Design and Selection of Performance Surfactants

Edited by DAVID R. KARSA Akzo Nobel Surface Chemistry AB Manchester





ONO 2031, pg. 1 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219 First published 1999 Copyright © 1999 Sheffield Academic Press

Published by Sheffield Academic Press Ltd Mansion House, 19 Kingfield Road Sheffield S11 9AS, England

ISBN 1-85075-993-6 ISSN 1460-5711

Published in the U.S.A. and Canada (only) by CRC Press LLC 2000 Corporate Blvd., N.W. Boca Raton, FL 33431, U.S.A. Orders from the U.S.A. and Canada (only) to CRC Press LLC

U.S.A. and Canada only: ISBN 0-8493-9742-1 ISSN 1097-6973

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying or otherwise, without the prior permission of the copyright owner.

This book contains information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission, and sources are indicated. Reasonable efforts have been made to publish reliable data and information, but the author and the publisher cannot assume responsibility for the validity of all materials or for the consequences of their use.

Trademark Notice: Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation, without intent to infringe. No claim to original U.S.A. Government works.

Printed on acid-free paper in Great Britain by Bookcraft Ltd, Midsomer Norton, Bath

British Library Cataloguing-in-Publication Data:

A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data:

A catalog record for this book is available from the Library of Congress

ONO 2031, pg. 2 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

8 Fluorinated surfactants in practice

Charles K. Taylor

8.1 Introduction

Fascinating research concerning the fundamental understanding of surfactants and interfaces influences our world. This chapter gives a very brief review of the physical chemistry aspects of the behavior of fluorinated surfactants, and, with all due respect to Young, LaPlace, DuPré and Gibbs, focuses on the more practical aspects of using fluorinated surfactants in the real world. In commercial application, fluorinated surfactants are chosen for their unique characteristics-places where a 'conventional' surfactant is lacking in some performance aspect. They are not often used, alone, as pure components in 18 megaohm water; rather, they are used (most frequently as additives, in exceedingly small percentages) in the presence of hydrocarbon-based surfactants, resin systems, oxidants, dispersed phases (oils and solids), salts, acids, and the list goes on. Applications-based research aimed at the use of fluorinated surfactants is widening the understanding of how these materials function in the presence of the other necessary components of commercial formulations. The practitioners of this kind of research are rather secretive, for they believe that 'know how' in the use of fluorosurfactants provides them with competitive advantage-one that they would rather not share with competitors. Although fluorinated surfactants have been 'around' for about 40 years, studied extensively as independent entities, and widely used in consumer and industrial applications, a practical source of information about how and why they work is, hopefully, a useful addition to the literature.

8.2 Surfactants

Surface-active agents (surfactants, for short) have a role in nearly every biological, industrial and consumer process imaginable. The production of 'soap' by the saponification of animal fat with lye represents one of the earliest practiced chemical processes (commercially, and at home). It's no mistake that this process produced a surfactant that was used everywhere to provide the cleaning power needed for home and industry.

Surface-active molecules selectively aggregate or adsorb at interfaces. That is, they tend to concentrate where phase boundaries (liquid/solid,

> ONO 2031, pg. 3 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

272 DESIGN AND SELECTION OF PERFORMANCE SURFACTANTS

solid/gas, liquid/gas, or liquid/liquid) exist. In doing so, surfactants provide many useful functionalities, e.g. wetting, leveling, foaming, and emulsification. These observed behaviors are the result of the basic structure of a surfactant (represented in Figure 8.1). The minimum components include a hydrophobic 'tail', represented by the long line, and a hydrophilic 'head', represented by the oval.



Figure 8.1 Schematic drawing of a simple surfactant molecule.

8.2.1 The hydrophobe

A wide variety of surfactants are available. One means of classifying these compounds is by describing their hydrophobic 'tail'. The vast majority of commercial surfactants are derived from natural sources, and petroleum feedstock. The hydrophobic portions of this class of surfactants are primarily long-chain (C10-20) alkyl groups. This group of surfactants is referred to as 'hydrocarbon surfactants'. The second commercially important class of surfactants is silicon based. In this case, the 'phobe' is an alkyl silane or siloxane. Such silicone surfactants can offer performance that is quite different from their hydrocarbon analogs. The primary subject of this work is a third type of surfactant—a fluorinated surfactant—where the 'phobe' is a fluoroalkyl chain (typically C6-12). Although there are several sub-classifications, particular attention will be given to perfluorinated, or perfluoroalkyl, surfactants. At present, these represent the most widely used type of 'fluorosurfactant'

Surface-active materials with polymeric, or multiple hydrophobes also deserve mention. The study of 'polysoaps', the purposeful inclusion of hydrophobic segments in polymeric resin systems in coatings applications, and the use of fluorinated polyethers as surfactants are but a few examples of this interesting grouping.

8.2.2 The hydrophile

To understand how surfactants function it is also useful to classify surfactants by their hydrophilic 'head' group. In general, surfactants are either ionic or non-ionic. Ionic surfactants can, unlike non-ionic surfactants, dissociate into ions in an aqueous medium. The hydrophobic

> ONO 2031, pg. 4 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

part can belong to a negative or positive ion. Some surfactants have negatively and positively charged functional groups on the same backbone. An excellent and recent review of this topic, focused on fluorinated surfactants, is available [1]. Four general types exist.

8.2.2.1 Anionic surfactants

The hydrophobe is an anion, e.g. $RCOO^-Na^+$, where R is, for example, $C_{12}H_{25}$ alkyl. Four important sub-groups exist:

Carboxylates:	RCOO M ⁺
Sulfates:	$ROSO_3^- M^+$
Sulfonates:	$RSO_3^- M^+$
Phosphates:	$ROP(O)O_2^{2-}2M^+$

where R is the hydrophobe (alkyl, siloxane, or perfluoroalkyl), and M^+ an inorganic or organic cation. Anionic surfactants are, by a wide margin, the most widely used group of surfactants.

8.2.2.2 Cationic surfactants

The hydrophobe is a cation, e.g. $RCONH(CH_2)_3N^+(CH_3)_3 Cl^-$ where R represents the hydrophobe. Most cationic surfactants contain a hydrophobe connected directly or indirectly to a quaternary ammonium group, protonated amino group, or a heterocyclic base. They dissociate in water to form a surface-active positively charged ion and a negatively charged counterion.

8.2.2.3 Amphoteric surfactants

These have at least one anionic and one cationic group at their isoelectric point. They may function as either cationic or anionic surfactant, depending on the pH of the medium [2]. Amphoteric surfactants are often one of three types:

Carboxybetaine:	$RN^+Y^-(CH_3)_2(CH_2)_nCOO^-$
Sulfobetaine:	$RN^{+}Y^{-}(CH_{3})_{2}(CH_{2})_{n}SO_{3}^{-}$
Sulfatobetaine:	$RN^+Y^-(CH_3)_2(CH_2)_nOSO_2O^-$

In these examples, R represents the hydrophobe, Y^- an anion (e.g. chloride, sulfate, and acetate...).

8.2.2.4 Non-ionic surfactants

Non-ionic surfactants do not dissociate into ions in water. They are, generally, less sensitive to electrolytes and changes in pH, and more soluble in organic media. Further, they are widely compatible with other surfactant types. The hydrophile typically consists of polyoxyethylene segments. For a given hydrophobe, variation of the length of this hydrophilic chain is a ready means for modifying the characteristics of the surfactant. Example:

RCH2CH2O(CH2CH2O),H

where R is the hydrophobe, and n the number of oxyethylene groups.

8.2.3 Fluorinated surfactants without a hydrophile

One of the important differences between fluorocarbon and hydrocarbon surfactants is that the fluorocarbon surfactants can be surface active in hydrocarbon solvents. Surfactants are most often used in aqueous systems, where the presence of a hydrophilic group and a hydrophobic group gives rise to their amphiphilic character and aggregation behavior at phase boundaries. Fluorocarbons are also oleophobic. A molecule that is surface active in hydrocarbon solvents can be made by attaching an oleophilic segment to an oleophobic segment. This gives a system which behaves as an amphiphile in an organic solvent, and exhibits behavior analogous to 'normal' surfactants in aqueous systems. Examples of such systems would be block co-polymers of normal perfluorocarbons and hydrocarbons $F(CF_2)_n(CH_2)_m H [3]$, polymeric surfactants (HFPO)_nAr where (HFPO)_n is an oligomer of hexafluoropropylene oxide and Ar an aryl group [4] and fluoroalkyl esters such as Zonyl³⁰ FTS (a fluoroalkyl ester of stearic acid, sold commercially by E.I. DuPont de Nemours & Co.).

8.3 Fluorinated surfactants-general

Fluorinated surfactants are typically 5–20 times more expensive than their hydrocarbon or silicone counterparts, yet they enjoy widespread commercial use—with good reason. Substitution of fluorine for hydrogen in the hydrophobic portion of a surfactant drastically changes the properties of the surfactant and offsets the cost differences in practice [5]. The commercial significance of each of these properties will be discussed later in this work. Summarizing:

- The strong carbon-fluorine bond makes the hydrophobe of fluorosurfactants highly resistant to chemical and thermal attack. Thus, many fluorosurfactants enjoy use in applications where their hydrocarbon or silicone analogs would not survive.
- Fluorosurfactants lower the surface tension of aqueous systems below 20 mN/m, substantially lower than hydrocarbon surfactants.
- The concentration of fluorinated surfactant required to achieve these low surface tensions is 5-10 times less than would be required

for hydrocarbon- or silicone-based surfactants IF they could achieve this low surface tension. This is key to their economic success.

- The 'phobe' of a fluorosurfactant is both hydrophobic and lipophobic. This makes fluorinated surfactants effective in solvent systems, something not possible with other surfactants.
- If available, a fluorinated surfactant will preferentially adsorb on a gas interface (liquid/gas or solid/gas).
- Due to the nature of the hydrophobe (because it is also lipophobic), fluorosurfactants are ineffective as emulsifiers for hydrocarbon-based oils, but are extremely effective as emulsifiers for halogenated materials.

8.4 Preparation of fluorinated surfactants

Commercially important routes to create the fluoroalkyl hydro/oleophobic 'tail' of fluorinated surfactants are electrochemical fluorination (ECF), telomerization, and oligomerization of tetrafluoroethylene [5]. Also worthy of mention is the oligomerization of HFPO (hexafluoropropylene oxide) [6, 7].

8.4.1 ECF-Derived fluorosurfactants

The Simons process for electrochemical fluorination [8] is practiced on the largest scale. In this process, the organic substance to be fluorinated is dissolved or dispersed in anhydrous hydrogen fluoride and a voltage is applied that is sufficient for fluorination at the anode, but inadequate for fluorine evolution. All hydrogen atoms in the molecule are replaced by fluorine, but some functional groups, importantly, acyl and sulfonyl halides, are retained. The mechanisms of this reaction are not completely understood [9–12]. The fluorinated hydrophobe produced by the reaction is chiefly one homolog, e.g. perfluorooctyl sulfonyl fluoride derived from the corresponding hydrocarbon analog. The resultant carbon chain is largely linear, but some branching (15–30% of the chains, depending on reaction conditions) occurs due to carbonium ion rearrangements, which occur during the fluorination. The sulfonyl fluoride moiety can be functionalized in a number of ways to give a variety of commercially useful fluorosurfactants.

8.4.2 Telomer-derived fluorosurfactants

Telomerization of tetrafluoroethylene was developed as a commercial process by the DuPont Company [13, 14]. In the process of telomerization, a telogen (AB) reacts with two or more ethylenically unsaturated molecules (C) called taxogens:

ONO 2031, pg. 7 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

$$AB + nC \longrightarrow A \longrightarrow (C)_n \longrightarrow B$$

The original work was based on free-radical chemistry, but has since been expanded to include cationic-, anionic-, and metal-catalyzed telomerization. A number of improvements to the DuPont process have been patented (see Ref. [1], p. 31). The commercially important product of this reaction is a mixture of normal perfluoroalkyl iodides with an even number of carbon atoms:

$$CF_3CF_2(CF_2CF_2)_nI$$

Mixtures that are most useful as surface-active hydrophobes have an average n value of approximately 3. The strong electronegative character of the fluorine atoms restricts the reactivity of such perfluoroalkyl iodides with common nucleophiles. To generate intermediates that are synthetically useful for the preparation of surfactants and other uses, the iodide is reacted with ethylene to form the corresponding mixture of perfluoroalkyl ethyl iodides:

 $CF_3CF_2(CF_2CF_2)_nI + CH_2CH_2 \rightarrow CF_3CF_2(CF_2CF_2)_nCH_2CH_2I$

The partially fluorinated material so formed is used to produce a wide variety of materials for commercial surfactants, intermediates, and monomers for further modification. See Figure 8.2. Fluorosurfactants



Figure 8.2 Fluorinated surfactants derived from perfluoroalkylethyl iodides. R_f is a perfluoroalkyl group.

ONO 2031, pg. 8 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219 derived from the telomerization route differ from those prepared by the ECF route. Qualitatively, the differences are:

- Since the products contain a variety of fluorinated chain lengths, a clear CMC (critical micelle concentration) is not apparent when the surface tension of solutions of the surfactants is measured versus concentration in aqueous or hydrocarbon solvent systems.
- The fluorocarbon chains are all linear. They will generally 'pack' more densely at interfaces to produce slightly lower surface tension values, and generally have an increased propensity to foam, compared to branched-chain fluorosurfactants derived from ECF intermediates.
- The hydrocarbon segment reduces the resistance of the molecule to chemical and thermal degradation, making it more susceptible to oxidation and other sometimes-undesirable reactions. In one sense, this is favorable in that the hydrocarbon segment of the fluorosurfactant molecules partially degrade in the environment. A more complete treatment of this subject appears in the comprehensive review ([1], p. 415). In free-radical preparations, the hydrocarbon segment is more susceptible to chain transfer reactions.
- The acid strengths of the perfluoroalkyl sulfonates, carboxylates, and phosphates (ECF-derived) is significantly greater than that of the corresponding β-perfluoroalkyl analog (telomer products) [15, 16]. Correspondingly, this difference in degree of dissociation as a function of pH in a particular application will change the way in which the surfactant will behave.

8.4.3 Oligomerization of tetrafluoroethylene

ICI developed an anionic polymerization process for the oligomerization of tetrafluoroethylene [17] catalyzed by a metal fluoride. The products of this process are highly branched oligomers, principally the pentamer, which contain an olefnic bond that can be used to further functionalize the intermediate to form useful products [18]. Because of the branched nature of the fluorocarbon that results from this synthetic scheme, these products are unique, compared to the largely normal chain surfactants derived from either ECF or telomer-based chemistries.

8.5 Distinguishing characteristics of fluorocarbon surfactants

As stated earlier, fluorosurfactants have unique attributes, which permit their use in a broad spectrum of commercial applications. Summarizing:

> ONO 2031, pg. 9 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

278 DESIGN AND SELECTION OF PERFORMANCE SURFACTANTS

The strength and low polarizability of the carbon-fluorine bond largely precludes chemical or thermal attack. The ionic radius of fluorine is well suited to shielding the carbon nucleus from chemical attack, and induces relatively little steric stress; however, it does make the perfluoroalkyl backbone relatively rigid compared to analogous hydrocarbon counterparts [19]. This rigidity, coupled with the relatively large molecular volume swept out by a fluoroalkyl moiety is a very important aspect of the adsorption and aggregation behavior of fluorosurfactants. In a way, this can be thought of as a Bernoulli buoyancy effect [20]. Fluorocarbon surfactants show a lower affinity for water (and thus, a larger driving force to aggregate at phase boundaries) than their hydrocarbon counterparts. The mixing of hydrocarbon chains and fluorocarbon chains is unfavorable. A number of studies of mixed surfactant systems [21] show exclusivity in micelle formation and composition, and the debate is far from settled [22, 23]. Another key outcome of this reluctant miscibility is that fluorosurfactants are poor emulsifiers of hydrocarbons, a facet of their behavior that is widely exploited commercially.

8.6 Behavior of fluorosurfactants in aqueous systems

Oualitatively, dilute solutions of fluorosurfactants behave similarly to corresponding solutions of hydrocarbon- or silicon-based surfactants in water. They are solvated at low concentration, and tend to aggregate at phase boundaries (liquid/solid and especially liquid/air). As the concentration is increased, more of the material collects at the interfaces, and surface tension is reduced as a function of that concentration. At some concentration, the surface excess of adsorbed surfactant reaches a maximum value, and further addition of surfactant results in the formation of tiny (generally of the order of 10-100 molecules) selfassembled structures called micelles, which are dispersed in the water. This concentration is referred to as the CMC or critical micelle concentration-being defined as the lowest concentration at which micelles will form. By this definition, fluorosurfactants are much more effective than a hydrocarbon or silicon surfactant with the same carbon chain length [24]. Addition of surfactant beyond the CMC, for the most part, serves only to increase the concentration of the micelles. The value of the CMC is important in that it is a measure of the effectiveness of the surfactant. It is desirable commercially to have the smallest quantity of added surfactant to achieve the lower limit of surface tension. The CMC for a specified hydrophile is a function of the chain length of the hydrophobe at a given temperature, pH, counterion, and ionic strength.

> ONO 2031, pg. 10 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

This is quite effectively demonstrated by the data for anionic carboxylate fluorosurfactant series shown in Figure 8.3.



Figure 8.3 Surface tension for an homologous series: F(CF₂)_nCOO⁻NH₄⁺.

The explanations for the observation that fluorosurfactants are more effective than their hydrocarbon or silicon counterparts are based on two workable hypotheses:

- The argument that the surface of an aqueous surfactant with an adsorbed monolayer of surfactant behaves like the corresponding liquid made up of the hydrophobe (that is fluorocarbons cf. alkanes, with the surface tension of pure fluorocarbons being lower than that of hydrocarbons).
- 2. The lower surface tension is simply a result of their stronger adsorption at concentrations below the CMC.

ONO 2031, pg. 11 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

280 DESIGN AND SELECTION OF PERFORMANCE SURFACTANTS

In addition to the effect of carbon chain length of the hydrophobe, there are other important factors, which influence the CMC of a surfaceactive material. The CMC for a given hydrophobe (say, $C_7F_{15}COO^-$) is dependent on the counterion (or, more generally, the structure of the hydrophilic portion of the molecule), the pH of the solution, the ionic strength of the medium, the temperature, the structure of the hydrophobe (e.g. branched cf. normal-chain configuration of the fluorocarbon), and more. This topic has been extensively reviewed in the literature, most recently by Kissa ([1], chapter 4).

8.7 Dynamic surface tension-the kinetics of fluorosurfactants

Up to this point, the discussion of the behavior of fluorinated surfactants in solution has been centered on observations of the vapor/liquid boundary at equilibrium. The minimum surface tension (achieved at or above the CMC) is dependent on:

- 1. The number of surfactant molecules adsorbed per unit area.
- 2. The surface energy of the layer adsorbed at the interface.
- 3. The free energy of adsorption of a surfactant molecule at the surface of the liquid, from the bulk solution.

In the real world, the time required to decrease the surface (or interfacial) tension to some desired value is a very significant aspect of performance for a surfactant. Unfortunately, the real world does not wait for equilibrium. Consider, for example, the commercial process of putting a thin liquid coating on a piece of plastic sheeting. Typical manufacturing line speeds are approximately one meter per second (and can be much faster!). On a surface three meters wide, three square meters of new vapor/liquid interface are being created per second. Actually, another three square meters of a new interface are being created at the same time—the interface between the liquid and the plastic sheeting. Surfactant adsorption at condensed phase boundaries (liquid/liquid and liquid/solid) is discussed in subsequent sections.

The time needed to reduce surface tension depends on the processes involved in adsorption of the surfactant at the surface [25]. The first of these is transport of the surfactant to the surface, and the second is the orientation of the surfactant in an energetically preferred geometry. The first step is the slower of the two, and is a function of the concentration (the higher, the faster...) and hydrodynamic driving force. At concentrations above the CMC, the kinetics of the reversible formation and breakup of the micelles must also be considered. That is, as the bulk phase is depleted of 'solvated' surfactant (now adsorbed on the interfaces

> ONO 2031, pg. 12 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

of the system), the micelles act as 'reserves' of sorts, and replenish the bulk phase by dissociating. Miller [26] proposed a model which takes the kinetics of this process into account, building on the earlier work of Aniansson [27–29]. Shah [30] has recently updated this work with experimental methods designed to estimate residence time of surfactant molecules in micelles, and average lifetime of a micelle.

In general, the time required to achieve equilibrium surface tension is increased with increasing fluoroalkyl chain length, and by reducing surfactant concentration. It is dependent on the effective cross-section of the adsorbed surfactant, and the solubility of the components in mixed systems. Fractionation of the surfactant species can occur at concentrations above surface saturation, with normal chain species (which have smaller adsorbed cross-sectional areas per molecule) adsorbing preferentially to branched-chain isomers [31]. This work, again, is reviewed in more depth in Kissa's recent monograph [1].

Decreasing temperature also slows the attainment of equilibrium surface tension, and for a given hydrophobe, the rate is dependent on the counterion (or, in the case of non-ionic surfactants with polyoxyethylene or polyoxypropylene segments, the length of that chain...). The presence of impurities, cosurfactants, solvents and other surfactants also affect the adsorption rate. The effect of some of these substances in hydrocarbon systems is the subject of active research, and recent papers by Shah and Shiao [30, 32, 33] provide interesting insights into interactions of this type. These authors use a variety of techniques to map the effects of such additives, and observe the effects on dynamic surface tension, and the related phenomena of foaming, wetting, emulsification and detergency. Unfortunately, analogous data are not yet available for fluorinated systems.

Examples of dynamic surface tension measurements for two of the DuPont Zonyl[®] fluorosurfactants, Zonyl[®] FSO a non-ionic fluorotelomer ethoxylate of the formula $R_{f}CH_{2}CH_{2}O(CH_{2}CH_{2}O)_{a}H$ (Figure 8.4) and Zonyl[®] FSJ a phosphate of the formula $(R_{f}CH_{2}CH_{2}O)_{x}PO(ON-H_{4}^{+})_{y}(OCH_{2}CH_{2}O)_{x})$ (where $R_{f} = F(CF_{2}CF_{2})_{3.8}$, $n_{av} = 3$, $a_{av} = 7$ and x + y + z = 3) are shown below. The charts clearly show the dependence of surface tension on the age of the surface, and on the concentration of the surfactant. The fluorocarbon hydrophobes of these surfactants are quite similar, but their dynamic surface tension behaviors are not.

As stated above, the kinetics of adsorption and the resultant reduction in surface tension depend on the structure of the surfactant. Fluorination of the hydrophobe increases the rate of surface tension decrease, but the time required to attain equilibrium does not often differ greatly from the hydrocarbon analog. For example, 0.1% solutions of sodium

ONO 2031, pg. 13 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219



Figure 8.4 Surface tension vs. surface age for Zonyl[®] FSO.

perfluorooctyl sulfonate and sodium octanesulfonate reach equilibrium surface tension in about 15 h, but the surface tension of the solution of the fluorinated sulfonate is nearly 30 mN/m lower after one minute (40 mN/m cf. 70 mN/m) [34]. From a commercial standpoint, such comparisons are unfair, since the cost of the surfactant needed to achieve the desired results must be considered. The cost of a 'typical' fluorinated surfactant is approximately 25 times that of an ordinary hydrocarbon surfactant on a weight basis, and 60 times that on a mole basis. As stated before, the cost is often offset by significant performance advantages, and the increase in the efficiency of fluorinated surfactants, and there are tradeoffs.

> ONO 2031, pg. 14 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.5 Surface tension vs. surface age for Zonyl[®] FSJ.

In most places where fluorinated surfactants are used, they are added to products and materials that contain hydrocarbon-based surfactants to provide an optimum benefit to the formulated system from a cost standpoint. In aqueous formulations, this most often means using a relatively large percentage of hydrocarbon surfactant, with smaller quantities of fluorosurfactants added. This approach to formulation of, say, an aqueous coating (coating being here defined as anything relatively thin and most often applied to a solid surface, e.g. floor polish, paint, adhesives, varnishes, inks, etc.) with these two types of surfactants has a number of potential advantages:

> ONO 2031, pg. 15 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

- Less hydrocarbon surfactant is needed to achieve the desired surface tension.
 - This 'leaves room' in the formulation for other ingredients.
 - There is less residue on evaporation.
 - Wastes and residues contain less material, reducing the cost of waste treatment.
- Lower equilibrium surface tensions are possible, and improvements in dynamic surface tension performance are often observed. A more detailed discussion follows below.
- Fluorosurfactants tend to dominate the air interface, reducing surface tension. Hydrocarbon surfactants tend to adsorb more strongly at the condensed phase interfaces, so that in a coating application, there is a fractionation. (See Figure 8.6 in which the surface (1/v) tension and interfacial (1/1) tension of solutions of mixtures of Zonyl[®] FSA (anionic carboxylate) and Merpol[®]A (non-ionic hydrocarbon surfactant) are measured. The total surfactant concentration is held constant. Note that surface (1/v)tension is lowest when only fluorosurfactant is present, and that the interfacial tension is lowest when only hydrocarbon surfactant is present.) A similar example, for a mixture of an ECF surfactant (ammonium perfluorooctanoate) and a sodium di-octyl sulfosuccinate (Aerosol®OT), is given in Figure 8.7. Wetting and adhesion to a substrate are important aspects of a coating's performance, and this occurs where the liquid meets the solid surface. Reducing the surface tension at the upper boundary of the coating (where the fluorinated surfactant dominates) is equally important, as it is at this visible interface that surface tension gradients give rise to a number of defects such as Benard cells, picture framing, etc. Adsorption of surfactant at this upper interface also affects the wettability of the resultant surface, an important consideration in applications where multiple coatings are desired.

8.8 Dynamic surface tension in mixed systems

The mixture of hydrocarbon and fluorocarbon surfactants can have a very positive effect on the dynamic surface tension characteristics of formulated systems. Hirt and co-workers published the effect of mixing Tergitol[®] NP-10 (nonylphenol with 10 oxyethylene units, manufactured by the Union Carbide Corp.) with Zonyl[®] FSN (non-ionic fluorinated surfactant) [35]. At equivalent molar concentrations, the system exhibited lower dynamic surface tension values than either of the component surfactants alone. This is but one example, where both types of surfactant

ONO 2031, pg. 16 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.6 Surface and interfacial tensions for aqueous mixtures of $Zonyl^{26}$ FSA and $Merpol^{16}$ A. $a = Zonyl^{26}$ FSA, lot 2; $b = Merpol^{16}$ A, lot 175.

were non-ionic. The permutations of this experiment are virtually limitless when one considers the variety of surfactants available, and the possible combinations of anionic, cationic, non-ionic, and amphoteric hydrophiles with hydrocarbon, silicon, and fluorocarbon hydrophobes. Two more examples of this type of experiment are shown in Figures 8.8 and 8.9. In the case where the hydrocarbon is an alcohol ethoxylate (Merpol[®] SE), the synergy is excellent. In the case where the hydrocarbon surfactant is a non-ionic phosphate (Merpol[®]A) the synergism is evidenced by low surface tension at nominally 'half' the fluorine content.

> ONO 2031, pg. 17 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.7 Surface and interfacial tensions for aqueous mixtures of R_fCOONH_4 and Aerosol[®] OT. $a = R_fCOONH_4$, b = Aerosol[®] OT.

8.9 Foams

Some types of surfactants are useful in generating 'stable' foams. Foam will not form in a liquid that does not contain impurities; some manner of surface-active agent is required. Examples of foaming agents include (in addition to surfactants) fine particles, solutes, and polymeric materials. Foam can be described as a dispersion of a gas in a liquid. Interactions at the l/v boundary dominate this type of system, as every bubble has both an internal and an external l/v boundary, and the surface area is large. Solid foams, commonplace in our world, were once simply liquid foams.

ONO 2031, pg. 18 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.8 Surface tensions vs. surface age for 0.10% Zonyl[®] FSO, 0.10% Merpol[®] S and 0.05% Zonyl[®] FSO-100/0.05% Merpol[®] SE.

Fluorosurfactants, with their marked affinity for the l/v interface [36] are particularly well suited to this function. Indeed, the tendency of solutions of fluorosurfactants to foam is the curse of many practical applications; it's simply not wanted or needed in many places.

Foam forms as gas attempts to exit a bulk liquid (see Figure 8.10). The thin film of liquid is stretched as the gas 'rises'. If no mechanism is in place to strengthen the thin parts of the film, the areas will thin until the film ruptures.

As the film stretches, new surface area is being created in the region; the new surface forms rapidly, and the rate of transport of surfactant

287

ONO 2031, pg. 19 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219 288

Figure 8.9 Surface tensions vs. surface age for 0.10% Zonyl $^{\aleph}$ FSO, 0.10% Merpol $^{\aleph}$ A and 0.05% Zonyl $^{\Re}$ FSO-100/0.05% Merpol[®] A.

to the interface from the bulk liquid becomes quite important. (See the discussion of dynamic surface tension effects in the previous section.) Diffusion of the surfactant does not have time to reach an equilibrium state of adsorption, and the concentration of adsorbed species in the thinned sections is higher; hence the surface tension in that region is higher. The system will move to oppose this thinning, towards equilibrium, by moving surfactant molecules toward the area of higher surface tension (lower adsorbed surfactant concentration). This will also drag molecules of solvent (the 'solvation shell' of the 'phile' of the surfacatnt) along [37]. These phenomena are dynamic in nature, and are called Gibbs-Marangoni effects. Figure 8.11 illustrates this phenomenon.

ONO 2031, pg. 20 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.10 Gas bubble escaping a liquid, and stretching a film of liquid across its surface.

Figure 8.11 Movement adsorbed surfactant molecules to oppose a concentration gradient. This phenomenon has the net effect of moving to 'heal' a thinning in a film.

Foams are thermodynamically unstable, and once formed, will eventually break. The stability of a foam is, simplistically, dependent on the drain rates of the thin films, and the substantivity of the adsorbed layer of surface-active material. On a macroscopic scale, drain rates of the lamellae (thin film of liquid) are highly dependent on viscosity. As the lamellae thin, other shorter-range interactions with the 'solvation shell' of the head of the surfactant become important (a portion of the honeycomb-like structure of a foam is represented in Figure 8.12):

• As the film thins, the heads of the surfactants, which may be charged, get closer to one another, and the repulsion of like electrical charges opposes further thinning. In general, ionic and amphoteric surfactants have greater tendencies to form tenacious foams than their non-ionic analogs, for this reason.

ONO 2031, pg. 21 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.12 Drainage and stability of films. This shows a cutaway of a bubble structure with surfactant molecules adsorbed at the I/v boundary. Steric and ionic repulsion opposes thinning of the film.

• The 'phile' of the surface-active material retains a solvation shell of solvent, restricting movement, and thus drainage.

Another way of altering the stability of a foam is to change its surface viscosity, i.e. the tenacity of the adsorbed layer of surface-active materials:

- The use of mixed surfactant systems (see Figure 8.13). For example, mixing anionic and non-ionic surfactants results in a mixed monolayer which increases surface viscosity. The molecules can pack more densely due to a reduction in charge repulsion compared to an anionic surfactant alone. Mixing in 'twin-tailed' surfactants, those having two (or more) hydrophobic tails can increase the spacing through steric means, and decrease the resistance to stress (see Figure 8.14). A good example of this is Zonyl[®] FSP, a mixture of the ammonium salts of mono- and bis-fluorocarbon phosphates. Although it is an anionic fluorosurfactant, it foams relatively little compared to other commercially available anionic fluorosurfactants. Foaming varies with pH (see Table 8.1).
- Induce formation of extended structures at the interface. In a sense, this is holding together the adsorbed layer through the means of chemically bonded backbones. Good examples here would be 'polysoaps' [38, 39], fire-fighting foams, and the foam head on a glass of beer, which is really a polymeric protein/polysaccharide complex (see Figure 8.15). Viscosification, and the use of polymeric surface-active agents is critical in the foaming of hydrocarbon solvents, whose lower intrinsic surface energies and lower viscosities tend to preclude the formation and stabilization of foam structures.

ONO 2031, pg. 22 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.13 Schematic of anionic surfactant (upper layer) and mixed non-ionic/anionic surfactant (lower layer) representing the difference in spacing achieved due to a reduction in electrostatic repulsion.

Figure 8.14 Schematic of a mixture of anionic surfactants, some with one hydrophobe, some with two, representing the increased spacing that results from steric considerations.

Table 8.1 Ross-Miles foaming test (ASTM) for DuPont Zonyl® Fluorosurfactants at 41°C

Product name	Deionized water	pH 4 buffer	pH 7 buffer	pH 10 buffer		
	Ross-Miles Foam Height (mm)					
ZONYL [®] FSE	85	65	25	10		
ZONYL [®] FSJ	155	55	40	80		
ZONYL® FSN	145	140	130	145		
ZONYL [®] FSO	100	75	75	30		
ZONYL ^ℜ FSP	25	20	25	20		

8.9.1 Avoiding or eliminating foams

In many applications, chemical processes, and especially in coatings, foam generation is a nuisance, and to be avoided at all costs. Materials used to prevent or 'break' foams are called either antifoaming agents or defoaming agents; most commercial agents act in both ways. Foaming

> ONO 2031, pg. 23 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Anionic hydrophilic segments

Figure 8.15 Schematic representation of a surface-active substance with the backbone of the hydrophiles linked in a long chain. Examples of this include polysoaps and protein structures.

difficulties are most often encountered in aqueous systems, and will be the focus of the discussion which follows.

A common way of preventing the formation of foam is to add a waterinsoluble surfactant or liquid to the system, which forms a monolayer on the surface of the solution. In the case of a water-insoluble surfactant (see Figures 8.16a and 8.16b, which depict the sequence of the escape of a bubble with an adsorbed layer of water-soluble surfactant from a liquid with an adsorbed layer of a water-insoluble surfactant) as the bubble thins the liquid layer to escape, the Gibbs–Marangoni effect, which would tend to resist this thinning (see above) is not effective. Displaced surfactant on the outer layer of the film is not replaced from the bulk liquid (very limited availability due to limited solubility).

Another way of precluding foam formation, or reducing foam stability is to add a water-insoluble liquid or solid to a system. To be effective, liquids (or particles) that are insoluble in the coating medium must go to the l/v boundary, and spread to displace the foaming agent. The behavior of these materials does not parallel Gibbs-Marangoni effects observed for water-soluble surfactants. They act by causing dewetting around the droplet or particle, and subsequent rupture of the film (see Figure 8.17). Examples of materials used for this purpose include silicones, fatty acids, long-chain alcohols, dispersions of waxes or hydrophobic silica, alkyl phosphates, and polypropylene glycols.

In the case of coatings, the presence of an insoluble surfactant can have important effects on adhesion and rewet of subsequent layers of coatings. The presence of the insoluble material at the top layer of the film/coating, since it has relatively low water solubility (that is, low surface energy) makes wetting the resultant substrate difficult. This topic will be discussed more fully in the section on wetting.

> ONO 2031, pg. 24 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.16 (a and b) Escape of a gas bubble from a liquid containing a water-soluble and a water-insoluble surfactant. The film of the insoluble surfactant is weakened by stretching and thinning, and ruptures.

ONO 2031, pg. 25 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

294 DESIGN AND SELECTION OF PERFORMANCE SURFACTANTS

Figure 8.17 Representation of the interaction of a thin liquid film with an insoluble particle or droplet. Devetting occurs at the intersection of the film with the droplet, a weak point in the film.

8.9.2 Reducing foaming with mixtures of surfactants bearing opposite charges

In the previous section, it was noted that the foaming tendency of surfactant systems could be either enhanced or diminished by a choice of surfactants. Binary mixtures of cationic and anionic fluorosurfactants have shown in our laboratories, a remarkable capability to reduce foaming in aqueous systems. Figure 8.18 shows the foaming behavior for mixtures of Zony¹⁰⁰ FSD (a cationic fluorosurfactant) and Zony¹⁰⁰ FS-62 (an anionic fluorosurfactant). The results of Ross-Miles foam tests (ASTM Method D-1173-53) at pH 5, 7, and 9 are shown for mixtures of the two surfactants at 0.05% w/w total concentration. Foam heights appear as vertical bars on the charts, and are scaled on the left ordinate. Surface tension values for the system are depicted by the superimposed line chart, and are scaled on the right ordinate. Three things are quite clear:

- 1. Mixing the surfactants reduces the propensity of the system to foam.
- 2. Mixing the surfactants lowers the surface tension of the solution.
- 3. The phenomenon is pH dependent.

The reason for this behavior has not been fully elucidated. Possible hypotheses include:

- the fact that the mixture has relatively low solubility, and may act as a defoamer,
- kinetically, such a surfactant might not be able to diffuse to the surface quickly enough to support foaming behavior, or
- the surface tension vs. concentration gradient is not large enough to provide the necessary resistance to film thinning by Gibbs--Marangoni movements. Figure 8.19 illustrates this point. Ross--Miles foaming results for 0.1% solutions of the mixed surfactants in deionized water are shown as bars, and scaled on the left ordinate. Surface tension measurements for the system at 0.1%

ONO 2031, pg. 26 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.18 Ross-Miles foam height and surface tension measurements for aqueous solutions

Figure one reasonable out in legit and surface tension measurements for aqueous solutions of binary mixtures of Zonyl³⁶ FSD (cationic fluorosurfactant) and Zonyl³⁶ FS-62 (anionic fluorosurfactant) in deionized water.

(bottom curve), 0.01% (middle curve), and 0.001% (top curve) w/w show that, for the 1:1 mixture of FSD and TBS, the variation of surface tension with concentration is slight. This is also the mixture that foams the least.

It is perhaps even more significant that this phenomenon is also observed in mixtures of cationic fluorosurfactants with anionic hydrocarbon surfactants. The converse is also true, that is, the behavior is also observed in mixtures of cationic hydrocarbon surfactants and anionic hydrocarbon surfactants. The synergism of 'catanionic' mixtures of

> ONO 2031, pg. 27 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

296

Figure 8.19 Ross-Miles foam height at 0.1% and surface tension measurements vs. concentration for mixtures of Zonyl[®] FSD and Zonyl[®] FS-62.

surfactants, with both fluorocarbon and hydrocarbon hydrophobes has been noted by a number of researchers (e.g. [40-45]). These mixtures not only lower surface tension relative to their component parts, *but lower interfacial tensions as well*. These researchers concluded that the strong interaction between the oppositely charged ionic surfactants overpowered the mutual phobicity of the hydrocarbon and fluorocarbon hydrophobes, and is much stronger than the interactions seen between ionic and nonionic surfactants. Figure 8.20 shows surface tension measurements of a cationic hydrocarbon surfactant Avitex⁴⁶ E mixed with an anionic fluorosurfactant Zonyl⁴⁶ TBS. This figure is similar to Figure 8.18; foam heights (Ross-Miles) and surface tension (DuNuoy) values are shown for

> ONO 2031, pg. 28 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

mixtures of the two surfactants at different pH. The results are similar to those observed in the fluorocarbon-fluorocarbon 'catanionic' mixed surfactant experiments. It is significant that the addition of a relatively

Mass Fraction TBS in pH 5, Deionized Water, and pH 9

Figure 8.20 Mixed surfactant system of Avitex[®] E and Zonyl[®] TBS at variable pH.

small quantity of an inexpensive hydrocarbon quaternary ammoniumbased surfactant provides remarkable performance benefit for the fluorinated surfactant. This phenomenon has been observed in a number of analogous systems in our laboratories. In fact, in several of these systems, the surface tension values of mixed surfactant species are observed to be lower than that of the fluorosurfactant alone (at a much lower fluorine concentration) at concentrations below 0.005 wt%. (See Figure 8.21, where the surface tension of a hydrocarbon phosphate, Zelec[®] TY is compared to that of a fluorocarbon quaternary ammonium salt Zonyl[®] FSD and mixtures of the two.) Note that within the concentration range tested, the amount of added phosphate (which isn't terribly surface active on its own) didn't alter the results. This is likely due

> ONO 2031, pg. 29 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

298

Figure 8.21 Surface tension (DuNuoy ring method) of aqueous solutions of mixtures of Zonyl[®] FSD (cationic fluorosurfactant) and Zelec[®] TY (hydrocarbon phosphate) in deionized water at ambient temperature.

to the substantially lower molecular weight of TY (and thus, large molar excess) added in each case.

The fact that surfactants are most often used as mixtures has shifted (and accelerated) the emphasis of research, academic and industrial, on

> ONO 2031, pg. 30 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

this topic. The volume of publications around this issue is growing at a fast pace. This interest is fueled by the fact that surfactant efficiency is enhanced in mixed systems, and less material is needed to achieve the same result. The impact of understanding these phenomena on cost and environmental issues is large. The subject has been recently reviewed [46], and this monograph provides an excellent place to explore many facets of the behavior of mixed surfactant systems. Further, the body of scientific knowledge concerning the interactions of surfactants with polymers (resins) continues to grow, and information about these complex systems is becoming available.

8.10 Fluorosurfactants and condensed-phase interfaces

To this point, much of the discussion has centered around the adsorption of surfactants and its effect on surface tension at the liquid/vapor (l/v) boundary. As previously stated, fluorosurfactants tend to aggregate at this interface [36]. The l/v interface is key to the appearance of coatings and films, the rewet characteristics of coatings and films, and foaming. In commercial application of surfactants, the condensed-phase boundaries, liquid/solid (l/s) and liquid/liquid (l/l) are at least as important. Condensed-phase interfaces dominate considerations in emulsions (mixtures of immiscible liquids), dispersions (solids suspended in liquids), and the wetting of solid surfaces. In popular convention, these boundaries are referred to as interfaces, and the term 'interfacial tension' is used to describe relationships at the dividing plane between the two phases. Actually, in the presence of surfactants, condensed-phase interfaces have a boundary layer of adsorbed surfactant that changes the way in which the two substances interact.

8.10.1 Fluorosurfactants at the liquid/liquid boundary

Interactions at a liquid/liquid (1/l) interface are complicated compared to those at the 1/v boundary. The basic system is the contact area of two immiscible liquids. More frequently encountered in practical application are emulsions, where there is a continuous phase, and a dispersed phase. Three-phase systems are also possible, but are less frequently used. The liquids involved are most often water, hydrocarbon solvent, or a halogenated liquid. Commercially, the most common of such systems are emulsions, where water is the continuous phase, and an oil (usually hydrocarbon), is dispersed in it. Other common systems where two

> ONO 2031, pg. 31 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

immiscible liquids are mixed include: dispersions of water in a continuous oil phase, dispersions of halogenated liquids in water, and dispersions of halogenated liquids in a hydrocarbon solvent.

In most systems, the observed behavior is complicated by a plethora of factors, including the mutual solubility of the liquid phases, the partitioning of the surfactant between the two phases, the orientation of the surfactant at the phase boundary, and other additives in the formulation. The theoretical aspects of interfacial tension have been reviewed in a number of publications [47, 48]. In practical terms, interfacial tension is a very important consideration in the formation of emulsions, spreading of liquids on liquids, and wetting.

8.10.2 Emulsions

The formation of stable emulsions is of particular interest in practical application. The formation of a stable emulsion requires the input of energy (work) into the system to create the interface, and maintaining the large interface requires a very low interfacial tension between the two phases, because of the tremendous area of interface that is created. Consider the example of a container of an oil and vinegar salad dressing, where the contact area between the two phases is rather small. Input of energy into the system (shaking the container) results in an emulsion (small drops of oil dispersed in the aqueous (vinegar) phase) which spontaneously collapses back to a simple two-phase system in the absence of further agitation. Addition of a surfactant (often lecithin in practice) to the system increases the stability of this emulsion; shaking the container now gives an emulsion that is quite persistent, compared to the simple oil and vinegar system.

Two phenomena, gravitational separation (the tendency of the less dense phase to rise to the top of the mixture), and coalescence (the tendency for the droplets to join together, reducing the area of the interface, and increasing the individual droplet size) are driving forces in the separation of an emulsion. In practical terms, the stability of an emulsion, that is the time required for the dispersion to revert to the simple two-phase liquid system is dependent upon four factors (at a given temperature):

- The relative density of the two phases. It would be optimal for both phases to have the same density. This decreases the tendency of the system towards gravitational separation.
- 2. The droplet size. The smaller the better, reducing the tendency for gravitational separation. The lower limit of this phenomenon would be called a microemulsion, which is basically a structured

ONO 2031, pg. 32 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219 liquid with interfacial tensions nearing zero; that is, an emulsion in thermodynamic equilibrium [49]. There is some evidence that microemulsions are actually bicontinuous.

- 3. The viscosity of the system. In general, the higher the better. This reduces the movement of the dispersed phase, which both slows gravitational separation and reduces the number of droplet collisions that promote their coalescence.
- 4. The interfacial tension in the system. This is where the surfaceactive material plays the key role, moderating the interaction between the two phases in a number of ways.

The orientation of surfactant molecules at the surface of a droplet of oil (non water-soluble) in an aqueous medium (continuous phase) is represented by Figure 8.22. As shown, the diagram represents a twodimensional section cut from a spherical droplet. If the earlier convention of representing the hydrophilic head of the surfactant with a circle, and the hydrophobic tail of the surfactant is again used, it can be seen that the hydrophobic 'tails', which are partially solvated by the oil reside in the droplet, and the hydrophilic 'head' of the surfactant presents to the aqueous phase.

Surfactant molecules reduce the energy required to generate the formation of this type of interface since it is thermodynamically favorable for the surfactant to aggregate, adsorb, and orient in the boundary layer.

Figure 8.22 Cutaway schematic diagram of a surfactant adsorbed at the interface of a hydrophobic droplet dispersed in aqueous medium.

ONO 2031, pg. 33 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

302 DESIGN AND SELECTION OF PERFORMANCE SURFACTANTS

Presuming sufficient quantities of surfactant are added, creation of more interfacial area provides a place for the surfactant molecules to aggregate. In the absence of such a layer of adsorbed surfactant, the molecules at this boundary are exposed to a non-uniform environment which is energetically unfavorable, and the system will move to reduce the area of this interface through coalescence, ultimately reverting to a simple twophase liquid.

The boundary layer of adsorbed surfactant may also serve to hinder coalescence through electrostatic or steric means. In the case of an ionic surfactant, the electrostatic repulsion of like charges opposes the close approach of two droplets, and reduces the number of collisions that produce coalescence. Figure 8.23 gives an example. What's shown is a two-dimensional cutaway of a spherical droplet, with an adsorbed layer of an anionic surfactant. The counterions (cations) are in the hydration shell that surrounds the particle, and when the two approach one another, electrostatic forces tend to keep them apart. In the case of nonionic surfactants, stabilization towards coalescence is more influenced by steric considerations, helping the droplets to resist deformation in collisions that can lead to coalescence.

Fluorinated surfactants are widely used as emulsifiers for fluorinated monomers, e.g. tetrafluoroethylene, in the preparation of polymeric materials [50]. The use of fluorosurfactants as emulsifiers of halogenated

Figure 8.23 Schematic of two droplets with an adsorbed layer of an anionic surfactant (cations in the 'hydration shell') being held apart by electrostatic repulsion.

materials has also been explored because of the medical possibilities that fluorocarbons emulsified in water present: these systems have the capacity to dissolve oxygen, and thus present fluid emulsions with low surface tension and low viscosity that can be used as blood substitutes for transfusion and organ perfusion [51].

> ONO 2031, pg. 34 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Although fluorosurfactants produce low interfacial tensions in interactions between fluorocarbons and water, they are not particularly effective in reducing the interfacial tension between water and hydrocarbon oils. This is intuitive, if one considers the orientation of the fluorosurfactant at the oil/water interface (refer back to Figure 8.22). The orientation as shown depicts the fluorocarbon chain residing inside the oil droplet. Since fluorocarbons are oleophobic, this is not favorable. The converse orientation is even less favorable from an energy standpoint, i.e. if the surfactant molecule were oriented in the opposite direction, not only would the hydrophobe present to the aqueous medium, but the hydrophile would reside in the oil phase.

It should be noted that in the case of non-ionic fluorosurfactants, or fluorosurfactants without a hydrophile, emulsification of hydrocarbons is possible (e.g. [52]). In general, fluorosurfactants are slightly more effective (that is, they show effects at vanishingly small concentrations) at reducing interfacial tensions in water/hydrocarbon systems, but they are limited in their ability to achieve low absolute values of interfacial tension. This concept was demonstrated beautifully in work published by Thoay [53] carried out in water/heptane systems. The limiting interfacial tension with a perfluoroheptyl hydrophobe was about 25 mN/m (cf. about 40 mN/m with no additive), and about 1 mN/m with the analogous heptane hydrophobe. At low concentrations (below 10^{-4} molar) the fluorosurfactant outperformed the hydrocarbon surfactant, but above that, the hydrocarbon surfactant continued to reduce interfacial tension values, reaching the lower limit at about 2×10^{-3} molar. This important paper also explored the effect of the length of the fluorinated chain on the effectiveness of the fluorosurfactant, and the lower limits of interfacial tension achievable

8.10.3 Fluorosurfactants at the solid/liquid boundary. 'Wetting'

Wetting is a phenomenon familiar to most, and generally is the term used when describing the behavior of a liquid on a solid surface. It includes spreading of a liquid over a surface (solid or liquid...), penetration of a liquid into a porous medium, or displacement of a liquid from a solid surface by another liquid (generally referred to as detergency). It's very similar in many ways to the interactions at the liquid/liquid boundary, but the differences are important enough to warrant an independent discussion. Coming to terms with what's really happening at the interfaces and boundary layers of this multiphase system has been the subject of a number of reviews [1, 54]. These references provide access to the primary literature, and fundamental derivations of wetting behavior on 'ideal' or low energy surfaces. An ideal surface is smooth,

ONO 2031, pg. 35 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

304 DESIGN AND SELECTION OF PERFORMANCE SURFACTANTS

homogeneous, non-deformable, and does not allow for solubility of the liquid in the solid phase. A drop of liquid placed on such a surface assumes a characteristic shape (see Figure 8.24) that can be characterized by the 'contact angle' at the 'triple point' (the place where solid, liquid, and vapor meet). If the drop is disturbed, it will return to its original shape. These kinds of systems were studied carefully by Zisman and co-workers [55] who developed experimental methods to further the theoretical work done by Young, and extended by Gibbs. This work represents the fundamental underpinnings of the understanding of wetting, but is not sufficient to describe wetting in the 'real world'.

The key to understanding wetting is recognizing that it's determined by a balance between the adhesive forces between the liquid and the solid,

Figure 8.24 A standing, or 'sessile' drop at rest on an ideal surface. The observed 'contact angle', Θ , is a measure of the wettability of the surface by a particular solution.

and the cohesive forces in the liquid. Adhesive forces cause the liquid to spread, and cohesive forces do the opposite, tending to cause the drop to 'ball up'. Simple vector analysis of the forces present at the triple point

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cos \Theta$$

Equation 8.1 Balance of forces at the 'triple point'.

(the place where the three phases meet) gives the equation derived by Young and DuPré. It's recognition that for every unit of s/l area gained, a unit of l/v area is gained (accounting for the contact angle...) and a unit of s/v area is lost. At equilibrium, these forces are in balance. More important, in most systems, is a non-equilibrium measure referred to as the 'spreading coefficient', S, again a measure of the interactions of

ONO 2031, pg. 36 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219 cohesive and adhesive forces in the interaction of a liquid with a solid surface.

$$S = \gamma_{SV} - (\gamma_{LV} + \gamma_{SL})$$

Equation 8.2 Simplified expression for spreading coefficient, *S*. A positive value for *S* indicates the tendency of a liquid to spread spontaneously on a surface.

A positive value of S (the higher, the better, for spreading or wetting) occurs when the adhesive energy gained by creating the new s/l area outweighs the energetic 'cost' of creating the new l/v area. To be sure, this is a great simplification of a complex derivation, but it is a functional definition that is useful to the practitioner: a liquid will spread on a solid as long as the surface tension of the liquid is lower than the surface energy of the solid surface. In truth, this is a necessary, but not sufficient condition for wetting. May Gibbs forgive me for these oversimplifications.

In practice, solutions containing a variety of ingredients are applied to real surfaces—ones that are rough, heterogeneous, with defects such as capillary pores, contaminated and importantly, in many cases, moving! The task of generalizing behavior in such systems with a plethora of independent variables is daunting. In many cases, advances in this arena have been achieved by 'Edisonian' means (i.e. by trial and error). Few publications exist concerning the characterization of the interaction at the l/s boundary in commercial (that is, mixed) product formulations. Some of this is because of the proprietary nature of the interactions, and some is because of the difficulty in separating the individual effects of the large number of variables involved.

For the most part, again, the present discussion will center on the use of fluorinated surfactants in aqueous systems. This choice is based on the fact that most formulators are striving to use water-borne formulations to avoid the hazards (flammability, personal exposure), and regulatory issues that accompany the use of hydrocarbon or halogenated solvents. Still, one of the key differences between 'conventional' surfactants and fluorosurfactants is that they are oleophobic as well as hydrophobic and thus function in solvent-borne liquid formulations. The choice of fluorosurfactant for use on a particular substrate can either facilitate or hinder wetting; this has to do with the interaction of the surfactant at the l/v boundary and at the s/l boundary (see Figures 8.25 and 8.26).

The adsorption of surfactants at the s/l interface has been extensively reviewed. Publications by Parfitt [56] and Chattoray [57] give good entry points into the primary literature on this topic. The surfactant is oriented at the solid/liquid boundary, and held in place by a physical, ionic, or covalent force. The mechanisms for surfactant adsorption, listed in ascending order of their tenacity are:

305

- Physical absorption. This phenomenon is chiefly the result of Van der Waals forces, which result from hydrophobic bonding, hydrogen bonding, dispersion force, or the formation of chargetransfer complexes.
- Ionic adsorption. The result of the formation of an ionic bond between sites having opposite net electrical charges.
- Chemisorption. The result of the formation of a covalent bond.

How the surfactant orients at the site (geometry, for a schematic representation of the role of a surfactant in wetting a hydrophobic surface

Figure 8.25 The role of adsorption in wetting. Note the orientation of the surfactant's hydrophilic and hydrophobic segments on the hydrophobic surface and at the air interface.

Figure 8.26 The role of surfactant in wetting. Interaction of a surfactant with a hydrophilic surface. Note the orientation of the surfactant molecule at the interfaces.

see Figure 8.25, and for a hydrophilic surface, see Figure 8.26), the tenacity with which it holds to the interface and the speed at which it will 'arrive' at the interface, depend on a number of factors:

ONO 2031, pg. 38 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

- The nature of the substrate. The polarity of the surface, it's porosity, surface functionality (chemical composition) and topography. Examples of low energy (hard to wet) substrates include polytetrafluoroethylene, paraffinic polymers such as polyethylene or polypropylene and polyesters. Examples of higher energy surfaces (easier to wet, and likely to have strong interactions with surface-active components in liquids) are glass, metal oxides and carbohydrate structures.
- The structure of the surfactant. The solubility of the surfactant, the structure of the hydrophobe and hydrophile—and the type of interaction between these segments of the molecule and the substrate—dominate the interaction at the s/l interface. Generally, ionic surfactants are more strongly adsorbed, especially on polar 'high surface energy' substrates.
- The nature of the liquid phase. The solubility of the surface-active material in the liquid, the affinity of the bulk liquid for the surface, the presence of more than one type of surface-active agent.
- Physical conditions. Kinetic considerations (surface age and the rate of new surface generation). Also pH, temperature, concentration, mixing, pressure, and viscosity.

As is the case with 1/v and 1/l interfaces, the adsorption of a surfactant at a s/l interface increases with increasing concentration of surfactant until it reaches saturation, and interfacial tension decreases (usually) as a result of adsorption at the interface. It is useful here to discuss the special case of autophobicity, or a decrease in wettability as a result of strong adsorption of a surfactant at an interface. A number of examples have been published, for example the adsorption of a layer of molten perfluorooctanoic acid on a glass surface [54]. A good practical example of this phenomenon is the use of Zonyl® FSP (an ammonium salt of a fluorocarbon phosphate) in metal cleaning applications. When dilute aqueous solutions of FSP are applied to metal surfaces, the phosphate hydrophilic group adsorbs quite strongly to the metal oxide surface. This, in effect, changes the apparent surface that the aqueous layer 'sees' from metal oxide functionalities to perfluoroalkyl functionalities. Since the perfluoroalkyl group is quite hydrophobic, the surface becomes quite hydrophobic, and the solution loses its ability to wet the surface. The water beads up, and rolls off the hydrophobic surface. This dewetting is referred to as 'water break' in the industry, and reduces water retention and spotting on metal surfaces, decreasing the amount of energy required to dry the part prior to further processing. This same phenomenon makes Zonyl[®] FSP a useful additive in mold release applications. See Figure 8.27.

ONO 2031, pg. 39 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.27 Autophobicity. A layer of strongly adsorbed surfactant changes the wettability of the surface.

8.10.4 Wetting and spreading in mixed systems

As discussed in the section that explored surfactant adsorption at liquid/ liquid boundaries, in mixed surfactant solutions, fluorosurfactants tend to occupy the l/v interface, and hydrocarbon surfactants tend to occupy condensed phase (1/l, or s/l) interfaces, providing functional benefit in many applications. This phenomenon is illustrated by examining the wetting of a paraffinic (hydrophobic) surface by aqueous solutions of mixtures of fluorosurfactants and hydrocarbon surfactants. Figure 8.28 is a plot of spreading coefficients for mixtures of ammonium perfluorooctanoate and a sodium di-octyl sulfosuccinate Aerosol[®] OT at 0.1 and 0.2 wt% total concentration in water. Remember that a positive spreading coefficient, S, connotes that the liquid will spread spontaneously, or 'wet' the surface. No combination of the fluorosurfactant or the hydrocarbon surfactant is sufficient to spread on the low-energy surface at 0.1% concentration, and at 0.2% concentration only mixtures of the two surfactants give positive spreading coefficients. Refer back to Figures 8.6 and 8.7 to give a sense of why this is observed. An effective combination of the lowering of surface tension (1/v) and interfacial tension (s/l) gives the desired effect-spontaneous wetting on the surface.

This behavior is typical of mixtures of fluorosurfactants and hydrocarbon surfactants. Figure 8.29 shows spreading coefficients for mixtures of three different types of fluorinated surfactants (Zonyl[®] FSC, Zonyl[®] FSA, and Zonyl[®] FSK; cationic, anionic, and amphoteric, respectively) with non-ionic hydrocarbon surfactant Merpol[®] A. Only in the case of FSC does any one surfactant, alone, have the ability to spontaneously wet the surface. Minimizing the SUM of the surface (l/v) tension and the interfacial (l/s) tension gives maximum wetting power.

> ONO 2031, pg. 40 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.28 Spreading coefficients for aqueous mixtures containing $R_{f}COONH_{4}$ and Aerosol[®] OT. $a = R_{f}COONH_{4}$, $b = Aerosol^{\%}$ OT.

8.10.5 Fluorosurfactants and 'Rewet'

If a thin film of a liquid coating containing surfactants is allowed to evaporate to dryness, it follows that the uppermost layer of the dried film will have a surface excess of surfactant molecules. Unless rinsed away by a subsequent operation, this layer will affect the rewet characteristics of the film/coating, an important consideration in practical applications where multiple layers are frequently the norm. Commercial examples of

> ONO 2031, pg. 41 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

Figure 8.29 Spreading coefficients for aqueous mixtures containing Merpol[®] A and Zonyl[®] FSA, Zonyl[®] FSC and Zonyl[®] FSK.

multilayer systems with the need for a good rewet mechanism include automotive paints, floor polishes, and paper coatings, to name just a few. In all these cases, it's important that the existing 'lower' layer be accepting of the next layer to be applied. There are also many examples of applications where a wettable surface is not desired; these include 'release' surfaces, such as the backing for adhesive labels, overprint varnishes and topcoats used to protect finished surfaces.

The mechanism for rewet is quite simple in that if the fluorinated surface-active agent is not tightly held in its existing adsorbed state, it can

> ONO 2031, pg. 42 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

ţ

migrate into the new liquid layer and serve then to lower the surface and/or interfacial tension of that layer. Conversely, if the fluorinated surface-active layer is tightly held, say, through physical or chemisorption, migration of the fluorine-containing molecule is precluded, and the surface can be quite repellent. Autophobicity, described earlier in this section, is an example of this type of behavior.

Recently, a number of manufacturers of fluorinated surfactants have extended this concept by developing a class of 'reactive surfactants' that behave like fluorosurfactants in that they aggregate at the air interface of a liquid coating while the coating is fluid. These materials have the added feature that they contain a reactive segment (e.g. isocyanate, epoxide, alkyd, acrylate or vinyl ether) that participates in the curing mechanism of the coating, effectively locking the fluoroalkyl group into the top layer of the coating as it dries and cures. These additives are effective in reducing the surface energy of a coating, and can be designed to function in either water-borne or solvent-based coatings. Since the resultant surface, presuming saturation, is an adsorbed monolayer of fluoroalkyl groups covalently bonded to the resin system of the coating, such coatings are both water- and oil-repellent. Commercial examples of this type of coating additive are Zonyl³⁸ 8857a (fluorinated alkyd manufactured by E. I. DuPont, Wilmington, DE) and FAVE® (fluorinated alkyl vinyl ether, manufactured by Allied Signal Corp., Morristown, NJ). Another related approach to durable fluorinated surfaces based on further extension of this concept is the construction of fluorinated (and thus, surface active) segments on polymeric backbones [58].

8.10.6 Fluorosurfactants and dispersions

Surfactants play an important role in the wetting of finely divided solids, and suspending them in liquids (forming 'stable' dispersions). Principles which apply to the wetting of solid surfaces generally apply to the wetting of small solid particles. Importantly, an adsorbed layer of a surfactant opposes the tendency of small particles to agglomerate, or form larger clumped aggregates, by providing a 'wrapper' around each particle. The principles that were discussed concerning the formation and stabilization of emulsions are applicable here as well. That is, stable dispersions are favored when the density of the liquid and suspended solid are similar, when the particles are small, when the viscosity of the system is high, and when the particles have an adsorbed layer of a surface-active material. As in emulsions, this adsorbed layer can resist agglomeration (the parallel of coalescence in liquid systems) through electrostatic or steric means. In some practical applications, it is useful to place the surface-active agent on the solid surface prior to contact with water.

311

ONO 2031, pg. 43 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219 In this way, a powder with an adsorbed surfactant layer that renders it wettable is prepared to readily disperse in the desired liquid medium.

Predicting a surfactant structure that functions to promote wetting of powdery substances, and stabilizing their suspensions in liquids is aided by consideration of the polarity and nature of the two media to be 'bridged' by the adsorbed layer. For example, to suspend a powdered form of PTFE (polytetrafluoroethylene) in a paraffinic hydrocarbon solvent, the choice of a material like Zonyl[®] FTS (fluorotelomer stearate) would be warranted. One portion of the molecule is a long-chain hydrocarbon, the other, a fluorocarbon. At the interface, the surfactant will orient with the fluorocarbon adsorbed on the surface of the PTFE particle, and the hydrocarbon chain will present to the hydrocarbon solvent. Similarly, the choice of an anionic fluorosurfactant with a carboxylate hydrophile would be suitable for dispersion of the PTFE powder in water; the surfactant will adsorb with its fluorocarbon tail on the surface of the PTFE powder, and present its hydrophilic carboxylate head to the aqueous phase (see Figure 8.30).

Figure 8.30 Surfactant orientation in dispersions.

8.11 Detergency

The removal of soils and contaminants from solid surfaces, aided by surfactants, represents one of the largest commercial applications for this

> ONO 2031, pg. 44 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

class of compounds. Surfactants play an important role in the two key steps of detergency. The first is wetting of the surface (both the substrate, and the contaminant), which serves to displace the contaminant from the surface with an adsorbed layer of surfactant. The surfactant has a strong affinity for the surface, and simply displaces the soil from the surface (see Figure 8.31). The second, and equally important, phase of detergency is stabilization of the particle or droplet that's been lifted off the surface, opposing its redeposition on the surface. This process is also effected with a layer of adsorbed surfactant (see the sections on emulsions and dispersions).

Figure 8.31 The role of surfactants in detergency.

Fluorosurfactants have unique roles in cleaning formulations, especially where their 'wetting power' (i.e. low surface tension value) is needed. Further, they provide this cleaning power at low concentrations, which translates to low levels of residue on evaporation. This is an important consideration in applications such as the cleaning of oxygen systems [59, 60] where residuum is a safety consideration. This functionality is also valued when cleaning glass, or other shiny surfaces, where residuum translates to haze, or streaking, on the surface. Recently, the use of fluorosurfactants as cleaning and polishing agents in the manufacture of semi-conducting devices for the electronics industry has been explored [61]. In this application, the industry's drive toward increasing circuit density is aided by the small quantities of fluorosurfactant required to effectively clean these critical surfaces.

Since fluorosurfactants are less effective in dispersing and stabilizing hydrocarbon soils, they are often accompanied in cleaning formulations by hydrocarbon surfactants. The hydrocarbon surfactant capably fills the role of dispersant, slowing the rate of redeposition of the materials that have been lifted off the surface. In tandem with fluorosurfactants, it is truly an effective partnership.

> ONO 2031, pg. 45 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

314 DESIGN AND SELECTION OF PERFORMANCE SURFACTANTS

In non-aqueous systems, the unique ability of fluorinated surfactants to reduce surface and interfacial tension provides another avenue for their commercial use. Of particular interest is the use of fluorinated surfactants and polymers in carbon dioxide systems. Liquid CO_2 systems are currently being explored as replacements for halogenated fluids (facing regulatory pressure as a result of their deleterious effects on the earth's atmosphere) in a number of critical cleaning applications, and are being considered for use in the dry-cleaning industry [62]. To date, fluorinated materials alone provide the adsorption characteristics needed to clean in these specialty solvent systems.

8.12 Interactions of fluorinated surfactants with charged surfaces

The attractive forces between a surface and a surfactant are near their strongest when the two surfaces bear opposite charges. Chemisorption by electrostatic attraction has been used in a number of practical applications to adsorb a layer of fluorosurfactant on fibers (e.g. hair and textiles) to render the surface both hydrophobic and oleophobic. Further, this layer changes the surface lubricity of a fiber, a benefit in hair-care formulations [63–65]. A majority of synthetic and naturally occurring fibers tend to bear a negative static charge, and so, cationic fluorosurfactants and polymers are most often used to effect this 'coating.' Much of the work in this area appears in the patent literature, owing to the commercial importance of this phenomenon. A good review of developments through 1993 is given in Kissa's monograph [1].

References

- Kissa, E. (1994) Fluorinated Surfactants, Surfactant Science Series. Vol. 50, Marcel Dekker, New York.
- [2] Bluestein, B.R. and Hilton, C.L. (eds.) (1982) 'Amphoteric Surfactants', Surfactant Science Series, Vol. 12, Marcel Dekker, New York.
- [3] Gaines, G.L. (1991) Langmuir, 7 3054.
- [4] Ishikawa, N. and Sasabe, M. (1984) Journal of Fluorine Chemistry, 25 241.
- [5] Fielding, H.C. (1979) in Organofluorine Chemicals and Their Industrial Applications (ed. R.E. Banks) E. Horwood, Chichester, UK, p. 214.
- [6] Moore, E., Milian, A. and Eleuterio, E. (DuPont) (1966) U.S. Patent 3,250,808.
- [7] Moore, E. (DuPont) (1967) U.S. Patent 3,322,826.
- [8] Simons, J.H. et al. (1949) Journal of the Electrochemical Society, 95 47.
- [9] Burdon, J., Parson, I.W. and Tatlow, J.C. (1972) Tetrahedron, 28 43.
- [10] Drakesmith, F.G. and Hughes, D.A. (1976) Journal of Applied Electrochemistry, 6 23.
- [11] Clarke, J.S. and Juhn, A.T. (1977) Journal of Electroanalytical Chemistry, 85 299.
- [12] Lines, D. and Sutcliffe, H. (1981) Journal of Fluorine Chemistry, 17 423.
- [13] Brace, N.O. (DuPont) (1961) U.S. Patent 3,145,222.

- [14] Blanchard, W.A. and Rhode, J.C. (DuPont) (1965) U.S. Patent 3,226,449.
- [15] Brace, N.O. (1962) Journal of Organic Chemistry, 27 4491.
- [16] Hudlicky, M. (1962) Chemistry of Organic Fluorine Compounds, Macmillan, New York.
- [17] Deem, W.R. (ICI) (1973) British Patent 1302350.
- [18] Hutchinson, J. (1974) Fette, Seifen, Anstrichmittel, 76 158.
- [19] Bastiensen, O. and Hadler, E. (1952) Acta Chemica Scandinavica, 6 214.
- [20] Fletcher, P.D.I. (1997) Fluorinated and semi-fluorinated surfactants in Specialist Surfactants (ed. I.D. Robb), chapter 5, Blackie Academic & Professional, London, p. 104.
- [21] Caponetti, E., Martino, D.C., Floriano, M.A. and Triolo, R. (1993) Langmuir, 9 1193.
- [22] Almgren, M. and Barzykin, A.V. (1996) Langmuir, 12(20) 4672.
- [23] Das, A.R., Haque, M.E., Rakshit, A.K. and Moulik, S.P. (1996) Langmuir, 12(17) 4084.
- [24] Ravey, J.C., Gherbi, A. and Stebe, M.J. (1988) Progress in Colloid and Polymer Science, 76 234.
- [25] Ward, A.F.H. and Torday, L. (1946) Journal of Chemical Physics, 14 453.
- [26] Miller, R. (1981) Colloid and Polymer Science, 259 1124.
- [27] Aniansson, E.A. and Wall, S. (1974) Journal of Physical Chemistry, 78 1024.
- [28] Aniansson, E.A. and Wall, S. (1975) Journal of Physical Chemistry, 79 857.
- [29] Aniansson, E.A., Wall, S.N., Almgren, M., Hoffman, H., Kielmann, I., Ulbricht, W., Zana, R., Lung, J. and Tondre, C.J. (1976) Journal of Physical Chemistry, 80 905.
- [30] Shah, D.O., Patist, A., Chhabra, V., Pagidipati, R. and Shah, R. (1997) Langmuir, 13 432.
- [31] Klein, H.G., Meussdoerffer, J.N. and Niederprum, H. (1975) Metalloberflache, 29 559.
- [32] Shah, D.O., Patist, A., Huibers, P.D.T. and Deneka, B. (1998) Langmuir, 14 4471.
- [33] Shiao, S.Y., Patist, A., Free, M.L., Chhabra, V., Huibers, P.D.T., Gregory, A., Patel, S. and Shah, D.O. (1997) Colloids and Surfaces A, 128 197-208.
- [34] Meussdoerffer, J.N. and Niederprum, H. (1980) Chemiker-Zeitung, 104 45.
- [35] Hirt, D.E., Prod'homme, R.K., Miller, B. and Rebenfeld, L. (1990) Colloids Surfaces, 44 101.
- [36] Mukerjee, P. and Handa, T. (1981) Journal of Physical Chemistry, 85 2298.
- [37] Ewers, W.E. and Sutherland, K.L. (1952) Australian Journal of Scientific Research, A5 697.
- [38] Strauss, U.P. (1989) in *Polymers in Aqueous Media*, Adv. Chem. Series 223 (ed. J.E. Glass), Am. Chem. Soc. Washington DC, p. 317.
- [39] Laschewsky, A., Cochin, D. and Hendlinger, P. (1995) Colloid and Polymer Science, 273 1138.
- [40] Zhao, G.-X. and Zhu, B.-Y. (1983) Colloid and Polymer Science, 261 89.
- [41] Zhao, G.-X. and Zhu, B.-Y. (1986) Phenomena in Mixed Surfactant Systems (ed. J. Scamehorn), ACS Symposium Series, No. 311, p. 184, American Chemical Society, Washington, DC.
- [42] Kaler, E.W., Herrington, K.L., Miller, D.D. and Zasadzinski, J.A.N. (1992) in Structure and Dynamics of Strongly Interacting Colloids and Supramolecular Aggregates in Solution (ed. S.H. Chin), Kluwer Academic Publishers, Dordrect, Netherlands, p. 571.
- [43] Rosen, M.J. (1986) in Phenomena in Mixed Surfactant Systems (ed. J.F. Scamehorn), p. 144.
- [44] Falk, R.A. (1983) US Patent 4,420,434 (Ciba-Geigy Corp).
- [45] Falk, R.A. (1984) US Patent 4,472,286 (Ciba-Geigy Corp).
- [46] Ogino, K. and Abe, M. (eds.) (1993) Mixed Surfactant Systems, Surfactant Science Series, Vol. 46, Marcel Dekker, New York.
- [47] Ross, S. and Morrison, I.K. (1988) Colloidal Systems and Interfaces, Wiley, New York.
- [48] Bourrel, M. and Schechter, R.S. (1988) Microemulsions and Related Systems: Formulation, Solvency, and Physical Properties. Surfactant Science Series, Vol. 30, Marcel Dekker, New York.
- [49] Prince, L.M. (1967) Journal of Colloid and Interface Science, 23 165.

ONO 2031, pg. 47 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219

- [50] Bryce, H.G. (1964) Fluorine Chemistry (ed. J.H. Simmons), Vol. 5, Academic Press, New York, p. 380.
- [51] Vercellotti, G.M. and Hammerschmidt, D.E. (1988) Blood Substitutes (ed. K.C. Lowe), VCH Publishers, Cambridge.
- [52] Greiner, A. and Herbst, M. (1976) Zeitschrift fuer Chemie, 16 229.
- [53] Thoay, N. (1977) Journal of Colloid Science, 62 222.
- [54] Dettre, R.H. and Johnson, R.E. (1993) in Wettability (ed. J.C. Berg), p. 1.
- [55] Zisman, W.A. (1964) in Advances in Chemistry Series 43 (ed. R.F. Gould), American Chemical Society, Washington, DC, p. 1.
- [56] Parfitt, G.D. and Rochester, C.H. (1983) in Adsorption from Solution at the Solid/Liquid Interface (ed. G.D. Parfitt), Academic Press, New York.
- [57] Chattoray, D.K. and Birdi, K.S. (1984) Adsorption and the Gibbs Surface Excess, Plenum, New York.
- [58] Thomas, R.R., Anton, D.R., Graham, W.F., Darmon, M.J. and Stika, K.M. (1998) *Macromolecules*, 31(14) 4595.
- [59] Allen, G.J., Hoppesch, C.W., Johnson, R.S. and Buckley, M. (1993) Aqueous Nonvolatile Residue Validation of Precision Cleaned Hardware, ASTM Spec. Tech. Publ. 37.
- [60] Allen, G.J. and Fishell, K.A. (1995) Aqueous cleaning and verification processes for precision cleaning of small parts, NASA Conf. Publ. 411.
- [61] Hosali, S.D., Seturaman, A.R., Wang, J.F. and Cook, L.M. (1998) World Patent WO 9813218.
- [62] DeSimone, J.M. (1997) Design and application of surfactants for carbon dioxide. Book Pap. - Int. Conf. Exhib., AATCC, pp. 168-174.
- [63] Lewis, M.R. and Mitchell, S.A. (Unilever, Ltd.) (1981) British GB Patent 1598567.
- [64] Cella, J.A. and Fiebig, A.E. (Alberto Culver Co.) (1978) U.S. Patent 3,993,744.
- [65] Iovanni, C.F. and Basel, D.M. (Gillette Co.) (1988) U.S. Patent 4,765,975.

ONO 2031, pg. 48 Merck-Dohme v. Ono Pharm-Honjo IPR2016-01219