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# Theoretical evaluation of dispersed droplet radii in submicron oil-in-water emulsions

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## Summary

A theoretical model which predicts the mass mean radius for oil droplets dispersed in aqueous media is described. Using a modified equation of state for interfacially adsorbed films and the LaPlace equation, the oil droplet radii can be described as a function of several variables including the oil concentration, surfactant concentration and surfactant hydrophile/lipophile balance (HLB). All relevant parameters are measurable or readily calculated. Eighteen experimental emulsions were evaluated utilizing 10% or 20% v/v soy oil and 0.5–3.0% w/v non-ionic surfactant (Myrj 45/glycerol monostearate; HLB 9.5, 10.0 or 10.5). The emulsification technique used for the experimental emulsions utilized the Microfluidizer device, which produces uniform and highly turbulent homogenization. Using these components and processing techniques it is possible to produce submicron o/w emulsions with low interfacial surfactant concentrations. Under these conditions, there is good agreement between the measured droplet radii and the proposed theoretical mechanisms governing their production. This agreement also extends to published data where submicron emulsions have been produced at relatively low o/w interfacial surfactant loading. This non-empirical approach to emulsion droplet size analysis may have predictive value in optimizing submicron emulsion droplet size under the proposed conditions.

## Introduction

During emulsification competing processes of droplet size reduction, aggregation and coalescence simultaneously occur (Gopal, 1968; Mlynek et al., 1972). Factors which govern the final droplet size distributions include the physicochemical properties of the emulsion (Sherman, 1960) and its constituents (Rowe, 1965) and the hydrodynamic properties of the emulsification technique (Davies, 1972). Some of the important physicochemical properties studied herein include the internal (oil) phase volume, surfactant hydrophile/lipophile balance (HLB) and surfactant concentration.

Previous approaches describing emulsion droplet radii have not fully developed a mechanistic evaluation of results (Rowe, 1965; Walstra, 1983). Typically, *empirical* log-linear relationships are used to correlate bulk surfactant concentration and oil droplet size (Rowe, 1965; Carstensen, 1973). While these empirical correlations are potentially useful and applicable they are *independent* of any specific physical mechanisms.

For the case of submicron oil-in-water emulsions with low o/w interfacial non-ionic surfac-

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tant loadings, a non-empirical method of analysis and prediction of mass mean droplet radii is proposed and evaluated. Uniform and highly turbulent homogenization is desired so that a consistently high shear load is achieved during emulsification resulting in the production of submicron-sized droplets with a narrow polydispersity. This approach reduces some hydrodynamic variables to constants and allows for a more direct investigation of the physicochemical properties of the emulsion constituents which affect oil droplet size.

Submicron emulsion systems are investigated primarily because submicron emulsion droplets are more stable to post-homogenization coalescence at low surfactant loading than equivalent coarse emulsions (Korstvedt et al., 1984; Lostritto et al., 1987). In addition, submicron-sized emulsions possess potential utility as parenteral drug delivery systems (Davis et al., 1985). The role of droplet size in drug release control from these systems has been established (Lostritto et al., 1987).

## Theory

The net pressure ($\Delta P$, dyne/cm$^2$) across the oil/water interface for a dispersed *spherical droplet* of radius $r$ (cm) is described by a special case of the LaPlace equation (LaPlace, 1806) as:

$$\Delta P = 2\gamma_i / r \tag{1}$$

where $\gamma_i$ is the o/w interfacial tension (dyne/cm). The o/w interfacial tension is related to the interfacial tension of the pure liquid components ($\gamma_i^0$, dyne/cm) and the concentration of the surfactant ($C_i$, g/cm$^2$) actually present at the o/w interface and may be estimated by:

$$\gamma_i = \gamma_i^0 - BC_i \tag{2}$$

where $B$ (erg/g) is a constant for a given surfactant and represents a measure of the adhesional interaction between the interface and the surfactant.

To estimate $C_i$, it is assumed that essentially all of the surfactant is present at the o/w (Lostritto et al., 1987). It is further assumed that the droplets are monodisperse with a mass mean radius of $\bar{r}$. Under these constraints:

$$C_i = \frac{C_b V_t}{4\pi \bar{r}^2 N} \tag{3}$$

where $C_b$ is the bulk concentration of surfactant (g/cm$^3$) present in an arbitrary total volume of emulsion ($V_t$, cm$^3$) containing $N$ oil droplets of radius $\bar{r}$. The denominator of Eqn. 2 represents the total interfacial area for $N$ monodisperse spheres and serves as a good estimate of the total interfacial area for any symmetrical distribution of oil droplets with mean radius $\bar{r}$. Using Eqn. 2 and elementary geometric arguments it can be shown that:

$$C_i = \frac{C_b \bar{r} V_t}{3V_i} \tag{4}$$

where $V_i$ is the internal phase (oil) volume present in the total emulsion $V_t$.

Combining Eqns. 1 and 2, and rearranging yields:

$$\bar{r} = \frac{2\gamma_i^0}{\Delta P} - \frac{2BC_i}{\Delta P} \tag{5}$$

with $C_i$ described by Eqn. 3 or 4. A linear relationship between $\bar{r}$ and $C_i$ is predicted with a slope of $-2\ B/\Delta P$ and an intercept of $2\gamma_i^0/\Delta P$. The net interfacial pressure, $\Delta P$, is assumed to be independent of $C_b$ for a given emulsion system (constant $V_i$ and HLB). The rationale behind this assumption is as follows. When a droplet of radius $\bar{r}$ is formed during homogenization, it must be protected from aggregation and coalescence through the formation of a suitable surfactant film at the o/w interface. If this droplet persists and subsequently encounters a force greater than $\Delta P$, it will deform and may rupture into smaller droplets (Walstra, 1983) increasing the total interfacial area. Thus droplet formation decreases $C_i$. If sufficient time is spent homogenizing the emulsion, the surfactant is ultimately spread as thinly as possible over the maximum interfacial area possible. At this point, a maximum and constant value of $\Delta P$ is expected with that surfactant system. Thus, for a fixed oil volume, changing the bulk surfactant concentration ($C_b$) ultimately manifests as a larger number of smaller droplets. Furthermore, the ultimate $\Delta P$ value should be a function of the homogenization force, and evidence exists to support this (Siciliano et al., 1987; Korstvedt et al., 1984). Therefore $\Delta P$ may be assumed independent of $C_b$ only under conditions of uniform homogenization. It is assumed that the Microfluidizer device produces an essentially uniform homogenization force and that 5 cycles are sufficient to effectively reach maximum $\Delta P$. Previous results (Korstvedt et al., 1984) suggest that the minimum droplet size (i.e. maximum $\Delta P$) is attained after 5 cycles. Rearranging Eqn. 5 yields:

$$\bar{r}\Delta P/2 = \gamma_i^0 - BC_i \qquad (6)$$

From Eqn. 6 a linear relationship between $\bar{r}\Delta P/2$ and $B\ C_i$ is predicted with a slope of $-1$ and an intercept of $\gamma_i^0$. This relationship is normalized for changes in $\Delta P$ and $B$ between emulsion systems and allows for a comparison of all data so long as homogenization conditions are essentially constant.

Utilizing Eqn. 6 it is possible to demonstrate the relationship between the efficiency of a surfactant and the net film pressure. A "good" surfactant which stabilizes a given droplet of radius $\bar{r}$ at a lower interfacial concentration ($C_i$) must result in a higher net pressure ($\Delta P$) than a less efficient surfactant. The so-called "good" surfactant is capable of stabilizing a greater o/w interface at lower interfacial concentrations. For a given mass of surfactant, correspondingly smaller droplets are expected.

Solving Eqn. 5 for $\bar{r}$ in terms of the bulk concentration of surfactant ($C_b$) yields:

$$\bar{r} = \frac{\gamma_i^0}{\dfrac{\Delta P}{2} + \dfrac{BV_tC_b}{3V_i}} \qquad (7)$$

Eqn. 7 is a non-empirical equation which may be used to predict $\bar{r}$ as a function of $C_b$.

## Experimental

### *Materials*

Soy oil, USP (Sigma), glycerol monostearate (Baker), myrj 45 (Ruger) monobasic sodium phosphate (Baker) and sodium chloride (Baker) were used as received. All other chemicals used were of reagent grade or A.C.S. grades. Double glass distilled water was used throughout the experiments.

### *Methods*

All emulsions were prepared as follows. Three non-ionic surfactant mixtures (HLB 9.5, 10.0 and 10.5) of Myrj 45 and glycerol monostearate where prepared in advance. Isotonic phosphate buffer (0.066 M, pH 7.4) was prepared as needed. An appropriate amount of surfactant mixture to make a bulk concentration of 0.5, 1.0 or 1.5% w/v was combined with 5 ml soy oil; or 1.0, 2.0 or 3.0% w/v was combined with 10 ml soy oil in a 50 ml graduated cylinder. The final volume was adjusted to 50 ml with buffer. This mixture was heated at 100 °C for a maximum of 10 min to melt the surfactant mixture. Coarse emulsions were then formed by vigorously shaking the mixtures several times as the mixture cooled to room temperature.

All coarse emulsions were then microfluidized using a M-110 Microfluidizer device on loan courtesy of Microfluidics (Newton, MA). Each emulsion was cycled 5 times at inlet air pressures of approximately 80 psi. The resultant submicron emulsions were collected and droplet radii distribution analyses were performed courtesy of Microfluidics using dynamic laser light scattering (Nicomp 200).

## Results and Discussion

Table 1 summarizes the number mean ($\bar{r}_N$) and mass mean ($\bar{r}$) radii for the 18 experimental emulsions. These systems were stable for at least 8 days with no significant changes in mean droplet radii or droplet distributions during that time period. All size measurements were done within this period. Number and mass mean radii were determined from the respective frequency distribution data. Polydispersity ($P$) as $\bar{r}/\bar{r}_N$, is provided

TABLE 1

*Summary of droplet size data*

| HLB | % oil (v/v) | % surfactant (w/v) | $\bar{r}_N$ (nm) | $\bar{r}$ (nm) | $P$ |
|---|---|---|---|---|---|
| 9.5 | 10 | 0.5 | 209.8 | 291.0 | 1.38 |
| 9.5 | 10 | 1.0 | 119.1 | 183.3 | 1.54 |
| 9.5 | 10 | 1.5 | 82.5 | 108.3 | 1.31 |
| 9.5 | 20 | 1.0 | 290.3 | 379.6 | 1.31 |
| 9.5 | 20 | 2.0 | 163.7 | 226.7 | 1.38 |
| 9.5 | 20 | 3.0 | 107.8 | 154.0 | 1.43 |
| 10.0 | 10 | 0.5 | 112.7 | 153.0 | 1.36 |
| 10.0 | 10 | 1.0 | 86.9 | 115.9 | 1.33 |
| 10.0 | 10 | 1.5 | 77.0 | 101.0 | 1.31 |
| 10.0 | 20 | 1.0 | 186.5 | 272.6 | 1.46 |
| 10.0 | 20 | 2.0 | 106.6 | 152.3 | 1.43 |
| 10.0 | 20 | 3.0 | 88.9 | 112.6 | 1.27 |
| 10.5 | 10 | 0.5 | 104.8 | 157.2 | 1.50 |
| 10.5 | 10 | 1.0 | 101.1 | 121.3 | 1.20 |
| 10.5 | 10 | 1.5 | 78.8 | 98.5 | 1.25 |
| 10.5 | 20 | 1.0 | 101.2 | 159.1 | 1.57 |
| 10.5 | 20 | 2.0 | 91.8 | 140.8 | 1.53 |
| 10.5 | 20 | 3.0 | 81.9 | 107.5 | 1.31 |

TABLE 2

*Estimation of $\Delta P$ and $B$*

| HLB | % oil (v/v) | $\Delta P \times 10^{-5}$ (dyne/cm$^2$) | $B \times 10^{-7}$ (erg/g) |
|---|---|---|---|
| 9.5 | 10.0 | 4.90 | 3.69 |
| 9.5 | 20.0 | 4.08 | 2.75 |
| 10.0 | 10.0 | 24.7 | 2.51 |
| 10.0 | 20.0 | 4.95 | 4.00 |
| 10.5 | 10.0 | 19.5 | 2.96 |
| 10.5 | 20.0 | 30.0 | 0.675 |

as a measure of the dispersion of the emulsions. In no case was the polydispersity greater than 1.57 which demonstrates the relatively narrow droplet size distributions of the emulsions. The mean polydispersity ($\bar{P}$) was 1.38 ± 0.03 (±S.E.M., $n$ = 18).

Fig. 1 depicts 18 experimentally determined mass mean droplet radii ($\bar{r}$) vs bulk surfactant concentration ($C_b$) for two oil concentrations (10% and 20% v/v) and 3 surfactant HLB values (9.5, 10.0 and 10.5). The solid curves in Fig. 1 are *theoretical predictions* of the $\bar{r}$ and are discussed elsewhere in this section (infra).

Using Eqn. 5 and the experimental $\bar{r}$ values, $\Delta P$ and $B$ may be calculated for each case of fixed oil concentrations and surfactant HLB. These values are listed in Table 2.

As discussed in the theoretical section, more efficient surfactant systems will effectively stabilize smaller droplets with larger net interfacial pressures ($\Delta P$) at lower interfacial surfactant concentrations (Eqn. 8). Except for the HLB 10.5 at 20% oil concentration the $B$ values (Table 2) are similar ($\bar{B}$ = 3.18E7 ± 2.8E6, ±S.E.M., $n$ = 5). At the higher HLB 10.5 surfactant concentrations (with 20% oil) some foaming was observed in the coarse emulsion reservoir during microfluidization. It is possible that small air bubbles may have been trapped within the emulsion during microfluidization. Trapped air would alter the com-

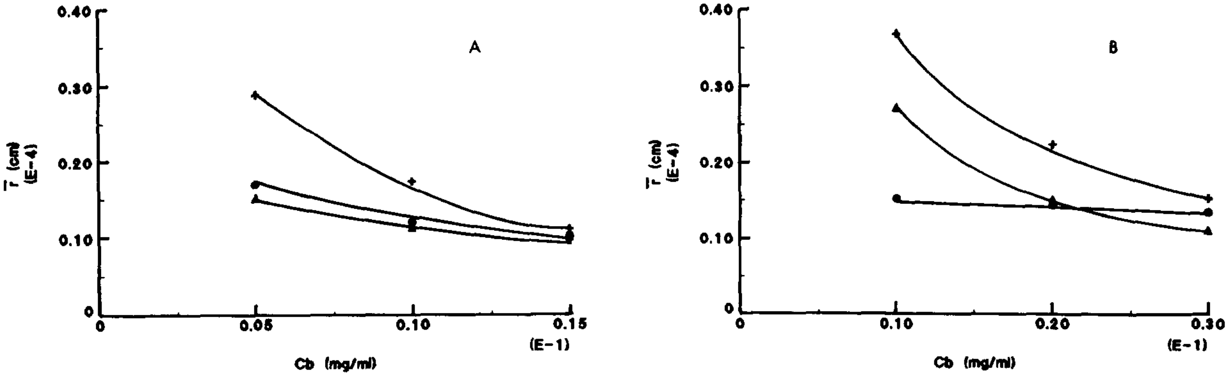

Fig. 1. Mass mean droplet radius ($\bar{r}$) versus bulk surfactant concentration ($C_b$) for 3-HLB values: 9.5 (+), 10.0 (●), and 10.5 (▲); and two oil concentrations: 10% (A) and 20% (B). The curves are theoretical estimates using Eqn. 9.

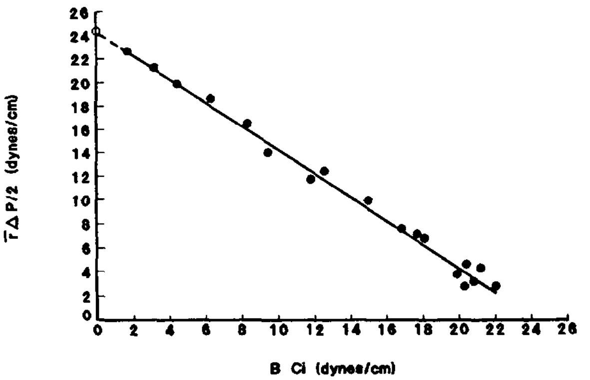

Fig. 2. Normalized linear relationship for 18 experimental emulsions (●). The line is the theoretical estimate using Eqn. 6 and the independently measured intercept (○).

pressibility of the emulsion which may effect the pressure gradient within the Microfluidizer interaction chambers. The other systems did not exhibit any observable foaming. Because the binary surfactant mixture does not radically change in composition from HLB 9.5 to 10.5, a *similar* o/w interfacial adhesion ($B$) with these surfactant systems is expected.

Using the $\Delta P$ and $B$ values in Table 2 and the $\bar{r}$ and $C_b$ data from Fig. 1, a plot of $\bar{r}\Delta P/2$ versus $BC_i$ was constructed (Fig. 2) for all 18 emulsions (solid circles). The open circle represents the predicted $y$-intercept of $\gamma_i^0$. The $\gamma_i^0$ value of 24.4 dyne/cm was measured using a DuNouy Tensiometer equipped with a 6 cm circumference Pt-Ir ring. The solid line represents the *theoretical* slope of $-1$ according to Eqn. 6. This theoretical slope is indistinguishable from a linear regression of the data depicted. Thus all 18 emulsions are comparable using a single theoretical relationship despite the lack of any unifying trend in the raw data ($\bar{r}$ versus $C_b$, Fig. 1).

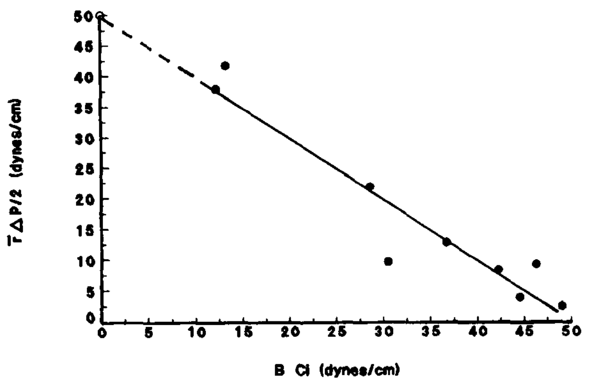

Fig. 3. Normalized linear relationship for 9 emulsions taken from the literature (●). The line is the theoretical estimate using Eqn. 6 and the intercept (○) is calculated from literature values.

A similar analysis was performed on data previously published (Korstvedt et al., 1984) for 9 mineral oil-in-water emulsions. These emulsions contained 10%, 20% or 30% v/v mineral oil and 0.5–8% v/v of a Tween/Span surfactant mixture (HLB Kit-Chem Services Co.). Their droplet size data, reported in their Table 1 as $\bar{r}$ versus $C_b$, was analyzed by our proposed methods. Fig. 3 represents the proposed linear plot of $\bar{r}\Delta P/2$ versus $BC_i$ for these 9 emulsions (constant HLB). The intercept represents $\gamma_i^0$ for the mineral oil/water interface and is calculated from the spreading coefficient of mineral oil on water and the surface tension of the pure liquids (Harkins, 1952). The slope is plotted as the theoretical value of $-1$. The slope and intercept values describe a line which is indistinguishable from a linear regression of the data.

Using Eqn. 7 and the calculated $B$ and $\Delta P$ values, the predicted $\bar{r}$ function for each case is depicted as solid lines in Fig. 1. The poorest $\bar{r}$ prediction differs from the experimental value by 6.4%. The mean absolute value percent difference between predicted and measured $\bar{r}$ value is 2.18 ± 0.41% (S.E.M., $n = 18$).

## Conclusions

A novel method of analyzing emulsion droplet size data has been presented which is based on the LaPlace equation for dispersed spheres and the o/w interfacial concentration of surfactant. It is possible to reduce certain physicochemical parameters of the emulsion constituents and the homogenization process into a form such that different systems may be compared under a unifying hypothesis. It is proposed that the effect of bulk surfactant concentration on dispersed droplet radii may be described using the non-empirical model described herein. This model has been shown to be applicable to experimental data as well as data reported in the literature where submicron-sized droplets are produced at low interfacial surfactant loads.

The theory does not extend to emulsions with high interfacial surfactant loadings nor does it apply to coarse emulsions. Emulsions formed under the conditions of high surfactant concentration or low shear processing techniques will contain oil droplets with multimolecular surfactant films. In addition, the possibility of the formation of surfactant micelles would exist. Such systems would violate the condition of low surfactant loading upon which this model is based and has been shown to apply. However, it is possible to accurately predict the mass mean radius to within a few percent provided the conditions and assumptions inherent in the model are met and that some size data is available to estimate $\Delta P$ and $B$.

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