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Physical methods for measurement of the HLB of ether and ester non-ionic surface-active agents: H-NMR and dielectric constant

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Summary

After a short review of the different physical methods of determination of the HLB (lipophilic/hydrophilic balance) value of surface-active agents, two techniques were investigated and experiments were performed on a large number of commercial surface-active agents: H-NMR which computes HLB with the help of the integration of the H-signals from the lipophilic and hydrophilic parts of the molecule and by dielectric constant measurement which computes the HLB from knowledge of the polarity of molecules under the influence of an electrical field. The results are described and discussed.

Introduction

The accurate determination of the HLB of a molecule with capillary activity is an important operation following the synthesis of a new substance of this class. Knowledge of this value would enable one to determine its ability to disperse into water or a lipophilic vehicle. Further, the HLB value would be useful in the formulation of stable emulsions, either regular emulsions (H/L and L/H) or multiple emulsions (H/L/H prepared by dispersion of an initial H/L emulsion into one aqueous phase added to a hydrophilic surface-active agent or L/H/L made by dispersion of an initial L/H emulsion in a lipophilic phase added to a lipophilic surface-active agent).

The determination of the HLB value uses a basic principle: assess the hydrophilic part of the molecule and by difference the lipophilic part can be evaluated, the ratio of the two yielding the HLB value. The notion of HLB was introduced by Griffin and co-workers (Griffin, 1949a,b, 1955; Griffin and Behrens, 1953; Griffin et al., 1966) and classification of non-ionic surface-active agents according to their hydrophilic properties was carried out as follows:

In the case of the ether surface-active agents, the HLB value is equal to 1/5 of the percentage in weight of the polyoxyethylenic chain.

In the case of the ester surface-active agents, calculation of the HLB involves the fatty acid index of the acid and the saponification index.

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Davies and Rimlinger (Davies, 1957; Davies and Rideal, 1961; Rimlinger, 1964) proposed another calculation scale based upon the additivity of incremential values related to the functional groups of the non-ionic surface-active agent, with specific values: positive increments for the hydrophilic groups and negative increments for the lipophilic groups. The two methods differ in the values of the increments and the weighting parameter coefficients. They are easy to use for the calculation of the HLB of a new surface-active agent.

In addition to the extensive use of these methods, some authors discussed and criticized the HLB scales (Seiller, 1971; Adamson, 1976; Tadros and Vincent, 1983; Vold and Vold, 1983; Deem, 1985) claiming them to be imprecise, empirical, indirect and unsuitable for every surface-active agents. Therefore, Schott (1990) performed a comparison of the HLB values of two series of non-ionic surface-active agents and showed that, within the normal range of HLB values used for micellar solubilization and emulsification, the scales showed unequal units and disproportional intervals.

Besides these methods using calculation, different experimental methods for both for non-ionic and ionic surface-active agents were proposed. Using the original definition of the HLB scales, different research works were undertaken to improve the determination of the HLB value using methods based upon either the behaviour of the surface-active agent in solution or physico-chemical properties.

The different methods can be classified into three categories in relation with the properties involved for determination: methods employing the behaviour of the surface-active agent used; those involving the partition coefficient of the surface-active agent between the solvent and the stationary phase; and methods measuring some specific parameters of the strucure of the surface-active agent.

Among the first category, determination of the following can be included: water index (Greenwald et al., 1956); critical concentration for micelle formation (Van Alstine et al., 1986); spreading tension (Ross et al., 1959; Becher, 1961); cloud point (Florence et al., 1975; Marszall, 1979, 1981); titration (Middleton, 1968); and phenol index (Marszall, 1978, 1980).

In the second category we can note: thin-layer chromatography (Hayano et al., 1968); HPLC (Schott, 1984); and gas chromatography (Huebner, 1962).

The third category comprises: calorimetric measurement of the heat of hydration (Racz and Orban, 1965; Rowe, 1992); determination of the interfacial tension (Chun and Martin, 1961; Heusch, 1970); mass spectrometry (Crooks et al., 1974); dielectric constant measurement (Gorman and Hall, 1963; Mouazen, 1978); and H-NMR (Ben-Et and Tatsarsky, 1972; Berguerio et al., 1978; Carrion et al., 1983).

Great similarity was observed between these HLB determinations especially with tests on homogeneous series of surface-active agents. However, none of the previous methods is currently empoyed as a standard for evaluation of HLB (Laurent, 1990; Lin, 1991): most yield results with an error of ± 1 unit. This approximation could be sufficient for the development of emulsions of which the HLB is not the main parameter. However, greater accuracy is required for fundamental research, quality control and production validation of a new batch of surface-active agents.

The main purpose of this work was to determine a reliable method for the HLB measurement of non-ionic surface-active agents. Such a method must be independent of the solution behaviour and be based upon accurate and reliable physical measurements. Two of the previously described methods were selected for accuracy, ease of use and efficiency: H-NMR and the other related to the dielectric properties of the surface-active agent molecule, i.e., the dipolar moment evaluated through measurement of the dielectric constant.

Materials and Methods

Materials

Various surface-active agents, both well-established and recently developed, were selected for the evaluation of HLB values by use of H-NMR and measurements on dielectric constant. Dielectric constant measurement was not performed on every surface-active agent due to the exigence of the liquid state of the sample containing neither salts nor water. The chemical compositions of the surface-active agents studied are reported in Table 1.

Methods

H-NMR determination of HLB

The method used was first described by Ben-Et and Tatarsky (1972). It consists of the direct measurement of the HLB by determining the area ratio between the hydrophilic and lipophilic H signals. The whole area under the curve of the NMR spectra matches the total H signal of the molecule. The method involves the hydrophilic behaviour of the molecule with the number of hydrogens linked with hydrophilic, oxygenated functional groups.

On the NMR spectrum, the hydrophilic protons gather in the 3.5–5 ppm band, being readily observable and well separated from both the lipophilic protons (0.5–3 ppm) and ethylenic and aromatic protons (5.5–8 ppm).

Measurement was carried out by dissolving 50 mg of the surface-active agent in 1 ml deuterated chloroform ($CDCl_3$) and introducing the mixture into an NMR sample tube (diameter = 5 mm), the NMR spectra being recorded on a continuous wave Varian T60 (60 MHz) or EM 390 (90 MHz) spectrometer at room temperature, after appropriate calibration of the spectrometer.

By appropriate use of the integrating device of the NMR spectrometer, measurements can read-

TABLE 1

Chemical structure of commercial surface-active agents

Tween®	sorbitan ester (20 OE) fatty acid: C12 (Tween 20), C16 (Tween 40) C18 (Tween 60), C18 unsaturated (Tween 80 and 85)
Span®	sorbitan ester fatty acid: C12 (Span 20), C16 (Span 40), C18 (Span 60) C18 unsaturated (Span 80)
Myrj®	PEG stearate OE = 8 (Myrj 45), OE = 20 (Myrj 49), OE = 40 (Myrj 52) OE = 50 (Myrj 53), OE = 100 (Myrj 59)
Brij®	ethoxylated fatty alcohol C16–20OE (Brij 58), C18–2OE (Brij 72) C18–10OE (Brij 76), C18–20OE (Brij 78) C18 unsaturated-2OE (Brij 92), C18 unsaturated-10OE (Brij 96) C18 unsaturated-20OE (Brij 98)
Tefose®	polyol ester 63 and 70: ethylene glycol and PEG palmitostearate 1500: monodipalmitostearate of PEG 2000: palmitostearate of PEG
Mergital®	oleyl alcohol (60 OE)
Plurol®	polyglycerol ester oleic: palmitooleate stearic: palmitostearate
Cithrol®	PEG 4000 laurate
Hypermer A60®	polymerised ester
Dehymuls®	sorbitan ester STO: trioleate, SSO: sesquioleate SMO: mono-oleate,SMI: monoisostearate
Emulgin®	sorbitan ester 20OE STO: trioleate, SMO: mono-oleate
Monomuls®	glycerol oleate
Lameform®	triglycerol di-isostearate
Generol®	phytosterol 5OE (soya)

ily be performed, with a precision of better than $\pm 1\%$, of the area under the curve of the different signal groups without further investigation of individual signals or specification. Using the term I_{gph} to denote the integration amplitude of the hydrophilic groups and I_{tot} to refer to the total integration amplitude of the protons of the molecule, the ratio:

$$H = I_{\mathrm{gph}}/I_{\mathrm{tot}} \tag{1}$$

describes the relative hydrophilic part of the molecule.

Determination of the HLB value was performed according to the equation of Berguerio et al. (1978):

$$\mathrm{HLB} = 60H/(H + 2) \tag{2}$$

The reliability of the NMR method and the results obtained was assessed by an automatic recording procedure optimising the reproducibility of measurements. For most of the surface-active agents the standard deviation of the measurement was computed and the values obtained were below 0.3 HLB unit.

Dielectric constant determination of HLB

Polarity is a physical notion which permits the evaluation of the ability of a molecule to disperse or dissolve either in aqueous solution or in a lipophilic organic liquid. Polarity can be determined for a pure liquid with the help of the dielectric relative permittivity, the so-called dielectric constant (ϵ).

Such an evaluation is very simple to perform for a non-polar liquid and easy for the most polar liquids under the condition that they contain no dissolved electrolytic substance. The polarity (P) is directly related to the dielectric constant (Eqn 3), hence the term for the dielectric constant is always substituted for the polarity:

$$P = (\epsilon - 1)/(\epsilon + 2) \tag{3}$$

The experimental determination of the HLB has been described previously (Gorman and Hall, 1963): the first step consists of measuring the dielectric constant ϵ of the surface-active agent in the liquid state, the second step relating the experimental data to the HLB scale using the general equation:

$$\mathrm{HLB} = a \cdot \log \epsilon + b \tag{4}$$

Differents measurements of the dielectric constant of surface-active agents, previously dehydrated by heating in an oven overnight, were conducted using a Q-metre Ferisol M803A (Ferisol, Courbevoie, France) fitted with a thermostated hollow cell with an oscillator frequency of 1340 kHz. Heating of the sample was carried out at high temperature ($T = 60°\mathrm{C}$) in order to avoid error due to the presence of solid particles suspended in the liquid. The measurement cell was filled with the surface-active agent and a delay time of 5 min was employed to permit equilibration of the temperature of the sample. Two measurements were made at 5 min intervals to ensure reliability. The cell was then cleaned with water and dried with acetone.

Results and Discussion

The HLB data obtained from NMR and dielectric constant measurement are listed in Table 2. For the sake of consistency, a comparison of the experimental results with those in the literature and manufacturers' data was undertaken, leading to the following observations.

NMR data

For hydrophilic surface-active agents, the HLB value determined via NMR is close to the literature data (Table 2). For example, if we compare the ethylene oxide (OE) content in the same group of surface-active agents, i.e., Brij 72/76/78 and Brij 92/96/98 (2, 10 and 20 OE molecules), the similarity of the values is closer for surface-active agents with 20 and 10 molecules than those with two molecules. This is readily understood on consideration of the fact that NMR measurement computes the amplitude of the signal, which is greater in the case of 20 and 10 OE.

TABLE 2

HLB values of different commercial surface-active agents (literature, NMR determination and value of dielectric constant)

Surface-active agent	HLB (literature)	HLB (NMR)	Dielectric constant
Tween 20	16.7	16.5	9.89
Tween 40	15.6	15.5	9.49
Tween 60	14.9	15	8.27
Tween 80	15	15.2	9.52
Tween 85	11	11.4	7.53
Span 20	8.6	7.65	5.57
Span 40	6.7	7.1	4.88
Span 60	4.7	5.45	4.28
Span 80	4.3	3.7	4.73
Myrj 45	11.1	11.34	7.15
Myrj 49	15.1	15.5	7.6
Myrj 52	17.2	17.75	9.05
Myrj 53	17.9	17.8	8.45
Myrj 59	18.9	18.85	8.75
Brij 58	15.7	15.7	6.82
Brij 72	4.9	5.6	4.6
Brij 76	12.4	12.9	4.85
Brij 78	15.3	15.4	6.22
Brij 92	4.9	5.7	5.58
Brij 96	12.4	13	5.81
Brij 98	15.3	15.35	4.58
Tefose 63	9–10	9.15	4.9
Tefose 70	9	6	4.9
Tefose 1500	11	10.55	7.45
Tefose 2000	11	11.2	6.06
Mergital OA 6	9.8	9.85	
Plurol stearic	8	7.05	
Plurol oleic	10	7.6	
Cithrol	13.1	13.6	
Stearate PEG 600	13–14	14.65	
Dehymuls STO	1.8	2.3	
Dehymuls SSO	3.7	4.28	
Dehymuls SMO	4.3	4.7	
Dehymuls SMI	4.7	5.2	
Emulgin STO 20	11	11.23	
Emulgin SMO 20	15	14.85	
Monomuls 90098	3.8	3.5	
Lameform TGI		4.92	
Generol 122		0.82	
Generol 122 E5	5	7.52	
Ac. undecylenic 6 OE		14	9
Ac. undecylenic 8 OE		15	9.01
Ac. undecylenic 10 OE		15.3	10.01
Ac. undecylenic 12 OE		16.2	8.1
Ac. undecylenic 14 OE		17.5	8.56
Ac. undecylenic 16 OE		17.4	8.18

If comparison is made at the level of the chemical bond, i.e., the ester or ether linkage between the hydrophilic and lipophilic parts of the molecule (Brij 78: ether with 20 OE vs Tween 60: ester with 20 OE), the agreement is also satisfactory. Comparison between POE stearate and POE sorbitan stearate shows better agreement with the latter. Therefore, the sorbitan in the molecule does not disturb measurements.

With Tefose®, which is a mixture with C16 and C18 chains, the accuracy is mostly convenient (small standard deviation).

For lipophilic surface-active agents (C12 sorbitan ester and undecylenic acid with 6 OE) the results are poor. The rather low accuracy of the data obtained with lipophilic surfactants is due to the considerable spread and weak amplitude of the NMR signal. Hence, the NMR method is appropriate for hydrophilic surface-active agents. For this group one can observe great accuracy for the OE content of the molecule. In addition to this observation, it is interesting to note no loss of accuracy with the type of bond, nature of the hydrophilic part and level of unsaturation of the fatty acid part. The results are consistent since the method employs the computation of the amplitude of the OE protons.

Dielectric constant measurements

Fig. 1 shows a plot illustrating the linear relationship between the HLB value from the literature and the logarithm of the dielectric constant

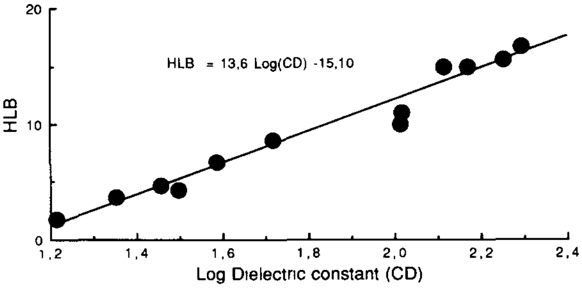

Fig. 1. Correlation between HLB and dielectric constant for POE and non-POE sorbitan esters (C12–C18).

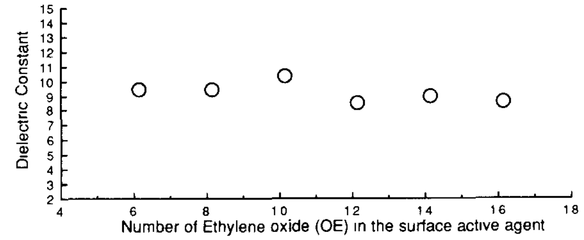

Fig. 2. Dielectric constant data: ether surface-active agents with 6–16 OE.

for the oxyethylated and non-oxyethylated sorbitan ester surface-active agents. This result allows one to determine an equation which correlates the HLB value to the dielectric constant. With this equation, the HLB value of a new surface-active agent in this group can simply be determined by measurement of its dielectric constant.

The linearity observed with the ester surface-active agents does not match that in the case of ether surface-active agents (Figs 2 and 3). With the POE stearates and POE undecylenic acids, the dielectric constant is independent of the number of OE groups in the POE part of the molecule. This observation could be explained as follows:

For the POE or non-POE sorbitan ester surface-active agents, the OE content in the molecule remains constant (either 20 or 0 OE), the variable proportion being the aliphatic part: the dielectric constant changes as a function therof. Consequently, good linearity between the HLB value and dielectric constant can be observed.

In the case of the ether surface-active agents, the molecular changes are related to the proportion of the POE group. It was determined that, in a PEG mixture, the dielectric constant demonstrated a slight change between short and long PEG. Hence, the correlation between the HLB value determined via the dielectric constant as a function of the length of the POE group was observed to be poor.

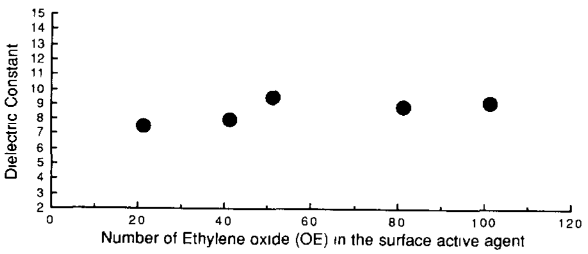

Fig. 3. Dielectric constant data: ether surface-active agents with 20–100 OE.

Taking into account the results obtained using both methods, whilst bearing in mind the limits to feasibility and accuracy according to the different groups of surface-active agents, the following conclusions may be drawn with regard to the technical advantages and drawbacks involved:

NMR determination of HLB values provides results which are consistent with the specific problem of HLB determination. Moreover, it is rapid and accurate, however, appreciable solubility in $CDCl_3$ and the availability of a specific apparatus with a trained operator are required.

Dielectric constant measurement of HLB is a suitable method, especially for esters. It is fast and can easily be run using inexpensive apparatus but is restricted to liquid samples without moisture present.

Conclusion

A large number of methods for the determination of HLB values were proposed, demonstrating a lack of a universal procedure. The main purpose of this work was ascertain which of the physical methods would be the most suitable for providing the best results with the most commonly employed non-ionic surface-active agents. The data for 46 surface-active agents were accurately determined by either H-NMR or dielectric constant measurements.

Neither method is totally appropriate for evaluation of the HLB of lipophilic ether surface-active agents. NMR is most suitable for hydrophilic ether surface-active agents. Both NMR and dielectric constant methods show good agreement for hydrophilic esters. These results are very satisfactory in view of the fact that hydrophilic esters, as a result of having a high HLB value and participating in ester bonding, demonstrate the greatest tolerance and are widely used in pharmaceutics, the food industry and cosmetics as emulsifiers, solubilizers, wetting agents and detergents.

References

Adamson, A.W., Emulsions: preparations and stability. In *Physical Chemistry of Surfaces,* Wiley, 3rd Edn, 1976, pp. 506–542.

Chun, A.H.C. and Martin, A.N., Measurement of hydrophile-lipophile balance of surface-actives agents. *J. Pharm. Sci.,* 50 (1961) 732–737.

Becher, P., Present status of hydrophile-lipophile balance. *Am. Perfumer,* 76 (1961) 33–41.

Ben-Et, G. and Tatarsky, D., Application of NMR for the determination of HLB values of non-ionic surfactants. *J. Am. Oil Chem. Assoc.,* 49 (1972) 499–500.

Berguerio, J.R., Bao, M. and Casares, J.J., Determination of HLB of non-ionic dispersants by NMR. *Anal. Quim.,* 74 (1978) 529-530; 1941–1942.

Carrion, J.L. and De la Guardia, M., Medina Determicion por espectroscopia de RMN de propriédades medias de condensados de oxido de etileno con nonilfenol. *J. Quim. Anal.,* 11 (1983) 271–276.

Crooks, P.A., Colett, J.H. and Witington, R., The determination of the hydrophile hydrophobe proton ratio in a serie of polyoxyethylene sorbitan esters. *Pharm. Acta Helv.,* 49 (1974) 274–276.

Davies, J.T. and Rideal, E.K., *Interfacial Phenomena,* Academic Press, New York, 1961, pp. 371–375.

Davies, J.T., A quantitative kinetic theory of the emulsion type: I. Physical chemistry of the emulsifying agent. *Proc. 2nd Int. Congr. Surface Activity, London* 1 (1957) 426–438.

Deem, D.E., Surfactant analysis in cosmetic preparations. In Rieger, M.M. (Ed.), *Surfactants and Cosmetics,* Dekker, New York, 1985, Vol. 16, pp. 103–131.

Florence, A.T., Matsen, F. and Puisieux, F., Emulsions stabilization by non-ionic surfactants: the relevant of surfactants cloud point. *J. Pharm. Pharmacol.,* 27 (1975) 385–390.

Gorman, W.C. and Hall, G.D., Use of the dielectric constant in the classification of surfactatns. *J. Pharm. Sci.,* 52 (1963) 442–448.

Greenwald, H.L., Brown, G.L. and Fineman, M.N., Determination of the hydrophile-lipophile character of surface-active agent and oils by a water titration. *Anal. Chem.,* 28 (1956) 1693–1700.

Griffin, W.C. and Behrens, R.W., Basis for test of emulsifiable concentrates of agricultural chemicals. *J. Agric. Food Chem.,* 1 (1953) 720–724.

Griffin, W.C., Ranauto, H.J. and Adams, A.D., Studies on emulsions systems. *Arch. Biochim. Cosmetol.,* 9 (1966) 87–88; 93–102.

Griffin, W.C., Classification of the surface-active agents by HLB. *J. Soc. Cosm. Chem.,* 1 (1949) 311–326.

Griffin, W.C., Calculation of hydrophile-lipophile balance values of non-ionic surfactants. *J. Soc. Cosm. Chem.,* 5 (1949) 311–326.

Griffin, W.C., Mixed higher polyalkylene ethers of hexitols. *Am. Perfum. Cosm.,* 65 (1955) 26–30.

Hayano, S., Nihongi, F. and Asahara, T., Thin layer chromatographic analysis of polyoxyethylene nonyl phenol ether. *Chim. Phys. Appl. Prat Ag. Surface, CR Congr. Int Detergents,* 2 (1968) 843–851.

Heusch, R., Experimental method for the determination of the HLB of surface-active agents. *Kolloid Z. Polym.,* 236 (1970) 31–39.

Huebner, V., Determination of the relative polarity of surface active agents by gas-liquid chromatography. *R. Anal. Chem.,* 34 (1962) 488–491.

Laurent, A., Emulsification de mélanges d'hydrocarbures aliphatique et aromatique en milieu ionique concentré Thèse Doctorat Sciences pharmaceutiques Paris XI, No. 43, 1990.

Lin, T., Adverse effects of excess surfactants upon emulsification. *J. Cosm. Toiletries,* 5 (1991) 71–77.

Marszall, L., Relationship of HLB, cloud point and the phenol index of non-ionic surfactants. *Cosm. Toiletries,* 94 (1979) 29–36.

Marszall, L., The effective hydrophile-lipophile balance of non-ionic surfactants in presence of additives. *J. Colloid Interface Sci.,* 65 (1978) 589–591.

Marszall, L., A titration method for the determination of the effective HLB of non-ionic surfactants. *Pharm. Ind.,* 42 (1980) 416–419.

Marszall, L., Measurements of the effective HLB value of the non-ionic surfactants in the presence of electrolytes. *Tenside Deterg.,* 18 (1981) 25–32.

Middleton, J.J., Titration determination of hydrophile-lipophile balance of emulsions. *J. Soc. Cosm. Chem.,* 19 (1968) 129–165.

Mouazen, F., Propriétés dielectriques de solvants et de surfactifs. Etude comparée des notions de constantes diélectriques et de HLB. Thèse Doct. Etat Pharm. série E80 Paris XI, 1978.

Racz, I. and Orban, E., Calorimetric determination of the hydrophile-lipophile balance of surfaces substances. *J. Colloid Interface Sci.,* 20 (1965) 99–103.

Rimlinger, G., Emulsions and thermodynamics. *Parfum. Cosm. Sav.,* 7 (1964) 396–402.

Ross, S., Chen, E.S., Becher, P. and Ranavio, H.J., Spreading coefficient and hydrophile-lipophile balance of aqueous solutions of emulsifying agents. *J. Phys. Chem.,* 63 (1959) 1681–1684.

Rowe, R.C., Calorimetric studies on some non-ionic surfactants in *Int. J. Pharm.,* 79 (1992) 251–255.

Schott, H., Solubility parameter and HLB of non-ionic surfactants. *J. Pharm. Sci.,* 73 (1984) 790–793.

Schott, H., Comments on hydrophile-lipophile balance systems. *J. Pharm. Sci.,* 79 (1990) 87–88.

Schott, H., Hydrophile-lipophile balance and cloud point of non-ionic surfactants. *J Pharm. Sci.,* 58 (1969) 1443–1452.

Seiller, M., Les émulsions. Etude du HLB critique d'une huile de vaseline, Th. Doct. Etat Pharm. Univ. Paris V, No. 224, 1971.

Tadros, T.F. and Vincent, B., Emulsion stability. *Encycl Emulsion Technol. I,* Dekker, New York, 1983, Chap. 3, pp. 129–287.

Van Alstine, J.M., Sharp, K.A. and Brooks, D.E., Critical Micelle concentration dependence on head group size in polyoxyethylene non-ionic surfactants. *Colloid Surface,* 17 (1986) 115–121.

Vold, R.D. and Vold, M.J., *Coll. Interface Chem.,* Addison Wesley, Reading, 1983, pp. 398–347.