Preparation and Applications of Silicone Emulsions Using Biopolymers

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I. INTRODUCTION

A. Fundamentals

Dispersions of water in oil, or the inverse, are inherently unstable. Emulsification is thus a nonequilibrium process such that the average droplet size in an emulsion tends to increase over time. However, the characteristic time scales for coarsening of emulsions can span a remarkably wide range, from seconds to several years, that depends on the nature of the oil, the surfactants used to stabilize the emulsion, and the processing history. It is fair to say that not all the parameters affecting emulsion stability are completely understood. Current practices in emulsion formulation thus combine art with science. With silicones, being specialty materials and very unlike their organic counterparts, both theory and art are less well explored than organic surfactants.

B. Silicone Properties

Silicones possess very unusual properties by organic standards. For example, the low torsional force constant of the Si-O-Si-O linkage [1] results in exceptionally flexible molecules: simple dimethylsilicone polymers [polydimethylsiloxane, 1 PDMS (Me, SiO)n, Scheme 1] have $T_g$ values of approximately $-123^\circ$C irrespective of molecular weight over a range of 1000–1,000,000 [2]. This backbone flexibility, in combination with the high hydrophobicity of the gem-dimethyl groups and relatively high ionic character of the Si-O linkage, results in exceptional surface properties for silicone polymers [3]. These properties are greatly amplified when either nonpolar or polar functional groups are added to the silicone, creating true surfactants [4]. Depending on structure, silicones can be used as wetting agents, for foaming or defoaming applications, as lubricants, and,
perhaps most important of all, as compounds that render liquid/air or solid/air surfaces hydrophobic: the methyl groups extend into the air at the interface generating very low-energy surfaces [3]. The surface tension of silicones is a function of molecular weight, increasing from about 16 mN/m for Me₃SiO-(Me₂SiO)ₙSiMe₃, \( n = 0 \), to 20–21 mN/m for medium and high molecular weight silicones, \( n > 10 \) [5].

PDMS is not compatible with aqueous media. If the molecular weight of a given PDMS is high enough, typically starting at six to eight Me₂SiO units, PDMS is also incompatible with mineral oils or more polar oils (e.g., ester oils, natural fats or oils). These hydrophobic and oleophobic properties make it very difficult to form emulsions between silicones and aqueous solutions or organic oils, though high shear can lead temporarily to emulsions that break down easily and rapidly [6].

C. Use and Interest in Silicone Emulsions

With the appropriate surfactant(s), silicones can be formulated into emulsions of a variety of types including w/o, o/w, o/w/o, w/o/w, etc. (W, water; O, oil; the oil may additionally be silicone oil or organic oil). The specific morphology of the emulsion depends on the surfactants used and the processing history.
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Silicone emulsions can also arise inadvertently, as a consequence of adventitious surfactants, particularly in biological environments, as shall be discussed below.

D. Impact of Silicone Emulsions in Biological Domains: Purpose of this Chapter

In this chapter, we shall outline some of the basic parameters associated with the formation of colloidal silicone dispersions and then provide some examples of typical silicone emulsions and their application. The remainder of the review will focus on silicone emulsions that form in contact with biological materials. Initially, we shall describe emulsions that spontaneously form in contact with the inner eyeball following retinal repair surgery. Finally, the utilization of proteins and atypical functional silicones to prepare water/silicone emulsions will be described. Both the features necessary for a stable emulsion and the consequences on protein/enzyme tertiary structure will be examined.

II. FUNDAMENTALS OF SILICONE EMULSIONS

A. Classes of Silicone Emulsifiers

A wide variety of surfactants has been used to emulsify and stabilize water/silicone emulsions. As early as 1958, Sato [7] examined the use of many conventional surfactants, including fatty acid esters of polyethylene glycol (non-ionic), quaternary ammonium salts (cationic), and alkyl sulfates or alkylarene-sulfonates (anionic) to stabilize poly(organoalkylsiloxane) emulsions. It was demonstrated that conventional surfactants based on hydrocarbon chains are generally not very efficient surfactants for silicone emulsions, although sodium dodecyl sulfate (SDS) is useful as a probe for examining the stability of silicone emulsions [6]. The adsorption of the alkyl groups at the silicone interface is not as strong as at an oil interface. In spite of this, because of their relatively low cost, these surfactants are commonly used in commercial emulsions (see discussion of oil-in-water emulsions below). More efficient, but more expensive, silicone-based surfactants were developed both as emulsifiers and stabilizers for silicone emulsions, particularly water-in-oil emulsions [4]. The most common silicone surfactants are described below.

B. Types of Surfactants

Although a variety of phenyl- and trifluoropropyl-modified silicones are sold commercially, there has been little investigation of surfactants based on these compounds. The vast majority of research has focused on modified dimethylsilicone. A wide variety of hydrophils have been combined with silicones to make viable surfactants, including ionic groups such as sulfonates [8], sulfosuccinates
[9], phosphates [10], thiosulfates [11], betaines [12], sulfobetaines [13], and quaternary ammonium salts [14]. The two major classes of silicone-based surfactants are based on amines or polyethers, with the latter holding the lion’s share of commercial usage.

Silicone-based emulsifiers involve linear oligomeric or polymeric silicone molecules modified with hydrophilic and, optionally, hydrophobic residues. Both linear block (AB and ABA) and comblike structures are known. In the linear surfactants, functional groups can be located only at the ends of the structures. By contrast, the distribution of functional groups in comb structures is ruled by statistics (Scheme 1).

1. Polyethers
The most important class of emulsifiers for silicones is based on polyethers. Both poly(ethylene oxide) and mixed poly(ethylene oxide)/poly(propylene oxide) polar blocks may be grafted to the silicone backbone (Scheme 1). Although linear block 2, 3, and comb 4 structures are available, the comblike silicone polyethers (often known as silicone or dimethicone copolys) are currently of greatest commercial importance. Even compounds with very low silicone content can be powerful emulsifiers, as exemplified by the trisiloxane 5 [15]. Mixed alkyl/polyether modified silicones are also known: these have applications in emulsifying organic oils [16].

2. Amino-Modified Silicones
Another important class of silicone-based emulsifiers is modified with organoamine groups 6 [1–20] or, in some cases, amine-modified copolys (polyethers) 7 [21]. Such compounds are widely used as hair softeners and conditioners as well as in cosmetic products (Scheme 2). Since the amine groups on these compounds will be protonated at pHs <10, these compounds are usually ionic surfactants.
C. Silicone Emulsion Formulations

Silicones can be formulated into emulsions of a variety of types including w/o, o/w, o/w/o, w/o/w, and microemulsions with the appropriate surfactant(s). The specific morphology of the emulsion depends on the surfactants used and processing procedures. As noted above, organic surfactants are not as efficient as silicone surfactants for stabilizing silicone/water emulsions. However, they are much cheaper and are commonly used in commercial formulations for coating applications and for hair conditioning. Oil-in-water emulsions are generally formed mechanically or through emulsion polymerization of cyclic monomers. In mechanically formed emulsions, the incorporation of the existing materials occurs with specialized agitation/mixing that is beyond the scope of this chapter; no chemical reactions take place. Alternatively, cyclic monomers [typically D4(Me2SiO)4] can be polymerized in the presence of emulsifying surfactants and water to form polymeric o/w emulsions. Emulsion polymerization facilitates the incorporation of water-soluble moieties that are not otherwise easily introduced to hydrophobic silicones. In addition, the emulsion composition can be manipulated to adjust the product characteristics as required [21].

While there is extensive knowledge of the stabilization of w/o emulsions by silicone emulsifiers (see next section), examples of o/w emulsions are less well described [22]. Nonionic dimethylsiloxane polyoxyalkylene copolymers are generally used to prepare such dispersions. They must, of necessity, carry a high degree of polyoxyalkylene substituents, which render the surfactant more hydrophilic. The resulting emulsions are sterically stabilized by the polyether chains. Alternatively, amino-modified silicones will form o/w emulsions.

The other important class of silicone emulsion is of the w/o type, for which polydimethylsiloxane-polyoxyalkylene copolymers are preferred as emulsifiers; organic surfactants are generally ineffective. Increasing the molecular weight of the emulsifier is an effective means of preparing emulsions with improved stability. Thus, emulsions containing potentially destabilizing alcohols in the aqueous phase can be successfully emulsified with silicone-copolyols having an approximate molecular weight of 30,000 [23]. The molecular weight of the emulsifier can be further increased by slight cross-linking. To achieve emulsions with even greater stability, organic w/o emulsifiers such as polyglycerol fatty acid esters may also be used.

D. Microemulsions

In both types of emulsions noted above, droplet sizes are typically rather large (>500 nm diameter) such that the emulsions are opaque. It is possible to prepare microemulsions of silicone oils and water with 5 as the emulsifier [17,24]. These optically clear dispersions are isotropic mixtures. Aminosilicone copoly-
ols also form microemulsions spontaneously in water [21], although in this case
the dispersion has internal phase particles of 5–50 nm. Because of their smaller
particle sizes, microemulsions are more stable than the conventional emulsions
[21]. At the time of writing, these emulsions are more of fundamental interest
[4,21] than commercial applications, although this situation is expected to
change as a result of their intriguing properties.

E. Water-in-Oil and Oil-in-Water Emulsions

The fascinating properties of multiple emulsions, which may be of the w/o/w
or o/w/o type, have attracted recurring interest, in particular when the protection
of sensitive ingredients or controlled release of active substances is required.
Two different water–oil interfaces have to be stabilized in both types of multiple
emulsions. Like other polymeric surfactants, silicone-based emulsifiers are espe-
cially suited to stabilize these emulsions because their polymeric nature permits
them to be adsorbed strongly at the oil interface, which prevents the migration
of the emulsifiers from one interface to the other leading to destabilization. In
one example of this, a w/o/w emulsion was established using two polymeric
emulsifiers (see other examples, below) [25]: a hydrophobic polyacrylate copol-
ymer, which carries lipophilic alkyl and hydrophilic polyoxyalkylene groups for
stabilization of the oil–water interface, and poly(hexadecylmethylsiloxane)-co-
poly(ethylene/propylene oxide), which stabilizes the water–oil interface. The
hydrophilic–lipophilic balance (HLB) values of the emulsifiers should be above
10 for the hydrophilic emulsifier and below 6 for the hydrophobic emulsifier.

F. Theory

The classical and empirical approach to formulation of organic emulsions uses
the HLB [26] surfactant classification system. In general, one uses surfactants
that are soluble in the continuous phase to make emulsions successfully. Thus,
low HLB surfactants are used for w/o and high HLB for o/w emulsions [27].
The HLB system was developed for alkoxylated nonionic surfactants [27].
The characteristics of silicone surfactants are very different from this class of
compound. As a result, it is difficult to apply the HLB system to silicone emulsi-
fiers. Calculations based on critical micelle concentration (CMC) give some
idea of the hydrophobicity of the silicone component. Typically, each Me or
CH₂ group on a silicone contributes to the hydrophobicity in silicones as much
as a CH₂ group does in organic surfactants, while the Si-O does not significantly
affect the HLB [28]. More recently, researchers have attempted to predict emul-
sification behavior of silicone surfactants by use of three-dimensional HLB (3D-
HLB) [16]. Thus, an HLB of about 4 is calculated for a polymer of the structure
[Me(H₆C₁₆)SiO]ₙEOₘ of molecular weight 10,000–15,000; tests of actual emul-
sification ability placed the HLB value between 4 to 6, demonstrating reasonable
correlation between theory and experiment [29].

Silicone emulsions based on 6 have limited stability as a result of the fairly
narrow range of HLB they achieve [20]. Compound 7, which is made by emul-
sion polymerization in the absence of water, oils, and surfactants, expands the
ability of incorporating silicones in formulations, as the addition of polyether
group allows tailoring of the water solubility of these silicones, resulting in an
increase in the HLB range [21]. Silanol groups (typically found at the end of
linear polymers) also contribute to an increase in the HLB [21].

The origin of the utility of silicone polyethers to stabilize (particularly w/o)
emulsions has been the source of significant discourse. Several proposals have
been made to explain their notable ability to prevent droplet coalescence. Fac-
tors that increase the viscosity of the continuous phase increase emulsion stabili-
yty, and it is clear that the relatively long silicone spans between each hydro-
philic polyether group can serve this purpose. Furthermore, the highly flexible
silicone chains, which can extend to the silicone oil continuous phase, may also
provide steric stabilization. More careful studies of these systems with well-
characterized surfactants are warranted.

III. APPLICATIONS AND SPECIFIC EXAMPLES
OF W/O, O/W AND W/O/W, O/W/O EMULSIONS

A. Cosmetics
Silicones are important ingredients in body care, face care, and cosmetic prod-
ucts. Silicone w/o emulsions are used in skin care products such as skin cleans-
ers because they improve spreadability and, more importantly, because they are
aesthetically attractive: they impart a smooth and silky feel and reduce greasi-
ness. It is possible to formulate “non-oil” personal care products that have 60%
of their composition as silicones and no more than 10% as mineral oil [30].

Dispersions based on low molecular weight cyclomethicones and hexamethyl-
disiloxane are used in antiperspirant deodorant formulations, again for their aes-
thetic feel. With a lower heat of evaporation, they do not seem “cool,” as do
alcohols, the competing materials, and possess an attractive “feel” on the skin.

B. Hair Care
Silicones are extensively used as conditioners in hair care. They impart softness,
combing ease, fast drying, and shiny appearance. Two basic classes predominate
in this market. In the first, emulsified high molecular weight silicone droplets
are deposited on the hair. In the second, cationic amino-modified silicones (the
amino group in aqueous solutions/emulsions will be protonated below pH <10)
bind to anionic hair, a protein (see also below), and provide substantivity. Both formulations require extended colloidal stability on the shelf. The latter organo-functional silicones are important constituents of two-in-one shampoos, laminators, conditioners, and so forth. The aminosilicones used in hair treatment are generally used as o/w emulsion–based formulas.

C. Drug Delivery

Drugs are encapsulated, not only for taste and odor masking but also for drug stabilization, gastrointestinal tolerance, and controlled rate of release. Appropriately formed silicone emulsions can be considered as another form of drug encapsulation, as the drug is entrapped in the emulsion droplets, which serve as a carrier as well as protective shell for the drug.

Silicone oil, for instance, was employed as the external phase in an o/w/o multiple phase emulsion, during microsphere formation, using an emulsion/internal gelation technique [31]. In this process, the lipophilic encapsulant (Sudan orange G) was dissolved in the edible oil and then dispersed in alginate sol. This dispersion was dispersed again in silicone oil to form o/w/o emulsion. This was followed by an internal gelation process to give alginate microspheres that contain immobilized oil droplets, which were subjected to a further coating step using chitosan to control the release rate. Silicone is beneficial in this instance not only for its high hydrophobicity, which provides a control element in release kinetics, but also for its regulatory acceptance as an oral excipient in antacid and related applications.

The w/o/w emulsions have potential applications in many areas, such as pharmaceuticals, cosmetics, and agriculture. However, their inherent thermodynamic instability and their fast, uncontrolled release of the entrapped materials limit their use for drug delivery. In order to overcome these problems, Sela et al. [32] studied the release of ephedrine hydrochloride and other compounds from w/o/w emulsions stabilized with commercially available hydrophobic surfactants and hydrophilic silicone surfactants that they synthesized by grafting undecanoic esters of poly(ethylene oxide) (45 ethylene oxide units) to poly(hydromethylsiloxane)-co-(dimethylsiloxane) using hydrosilylation (for hydrosilylation, see Scheme 3). They found that this emulsion exhibited enhanced stability and rate of release. Other silicone emulsion systems for drug delivery have been described [33,34].

\[
\begin{align*}
\text{PDMS-H} & \quad \text{Si(OEt)₃} \\
\text{H₃PCl₆} & \quad \text{or Karstedt's catalyst} \\
\text{Si(OEt)₃} & \quad \text{Si(OEt)₃} \\
\text{TES-PDMS} & \quad \text{TMS-Si} \\
\end{align*}
\]

**Scheme 3**
IV. EMULSIONS OF SILICONES WITH BIOLOGICAL MATERIALS—ADVENTITIOUS EMULSIONIFICATION

A. Retinal Repair Fluids and Emulsions

Silicones have an impressive record for biocompatibility and have been used in many applications that require topical (e.g., cosmetics as noted above) or internal use. (At the time of writing, the breast implant controversy appears to have nearly run its course, with most epidemiological studies showing only very weak or no association at all between disease and silicone polymers [35]. Silicone elastomers are still constituents of a variety of medical implants, and silicone oils continue to be approved as oral antacid excipients.) Depending on the application, the surface activity of silicones may be beneficial. For example, silicones, usually in combination with hydrophobed silica, are widely used as defoamers in oral antacid formulations. However, their surface activity is not always desirable.

Silicones have been extensively used as replacement fluids following repair of retinal detachment. Following reattachment of the retina, silicone oils are used to replace the vitreous humor (fluid inside the eyeball) on a temporary basis for up to several months. The viscosity of the PDMS oil used in this process ranges from 1000 to 12,500 centistokes (cSt), while fluorosilicone oils [containing F3C(CH2)2(Me)SiO moieties] are somewhat lower, i.e., 1000 to 10,000 cSt. PDMS has a lower density than the intraocular fluid, and hence is considered useful in dealing with retinal detachment in the superior portion of the eye. Fluorosilicones, on the other hand, are considered more appropriate for repair of inferior detachment, as they possess a higher density than the intraocular fluid [36]. The optical clarity and high permeability to oxygen of silicones are of particular benefit; their ability to form emulsions is not.

It has been frequently observed that after incorporation in the eye, dimethyl-, phenylmethyl-, and fluorosilicones emulsify in vivo. The dispersion droplets migrate to several places including the interior chamber, occlude vision, and, more problematically, change the permeability of the corneal endothelium [37] and the ability of the eye to clear undesirable materials; small silicone oil droplets can cause secondary glaucoma by blocking aqueous outflow [38]. Neither dimethyl- nor fluorosilicones readily form stable emulsions when mixed with water or saline, and several groups have attempted to assess the source of the emulsifier in the eye and understand how the emulsions form. Very informative discussions by Miller clarify that spontaneous emulsification can occur under ideal conditions [39]. These depend on the specific o/w phase diagram, the characteristics of the oil, and the presence of at least a dilute concentration of surfactant(s), which may initially be present or may arise from chemical reaction [40]. What, however, is the active surfactant in the eye?
The relationships between physical and functional characteristics of the silicones and the ease of emulsification were thus assessed in vitro. Some general comments can be made. Lower molecular weight silicones, cyclic and linear oligomers in particular, are associated with emulsification, and great care is now taken by commercial suppliers of these materials to reduce the content of low molecular weight materials (personal communication, Labtician, Oakville, Canada) [41,42]. Phenyl groups were shown not to facilitate emulsion formation whereas, perhaps not surprisingly, the presence of silanol groups did [42]. Fluorosilicones, which have a higher density than the other silicones or of water, were also found to facilitate emulsification in vitro and in vivo [43,44]. In vitro tests, it was noted that the absence of an air interface (no head space), as is the case in the eye, greatly reduced the degree of emulsification. It was observed that methylsilicones were less emulsified than fluorosilicones of the same viscosity, suggesting that the smaller density difference between silicones and intraocular fluid makes intermixing more difficult compared with fluorosilicones. This, in combination with the observation that reduced emulsification accompanied the use of higher molecular weight, viscous silicones, [38,41], suggests that ease of mixing is an important aspect of emulsion formation.

1. In Vitro Tests

As noted above, emulsions involving silicones are not that easily formed in the absence of surfactants. By performing both in vivo and in vitro tests with plausible biological surfactants, several groups have attempted to determine if bodily fluids could provide surfactants in vivo to stabilize the silicone emulsions. Emulsification of medium molecular weight silicone (about 1000 cSt, MW 28,000) [2] was attempted with blood plasma, serum, lipoprotein-deficient serum, and high- or low-density lipoprotein, respectively [45] Lipoprotein-deficient serum did not support the emulsification, but emulsions formed readily in the presence of plasma lipoproteins and constituents of red blood cell membranes, including phospholipids [46], implicating them in the in vivo emulsification process. Other additives further enhanced emulsification [42]. Emulsions of droplet size about 45 µm were formed in vitro, which compares with 38-µm droplets found in patients. Emulsions could also be made simply by the addition of proteins to the silicone/water system. Emulsifying efficiency followed the order fibrinogen, fibrin, and serum, followed by albumin [44], gamma globulin [38], very low density lipoprotein, and acidic α₁-glycoprotein fibrin. An independent comparison of emulsification in the presence of vitreous humour, blood serum, or collagen showed that the former was the best emulsifier of high molecular weight (about 5000 cSt, 50,000 MW) silicone, although all three produced emulsions in vitro [47]. The presence of balanced salt solution, rather than deionized water, facilitated emulsification in all cases [38].
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2. In Vivo Tests

Short implantations (1 week) of silicone preemulsified with bovine serum albumin as the surfactant demonstrated that the combination of silicone and protein, and the ionic strength of the emulsifying liquid, are important factors in physiological effects in the eye (corneal permeability). Inflammation in the eye was observed to facilitate emulsification of the silicone [37]. In longer term implantation studies (6 months) of silicone oil, the surfactant necessary to form a water-in-silicone oil emulsion was judged by infrared spectroscopy to be a protein–silicone complex at the emulsion interface [47].

Two types of mechanisms were proposed to explain silicone oil emulsification in the eye: thermodynamic and hydrodynamic [44]. In the thermodynamic mechanism, emulsification occurs when some surface-active substances populate the interface and the interfacial tension decreases. In the case of the hydrodynamic mechanism, emulsification takes place as a result of oil surface deformation that is induced by external mechanical energy. The above mixing studies suggest the latter mechanism could be important when emulsification is facilitated by an air interface. Based on work with highly phenylated silicone copolymers, Ikeda suggested that the emulsification of the copolymer is more generally facilitated as the interfacial energy decreases, due to the attachment of proteins to the oil surface; that is, in this case the thermodynamic mechanism predominates [44].

3. Speculation About Specific Nature of Silicones and Biological Materials That Leads to Emulsions

In general, the ideal nonemulsifying intraocular tamponade should be an optically clear, nontoxic, hydrophobic liquid that is protein repellant, so there will be no attachment of protein at the oil–aqueous phase interface. However, is there a protein-repellant silicone? These studies suggest that proteins play an important role in stabilizing water-in-silicone oil emulsions. In the remainder of the chapter we shall focus on patents and fundamental studies of silicone emulsions in which proteins are a required constituent.

B. Silicones and Proteins as Cosurfactants

1. Cosmetics

Silicones, as noted above, have a wonderful aesthetic feel and are widely used in consumer products. A current trend in the cosmetics industry is the utilization of natural materials as cosmetic constituents either as “nutriceuticals” or because natural materials are perceived to be beneficial to consumers. In the case of cosmetics, different silicone emulsions containing proteins have been patented. The patents do not claim proteins as required constituents of the water–oil inter-
face, but their presence at the oil–water interface is very likely (see below).
Thus, patents have been issued for silicone oil/water emulsions containing non-
ionic silicone surfactants based on polyethers, with additional protein such as
collagen or protein hydrolysate that acts in concert with other agents to gel the
emulsion, [48] or that helps to form a film upon application to skin [49]. The
latter patent explicitly included the albumin and globulin fraction of soy pro-
teins.

2. Hair Care
The treatment of hair—a protein—was only briefly mentioned in this chapter
(see above). Here note is made of a patent describing an emulsion that incorpo-
rates a protein, which is added to facilitate silicone deposition on hair by exploit-
ing favorable hair–protein interactions. The inventors do not comment on the
role of the protein as a surfactant and add an emulsifier with HLB 8–10, such
as Neodol (a C_{12}/C_{13} linear alcohol) or Tergitol (nonylphenylethoxylate) to sta-
lize the emulsion [50].

3. Biodiagnostics
An interesting patent describes formation of an o/w emulsion in which the dis-
persed fluorocarbon or silicone phase is coated with a biodiagnostic protein
[51]. Although no claims are made about the stabilization of the emulsion, with
droplet sizes about 0.5–5 \( \mu \)m, the protein is critical in this regard. These surface-
active proteins serve a supplementary role. In addition to stabilizing the emul-
sion, they serve as binding sites for biomolecules contained in bodily fluids.
Binding to the surface-active proteins reduces the colloidal stability of the emul-
sion; agglutination is indicative that such binding has occurred. Thus, selective
binding of biomolecules to judiciously chosen surface-active proteins provides
a convenient biodiagnostic system.

V. PROTEINS INVOLVED IN WATER-IN-SILICONE
OIL EMULSIONS
Proteins have been shown to play an integral role in the stabilization of natural
emulsion systems, such as milk [52] and, as noted above, silicone oil in the
interior of the eye. The same principles that are involved in stabilizing these
natural systems should be applicable to engineered emulsions involving a water
and silicone oil interface.

A. Enzymes Entrapped within Emulsions—
PEO-Modified Silicone
As we have seen, commercial silicone polyethers are excellent surfactants with
which to generate stable water-in-silicone oil emulsions [53]. Water-in-D_{4}
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[(Me₂SiO₄)] emulsions, stabilized by a silicone copolyol, do not undergo phase separation over extended periods (in excess of 6 months). From small- (40 mL) to very large-scale emulsions (thousands of liters) may be readily formed using the same experimental protocol; the ability to perform such linear “scale-up” is rather rare. Particles were relatively monodispersed and averaged 2–5 µm in diameter. Much smaller volume emulsions (5 mL or less) required special mixers, which led to broader dispersity emulsions; most particles were submicrometer sized with a few larger droplets of water [52].

It has been shown, perhaps not surprisingly, that neither adding proteins to the emulsions nor changing the ionic strength of the dispersed phase had any significant effect on the ease of emulsification or the stability of the resulting emulsion: differing concentrations of α-chymotrypsin, lysozyme, and alkaline phosphatase have been entrapped within the dispersed phase of water-in-silicone oil emulsions stabilized by comb silicone polyethers [54–58]. This suggested that the protein itself does not play an integral part in stabilizing the oil–water interface. However, confocal microscopy experiments of fluorescently labeled enzyme entrapped within the emulsion droplets clearly revealed that the proteins preferentially adsorb at the emulsion interface, placing them in intimate contact with the functionalized silicone [54]. Thus, although they do not measurably alter the properties of the interface, they are a constituent of it. An added property of the silicone polyether–based emulsion system is its selective permeability. Emulsions formulated using this surfactant allowed the free exchange of neutral species across the oil–water interface, while charged entities did not traverse the interface [58].

Generally, silicone oils and elastomeric surfaces are powerful denaturants for protein tertiary structure [59]. Enzyme assays for the entrapped protein revealed that despite the fact that the enzyme was adsorbed at the water-in-silicone oil emulsion interface and was therefore in contact with the functionalized silicone, the enzymatic activity was equal to or in some cases greater than that of the same enzyme in a buffered solution serving as a control [54–57]. Silicone polyethers are thought to partition at the oil–water interface with the poly(ethylene oxide) chains inserted into the dispersed aqueous phase anchoring the silicone spacers to the water–oil interface [60]. The poly(ethylene oxide) chains must act to passivate the water–oil interface for the proteins that reside there, a phenomenon that is well known on solid surfaces [61–64].

B. Enzymes Entrapped within Emulsions—TES-PDMS

It is possible to prepare functional silicone polymers that possess alkoxyisilane groups (RO-Si). Such species are often used for elastomer formation catalyzed by water, among other things (RTV, room temperature vulcanization). One such
polymer, triethoxysilyl-modified polydimethylsiloxane (TES-PDMS), is prepared by the hydrosilylation of commercially available H-Me2Si-terminated silicone (Scheme 3). This material, irrespective of molecular weight (MW 500–60,000) does not function as a surfactant that will stabilize w/o emulsions. Similarly, albumin (human serum albumin, HSA), a protein well known for its high surface activity, will not stabilize a water-in-silicone oil emulsion for extended periods [65,66]. However, the combination of TES-PDMS and albumin leads to the formation of stable water-in-D4 emulsions. At about 2–5 µm, particle sizes are comparable to those observed in emulsions stabilized with a silicone copolyol surfactant. These emulsions can be formulated on 5-mL (micro-mixer), 40-mL, and larger scales, and are stable on the order of 25–45 days, although greater stability has been observed in some cases [53].

Confocal microscopy experiments on the emulsions utilizing fluorescein-modified HSA (FITC-HSA) clearly demonstrate that the labeled protein adsorbs at the oil–water interface. HSA has been shown to preferentially adsorb at the interface even in the presence of a second protein [67]. Fluorescence spectroscopy experiments have revealed that although HSA is in intimate contact with the TES-PDMS and is subjected to a great deal of shear stress during the emulsification process, it retains its native conformation. These results suggest that the TES-PDMS serves as a physical buffer against the mixing stress being imparted on the system during emulsification, and further that the alkoxysilyl groups present at the termini of the TES-PDMS are hydrophilic enough to passivate the protein against spontaneous denaturation [67].

Model studies that examined the desorption of HSA from well-defined HSA/TES-PDMS films demonstrated that protein desorption occurred at a much slower rate with functional silicone, compared to normal PDMS of the same molecular weight [68]. In addition, angle-dependent X-ray photoelectron spectroscopy and contact angle measurements were consistent with the interpretation that very high affinity exists between HSA and TES-PDMS, similar perhaps to the case at a water–silicone oil emulsion interface [69,70].

HSA entrapped in silicone-modified starch microparticles displays very interesting immunological properties. The microparticles are easily prepared by precipitating a water-in-vegetable oil emulsion containing the HSA in acetone containing the silicone [71,72]. When silicone-modified starch microparticles containing HSA are orally or nasally administered to animal models, a Th2 antibody response is generated [73]. Enhanced antibody titers (IgG) were observed with the TES-PDMS-modified microparticles when compared to animal models immunized intraperitonally with unmodified starch microparticles, PDMS-coated particles, or HSA alone. Following oral delivery of the microparticles, HSA-specific IgA antibodies were isolated from the gut washings [74]. Both sets of results indicate that the protein-containing microparticles are a via-
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ble means by which to nasally, orally, or via the peritoneum deliver entrapped antigens for vaccination as a result of the protective nature for the protein by the functional silicone.

VI. NATURE OF THE INTERACTIONS NECESSARY FOR THE STABILIZATION

It is apparent from the experiments described above that proteins can act in concert with silicones of various types to stabilize water-in-silicone emulsions. The active surfactant varies from the silicone (e.g., added silicone polyether or amine-modified silicone), the protein (e.g., the emulsifiers in retinal repair), or a combination of the two as in the TES-PDMS albumin emulsions. While there is no clear evidence for the specific nature of the silicone–protein interactions, particularly in the latter case, the commercial amine-modified silicones provide some clues. These compounds, as with the proteins, are ionized at physiological pHs, such that they possess charged end groups, hydrophilic (PEO) linkers, and the hydrophobic silicone. It is conceivable that the TES-PDMS surfactant is building up a similar structure once combined with the protein, except that the protein must act as both the hydrophilic linker and the charged hydrophil. There is little evidence in our experiments that there is a direct covalent bond between the trialkoxysilane terminus and the protein. However, an ionic interaction between a hydrolyzed alkoxy silane (silanolate-SiO−·H3N+) and a protein-based quaternary ammonium ion cannot be ruled out. Research into exact nature of the protein–silicone interaction is ongoing in our laboratory.

VII. CONCLUSIONS

Silicone/water emulsions of a variety of structural morphologies are readily formed in the presence of appropriate surfactants: normally, these surfactants are silicone based. Water-soluble/dispersible proteins favor sitting at silicone–water interfaces and can facilitate emulsification on their own or in combination with other excipients. Many applications for such emulsions can be envisaged, including as immobilized enzymes, for biodiagnostics, and for drug delivery (or personal care products). In order to realize these goals, it is necessary to first understand more clearly the nature of the protein–silicone interaction and to optimize their characteristics.

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26. HLB = (molar% hydrophilic group in a surfactant)/5. Thus maximum HLB = 20 (100/5). Surfactants with HLB = 0 are completely water insoluble.


34. Dahms, G.H. SO¨ FW J. 1999, 125, 6.


40. We thank a referee for this helpful suggestion.


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Au/Ed: Please answer the following queries for Elaissari

Chapter 26

Q1. Title of article?
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