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Solubility in water is an important property of surfactants for many purposes, including surface tension determination and (eco)toxicological studies. Surfactants have been categorized as “difficult to test”; the challenges associated with the determination of solubility in water will be discussed. OECD TG 105 is based on the definition of solubility in water as “saturation mass concentration”. For most surfactants, there is no saturation concentration, but rather formation of micelles or other surfactant aggregates. Unfortunately, there is a misconception that surfactant micelles are equivalent to droplets of hydrophobic material. This is not true, as there is a rapid exchange of surfactant molecules between those in a micelle and those present as single molecules in the bulk water – a true thermodynamic equilibrium. In addition, surfactants are able to solubilize hydrophobic substances within their micelles, enhancing their bioavailability.

### Introduction

Solubility in water is a crucial property and often a prerequisite for the physicochemical characterization and (eco-)toxicological evaluation of substances; thus, the term “solubility” appears 420 times in the 2635 pages of the REACH document (Regulation No 440/2008) [1,2]. The methods for the experimental determination of water solubility are the OECD Technical Guidelines 105 [3] and 120 [4]. Unfortunately, if taken literally, these guidelines are difficult to apply to surfactants and surface-active polymers. For this reason, surfactants have been listed in an OECD guidance document among the “difficult to test” substances [5]. However, surfactants not really “difficult”; they are just “different” since they do not follow the same rules as non-amphiphilic low MW molecules. Because of their amphiphilic molecular architecture, they have special properties in terms of phase and interfacial behavior, which is why they are crucial ingredients for many applications. Since OECD TG 105 and 120 are the only existing guidelines for assessing the water solubility of chemicals, both customers and regulators require data based on these – unsuitable – guidelines. The challenges involved are discussed in this paper, which will hopefully be useful not only for surfactants, but also for purposes in the field of polymers, including the consideration of polymers as potential microplastics [6–8].

### OECD Technical Guideline 105

Both the REACH document [1] and the OECD TG 105 [3] define the term water solubility as the “saturation mass concentration” of a chemical in water at a given temperature.

According to OECD TG 105, after a preliminary test, one of two methods should be used depending on the expected solubility: The column elution method or the flask method for solubilities below and above 0.01 g/L, respectively. Typically, the analytical challenge in such procedures is the quantitative determination of the potentially very small amounts of the chemicals being tested. For surface-active substances, however, there is a conceptual challenge: there is no saturation concentration (only one exception: ionic surfactants below the Krafft temperature), and many surfactants are very well soluble in water; most of them are even commercially available as more or less concentrated (30-70 wt%) aqueous solutions.

In the column elution method, the substance to be tested is loaded onto a support, which is then filled into a column. Using a recirculation pump, a defined amount of water is pumped through the column until a saturation concentration is reached. The aqueous phase should be checked for the presence of colloidal matter by light scattering (“Tyndall effect”), as the presence of particles will invalidate the result of the solubility determination. Fortunately, the absence of the Tyndall effect is only required in the column method for substances of low solubility. For the flask method, the guideline only refers to a “clear aqueous phase”, without any specification or guidance as to how “clear” should be assessed. If the absence of a Tyndall effect was also required in the flask method, very well water-soluble, micelle-forming surfactants would be insoluble – at all concentrations above the Critical Micelle Concentration (CMC), even though they

are marketed as concentrated aqueous solutions and used in water-based surfactant formulations. But: The term micelle is not mentioned at all in OECD TG 105, so for “normal” hydrophilic surfactants, the OECD TG 105 preliminary test is all that can reasonably be done: Visual observation of highly concentrated surfactant/water mixtures (e.g. 0.1 g of the sample in 0.1 or 0.5 mL of water). And since in most cases there is no sediment, is it really necessary to perform the flask method and do a quantitative analysis (e.g. by HPLC) of the solutions? This would be nothing but recording a calibration curve and a waste of resources.

## What is special about surfactants?

Apart from the lack of a saturation concentration, the main reason why surfactants are “difficult” to test is that most surfactants are not “pure” but mixtures of substances with different solubilities. This is not a bug, but an important feature that is either unavoidable from the viewpoint of synthesis and/or essential from the viewpoint of application performance. This inherent “heterogeneity” is caused by either alkyl chain length distributions (such as coco = C8 – C18) or unavoidable homologue distributions of the hydrophilic headgroups of ethoxylates. Another example are surfactants containing a carboxylate group such as Sodium Lauroyl Glutamate, Alkyl Ether Carboxylates or simply Sodium Oleate (a.k.a. soap); these are also mixtures – at intermediate pH values – consisting of the protonated (often insoluble) form and the neutralized (soluble, i.e. micelle-forming) salt form.

## Micelles are a soluble state of surfactants

There is a 2019 review on the determination of water solubility of difficult-to-test substances [9]. For whatever reason and without any reference, in the chapter entitled “Scientific Challenges” it has been stated that surfactants that cluster into micelles above the CMC are no longer freely dissolved. Moreover, the opinion has been expressed that micelles “can be viewed as equivalent to the formation of micro-droplets or emulsions of hydrophobic chemicals in water”. This statement is in contradiction with basic physical chemistry, and such “alternative facts” should not have made it into a peer-reviewed journal. Even above the CMC, surfactants are well-dissolved from a thermodynamics point of view. There is a rapid exchange of surfactant molecules between those forming the micelles and the free surfactant “monomers” in the bulk phase on a timescale of about 10  $\mu$ s (for the typical dodecyl chains); such a micelle has exchanged all of its surfactant molecules on a timescale of about 1 ms [10]. This is a real thermodynamic equilibrium and therefore micelles are not at all equivalent to emulsion (micro-) droplets of hydrophobic chemicals. Moreover, the difference in size between a micelle and an emulsion droplet is at least two orders of magnitude.

Unfortunately, this misconception about micelles has found its way onto poster 1.15PC.3 presented at the SETAC 2020 Conference [11] entitled “Surfactants: Substances of Concern? ECHA’s current challenges in safety assessment”. The abstract states that in REACH registration dossiers for surfactants, “physico-chemical data are often unreliable, e.g. water solubility is reported without taking into account the critical micelle concentration as the solubility limit, the values are approximated based on visual inspection only”. What was described as “unreliable” is the result of performing the preliminary test – by visual inspection, as required by OECD TG 105. The poster also stated that “concentrations above CMC in water do not represent the truly dissolved concentration, i.e. the bioavailable fraction.” Scientifically speaking, this can only be considered as “fake news”.

## Solubilization within micelles

The uptake of pharmacological actives is often facilitated by solubilizers, i.e. hydrophilic surfactants capable of accommodating hydrophobic materials within their micelles – in other words, the hydrophobic actives are made bioavailable with the help of surfactants [12]. Therefore, it is safe to assume that not only the hydrophobic actives, but also the surfactants forming the micelles are bioavailable. Such a solubilization within a micelle is a completely different story than the formation of a comparably macroscopic (several  $\mu$ m sized) emulsion droplet. Also in biodegradation, surfactants help to make hydrophobic materials bioavailable; as a recent example, rhamnolipids have been found to increase the yield of hydrogen from waste activated sludge during anaerobic degradation [13]. And why do microorganisms produce biosurfactants at all? To use hydrophobic materials as a carbon source (“food”), in other words, to make hydrophobic chemicals bioavailable [14].

## CMC = Maximum solubility?

As discussed above, from a regulatory point of view, the CMC of a surfactant is often considered to be the maximum solubility – as surfactant monomers. However, for “technical” surfactants, i.e. those containing a mixture of components of different hydrophilicity, the opposite is true: Only above the CMC of the more hydrophilic components, the more hydrophobic components can be solubilized. Consequently, solutions below the CMC may look turbid, which is exactly the opposite of what is expected for regulatory/ecotoxicological purposes. Furthermore, in these cases, the nominal concentration (on the x-axis of the CMC plot) does not represent the concentration of dissolved material. All of this poses a challenge when trying to determine CMCs from surface tension measurements, as discussed in the accompanying paper on surface tension [15].

Another use of CMC values as maximum monomer solubility is to generate the octanol/water partition coefficient  $\log K_{ow}$ , which was never meant to be used for interfacially active materials such as surfactants and emulsifiers [16]. Using the individual solubilities in water and octanol to calculate a value that allows some conclusions to be drawn about environmental fate seems to be the least of all evils. It turned out that by using the CMC as solubility in water (instead of the “real” macroscopic solubility of e.g. >50%), the calculated values of  $\log K_{ow}$  somehow agree with those obtained by the slow-stirring method [17].

### Example: Associative thickeners

Soluble polymers are not microplastics; accordingly, the final RAC/SEAC opinion on the draft microplastics restriction accepts that a “particle is a minute piece of matter with defined physical boundaries” [6–8]. Also based on this definition, a micelle or any other surfactant aggregate cannot be considered a particle (except for the “linguistic” problem that the result of a Dynamic Light Scattering experiment, which is the method of choice to determine the size of micelles, is a particle size distribution).

The associative thickener with the simplest molecular architecture – PEG-150 Distearate – has already been mentioned in the preceding paper [15]. As a bulk material, this highly ethoxylated ester is a solid due to the melting point of polyethylene oxide (about 68°C); therefore, the question was raised whether this product must be considered to be microplastic or not. Since the rather large and well water-soluble PEO chain (MW 6000 g/mol) is esterified with saturated C18-alkyl chains that crystallize easily, PEG-150 Distearate is not clearly soluble in water on its own. However, in aqueous surfactant formulations, this highly ethoxylated ester can be solubilized. It is then able to interconnect other surfactant aggregates (spherical micelles, worm-like micelles) and thus acts as an associative thickener. Moreover, this function can only be fulfilled if the polymer is in an expanded (soluble!) state and thus able to bridge the distance between the surfactant micelles. Proving the solubility of such soluble polymers is a challenge under current regulations.

### Conclusion and Outlook

It would be beneficial if OECD TG 105 on solubility could be applied to surfactants and surface-active polymers. One option would be to write an amendment to include substances that do not have a saturation concentration and to describe micelles of surfactants and surface-active polymers as a water-soluble state. The need to update TG 105 was also one outcome of the recent UBA/Fraunhofer/Ramboll project to evaluate which OECD guidelines need to be revised [18]. However, such an update is a time-consuming endeavor [19]. For the time being,

we have to live with the existing guidelines, but with this paper we wanted to raise awareness of the challenges involved. One final comment: Do we really need to use OECD TG 105 to demonstrate water solubility for those solids that are also marketed as aqueous (e.g. 50 wt%) solutions? Would this not show already water solubility without further testing? And if there was no sediment in the OECD TG 105 preliminary test, a quantitative analysis of the solution in a flask test should be obsolete.

### Remark

This paper is a joint effort of members of the CESIO Working Group “Test Methods of Surfactants” and the TEGEWA Working Group “Surface Active Substances”: Roland Borner (Chemische Fabrik Schärer&Schläpfer AG), Katrin Wunderlich (Zschimmer&Schwarz GmbH&Co KG), Karsten Holtin (Kolb Distribution Ltd.), Bernat Pi (Kao Corporation S.A.), Arjan Gelissen (Sasol Germany GmbH), Johannes Bookhold (Clariant Produkte (Deutschland) GmbH), Kati Schmidt (BASF SE), Louis Schwarzmayr (Nouryon Surface Chemistry AB), Michael Stapels (Kao Chemicals GmbH) and Joachim Venzmer (Evonik Operations GmbH).

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