be conveniently and effectively entrapped between the bilayers of silicone vesicles using the previously mentioned proprietary process. The process involves three steps: vesicle formation, size reduction, and structure lock-in. Vitamin-entrapped vesicles were first formed on dispersion, with mixing in water containing a processing aid, along with a few oil droplets, which was further
narrowed in size upon further homogenization. As a final step, the vesicle and aggregate structure was “locked in” upon stripping removal of a processing aid.

Cryo-TEM characterization confirmed the structure and quality of the assembly-required silicone vesicles. As evidenced in Figure 2, MD$_{70}$D$_{12}$ M PEG-12 dimethicone formed small, unilamellar vesicles singularly, evenly dispersed in water (A), and formed singular vesicles as well as “honey-comb” like aggregates for the vitamin A palmitate-entrapped system (B). These results are promising, as vesicles of desirable size and structure could be prepared to render variations in how the rate of vitamin is delivered and released on applications.

Figure 2. (A) Neat silicone vesicles, and (B) vitamin A palmitate-loaded vesicles and aggregates, both formed from MD$_{70}$D$_{12}$ M PEG-12 dimethicone (19187-8E).

Aqueous dispersions of silicone vesicles containing vitamin oils at various payloads were prepared and tested for 40°C accelerated aging stability. The stability of vitamin in these silicone vesicles was followed using an HPLC assay method. To evaluate the utility of silicone vesicles for delivery of actives, the vitamin-loaded vesicles were subsequently incorporated into model skin care formulations. The formulation latitude and compatibility with various common cosmetic ingredients were also investigated. The stability of the VAP-loaded silicone vesicles in these skin care formulations was also followed, together with the stability of the encapsulated vitamins.

A similar study was also carried out for the (AB)$_n$ dimethicone PEG-12 copolymers. The results will be presented in future reports.

Conclusions:
A novel silicone vesicle system derived from PEG-12 dimethicones and (AB)$_n$ dimethicone PEG-12 copolymer (proposed INCI name) is presented. Vitamin A palmitate was successfully entrapped within the silicone vesicles, as supported by cryo-TEM and particle size analyses. Its utility as delivery system for other oil-soluble actives is suggested.

A new class of silicone vesicle – “assembly-required” vesicle is presented. Singular and complex vesicle aggregates are made possible only, via a proprietary method, from PEG-12 dimethicones of higher D/D’ and new (AB)$_n$ silicone polyethers. A structure vs. vesicle-formation property and vesicle type is presented.

The utility of silicone polyether vesicles as delivery system was investigated. Vitamin-loaded vesicles were formulated into model skin care formulations; the formulation latitude with common cosmetic ingredients was presented, to facilitate works with silicone vesicle system for topical delivery of vitamins and other oil actives.
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References: