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MASS TRANSFER STUDIES ON MULTIPLE EMULSION AS A CONTROLLED MASS RELEASE SYSTEM

Myungsoo KIM* and Dinesh O. SHAH

*Korea Standards Research Institute, Taejon 305-606, Korea

Center for Surface Science & Engineering, University of Florida, Gainesville, FL 32611, U.S.A.

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Abstract—A novel type of multiple emulsions which contain a microemulsion in macrodroplets, was prepared by a two-step emulsification procedure. Mineral oil was used as the oil phase with a mixture of Aerosol OT and Span 20 as primary emulsifiers. A water-in-oil microemulsion was prepared by gradual addition of water in oil containing both these emulsifiers. This microemulsion system, when dispersed in an aqueous solution containing secondary emulsifier, produces water-in-oil-in-water (W/O/W) multiple emulsions.

The release rate of solute dissolved in the internal aqueous phase was measured using the dialysis technique. A theoretical model describing the diffusion of a multiple emulsion system was developed, which predicts the half-life for 50% of the internal solute to diffuse to the external phase. Experimental results showed the stability of multiple emulsions improved significantly upon using a thermodynamically stable microemulsion as a primary emulsion and a polymeric surfactant as a secondary emulsifier. As a result, half-life of these multiple emulsions is greater than that of conventional multiple emulsions.

INTRODUCTION

Emulsions have been known for a long time as mixtures of two immiscible liquids, one of them being dispersed as a droplet in the other [1-3]. Multiple emulsions are emulsions in which the drops of the dispersed phase contain even smaller droplets of the external phase [4,5]. Two major types of multiple emulsions can exist, one being water-in-oil-in-water (W/O/W) type where internal and external water phases are separated by an oil phase, and the other being oil-in-water-in-oil (O/W/O) type where two oil phases are separated by an aqueous phase. Because the inner and outer liquid phases of multiple emulsions are separated by another immiscible liquid layer, they are also called "liquid membranes" [6-8].

The ability of W/O/W multiple emulsions to entrap a water soluble material inside and to separate it from the external water makes them very useful in many areas of applications, particularly in separation industries [9-11] and pharmaceutics [12-14]. Multiple emulsions can be used either as a device for controlled mass transfer when the material to be released is solubilized in the internal phase as a source, or as a separating device when the internal phase acts as a sink for the material to be extracted from the external phase. However, their inherent physical instability makes them very difficult to use in practical applications [14,15].

The basic purpose of this study was to evaluate the multiple emulsions as a candidate for a controlled mass release system. Hence the problem is how to estimate the mass transfer rate from the internal to external phase of multiple emulsion and how to improve the stability of such systems for practical applications. A simplified mathematical model describing the mass transport across the membrane interface for a multiple emulsion system was presented. From the model, half-life for the concentration of a solute to decrease by 50% can be estimated. Also, the present study shows some approaches to improve multiple emulsion stability and experimental measurements of mass transfer rates for W/O/W multiple emulsion systems.

THEORY

A schematic representation of W/O/W type multiple emulsion is shown in Fig. 1. For mathematical simplification, we assume that all the internal water droplets form one large sphere in the center of the oil drop, and the corresponding concentration profile is also shown in Fig. 1.

Mass flux of internal solute across the membrane

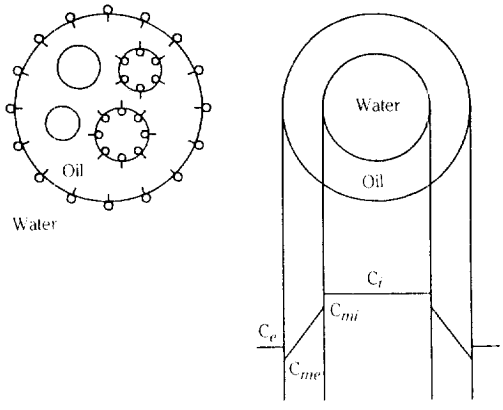

Fig. 1. Schematic representation of a W/O/W multiple emulsion and its simplified model and solute concentration profile.

(here oil layer) can be expressed by following Fick's first law,

$$\frac{dM_t}{dt}=DA\frac{dC}{dx}=DA\frac{C_{mi}-C_{me}}{\delta}=\frac{DAK}{\delta}(C_i-C_e) \quad (1)$$

where M_t denotes amount of mass diffused during time t, D is diffusion coefficient, A is surface area of inner droplet, C is concentration in each phase, δ is thickness of membrane(oil) layer, and K is partition coefficient of solute in oil and water phase which is solubility ratio between membrane and bulk phase (C_m/C). And subscripts i, e and m denote the interna , external and membrane phase respectively.

Total mass of solute is kept constant during the time as a sum of the solute mass in the internal and external phases.

$$M^T=M_i+M_e=\text{const.} \quad (2)$$

Initially all the solute mass exists inside the internal water droplet, such that $M^T=M_i$ at $t=0$. If we assume that the volume of each phase does not change with time, then the concentration in each phase is given by

$$C_i=M_i/V_i,\quad C_e=M_e/V_e. \quad (3)$$

Eq. (1) can be rewritten by using Eqs. (2) and (3),

$$\frac{dM_e}{dt}=\frac{DAK}{\delta}\left(\frac{M^T-M_e}{V_i}-\frac{M_e}{V_e}\right)$$

$$=\frac{DAK}{\delta V_i}\left(M^T-\left(1+\frac{V_i}{V_e}\right)M_e\right). \quad (4)$$

After rearranging Eq. (1) and integrating,

Table 1. Estimated half-life for spherical aggregate systems

Spherical system	Thickness (δ)	Radius (R)	Half-life ($t_{1/2}$)
Emulsion	20 Å	100 Å-1 μ	0.05- 5 s
Liposome	40 Å	0.1-1 μ	1-10 s
Multiple emulsion	1-10 μ	0.1-1 μ	4 min- 6 h

$$\ln\left[1-\left(1+\frac{V_i}{V_e}\right)\frac{M_e}{M^T}\right]=\left(1+\frac{V_i}{V_e}\right)\frac{DAK}{\delta V_i}t. \quad (5)$$

For spherical structure, the surface area to volume ratio is $A/V_i=3/R$, where R is the radius of an inner sphere. Let $E=V_i/V_e$, the volume ratio between the internal and the external phase, then the fractional amount of mass released to external phase becomes

$$\frac{M_e}{M^T}=\frac{1}{1+E}\left\{1-\exp\left[-\frac{3DK}{\delta R}(1+E)t\right]\right\} \quad (6)$$

Half-life when 50% of the initial solute amount released to external phase, i.e., $M_e/M^T=1/2$ becomes

$$t_{1/2}=\frac{\delta R}{3DK(1+E)}\ln\left(\frac{2}{1-E}\right). \quad (7)$$

In practical systems, the internal volume is quite small compared to the external volume, $V_i \ll V_e$, hence $E\to 0$. With typical values of $D=10^{-8}$ cm^2/s, $K=10^{-4}$ [16,17], the estimated half-life for different spherical systems are compared in Table 1. From Eq. (7), the half-life of the system is proportional to the thickness of the interfacial layer and the size of droplets. For spherical structures such as emulsions, liposomes and multiple emulsions, the size of droplets is in the same order of range (0.1-1 μ). Hence the half-life is mainly dependent upon the thickness of interfacial layer.

For emulsion systems, the interfacial layer is the monolayer of surfactant film, hence the membrane thickness is about 20 Å and the estimated half-life is less than 5 seconds. For the liposome systems whose interface is the bilayer of surfactant film, the estimated half-life is in the order of 10 seconds. For the multiple emulsion systems, the interfacial layer is the bulk oil phase instead of the molecular surfactant layer, hence the thickness of the membrane layer can go up to 10 μ and correspondingly the half-life is increased to the order of several hours.

EXPERIMENTALS

1. Preparation of multiple emulsions

A two-step emulsification procedure [4,5] was used

to prepare a series of W/O/W type multiple emulsions.

In the first step, primary emulsions of W/O type are prepared. The inside water contains 5% of pyridine as a diffusing probe. Light mineral oil (Witco Chemical Co.) with a surfactant mixture of Span 20 (sorbitan monolaurate, ICI Americas) and Aerosol OT (sodium dioctyl sulfosuccinate, Sigma) in the 3:5 weight ratio was used for the formation of W/O microemulsions without using alcohol [18]. The volume fraction of water was 0.1 and the surfactant fraction in oil phase was 0.2.

In the second step, the W/O microemulsion prepared during the first step, is poured into an aqueous solution of hydrophilic surfactant to form a W/O/W type multiple emulsion. The hydrophilic surfactants commonly used are nonionic surfactants such as, Tween 20 (polyoxyethylene-20 sorbitan monolaurate, ICI Americas) or polymeric surfactant Pluronic F108 (BASF) which is an ABA type block copolymer surfactant containing 80% polyoxyethylene and 20% polyoxypropylene with a molecular weight of 14600. The volume fraction of the W/O phase was 0.2 and the surfactant fraction in the aqueous phase was 5 to 10%. Also anionic surfactants, SDS (sodium dodecyl sulfate, Fisher) and sodium laurate (Sigma) with the 1:1 mole ratio of dodecanol, were used as a secondary emulsifier.

2. Measurements of mass transfer rate

To measure the amount of probe material released from the internal phase to the external phase, it is necessary to separate the dispersed phase from the external continuous phase. We adopted dialysis technique which gave an optically clear solution after separation of the solute from the dispersed phase. Dialysis is basically a diffusion process of separation of substances in solution due to the molecular size difference. Only molecularly dispersed material can pass through the dialysis membrane [19]. When applied to a multiple emulsion system, only the probe material released from the internal to external phase can diffuse out to sink solution which is separated by dialysis membrane.

For dialysis measurements, 10 ml of freshly prepared multiple emulsion is poured into a dialysis sack (Spectropor 2 cellulose membrane with molecular weight cutoff 12000-14000) and placed in a flask containing 240 ml of 0.1 M NaCl solution as a diffusion sink. Salt solution has been used to prevent backward diffusion of solvent due to the osmotic effect, and the sink solution is kept well stirred to provide homogeneous distribution of released material. The amount of probe material, here pyridine, diffused out to the external sink solution separated by a dialysis membrane was measured by spectrophotometer (Perkin-Elmer model 576) at certain time intervals. Absorbance measured at 256 nm wavelength was compared with those of calibration curve for standard solution.

RESULTS AND DISCUSSION

1. Approaches to improve stability of multiple emulsions

There are several mechanisms of the breakdown of a multiple emulsion [20,21]. One of the major problems associated with multiple emulsion is "creaming" phenomenon. Multiple emulsions are easily separated into two layers upon standing, one oil-rich (top) and the other oil-lean (bottom) layer, that is due to the large size of multiple drops.

If the initial primary emulsions are unstable, they will easily coalesce to form large droplets inside and consequently break the interfacial layer. The osmotic imbalance between the internal and external phases leads to either swelling or shrinkage of internal droplets, depending on the direction of osmotic gradients. Also, multiple drops themselves may coalesce with each other to rupture the interfacial layer and release the internal droplets.

From the above-mentioned breakdown phenomena, we can improve the stability of multiple emulsions in several ways as follows;

1. Instead of unstable macroemulsion, thermodynamically stable microemulsion can be used as a primary emulsion to prevent internal droplet coalescence.

2. The interfacial film breakdown can be reduced by forming a rigid film around multiple drops with close packed surfactants. A closer molecular packing in the interfacial region can be obtained by combination of a straight chain anionic surfactant with the same chain length alcohol as a secondary emulsifier.

3. The coalescence of multiple drops can be reduced by decreasing the fluidity of the external phase. As the viscosity of the external phase increases, the mobility of drops decreases. We used a polymeric surfactant (Pluronic) in the external phase that would increase the viscosity (Fig. 2) as well as the thickness of interfacial region.

For W/O/W multiple emulsions, the effect of coalescence and breakdown of multiple emulsions can be monitored by observing changes in the viscosity [22,23]. In general, the viscosity of multiple emulsions would decrease due to coalescence and breakdown. This technique has been applied to estimate the stability of multiple emulsions. For the multiple emulsions studied here, the viscosity was measured by the cone-

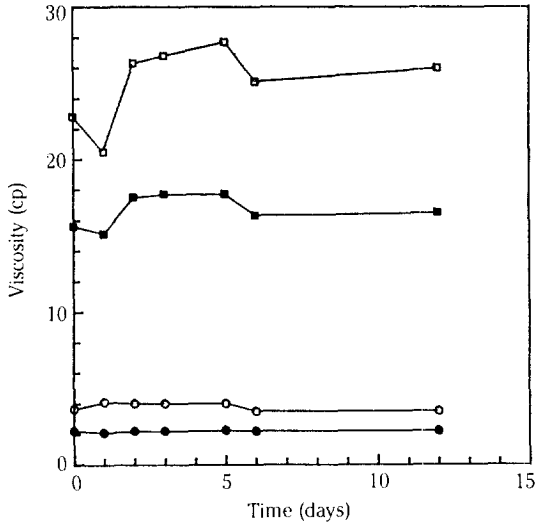

Fig. 2. Viscosity changes for multiple emulsion systems.

- ● W/O microemulsion in 10% Tween 20 aqueous solution
- ○ W/O microemulsion in 20% Tween 20 aqueous solution
- ■ W/O microemulsion in 10% Pluronic F108 aqueous solution
- □ W/O microemulsion in 20% Pluronic F108 aqueous solution

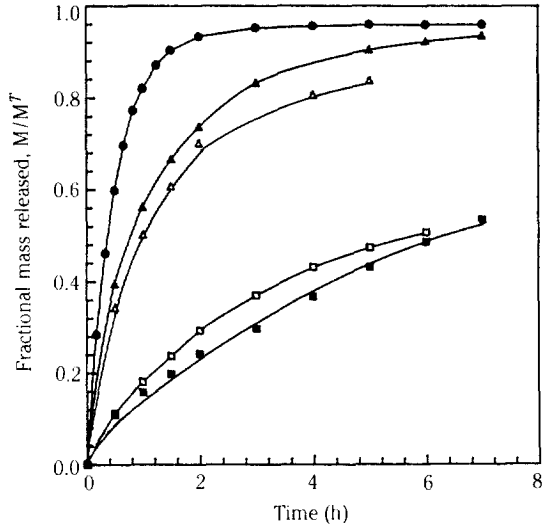

Fig. 3. Comparison of fractional amount of pyridine release measured by dialysis technique.

- ● 0.2% Pyridine in water (reference)
- ■ water:Span 20:mineral oil = 2:1:7 (W/O macroemulsion)
- □ water:(Span 20 + AOT):mineral oil = 1:2:7 (W/O microemulsion)
- ▲ W/O macroemulsion in 5% Tween 20 aqueous solution
- △ W/O microemulsion in 5% Tween 20 aqueous solution

and-plate viscometer (Brookfield model LVT), but the changes over time period were not significant as shown in Fig. 2, once they form multiple emulsions.

2. Mass transfer rate of multiple emulsions

The release rate of a solute from the multiple emulsion depends on several factors, such as the type of primary emulsion, kind of secondary surfactant and concentration, etc. As a reference for the dialysis system, the pyridine release rate from pure water solution was measured. As shown in Fig. 3, almost 90% of pyridine was diffused out within 1.5 hour with a half-life of 20 minutes. Also, the release rates of simple W/O macro- and microemulsion are compared with those of multiple emulsions in Fig. 3. We can compare qualitatively the nature of release pattern of multiple emulsions from the results shown in Figs. 3 and 4.

1. A microemulsion has a large total surface area compared to a macroemulsion, hence the solute diffusion rate should be faster. Although the diffusion rate of a microemulsion is seen to be faster than that of a macroemulsion as shown in Fig. 3, the difference is not significant. This is due to the high resistance of the external oil phase to the water-soluble material to diffuse out.

2. Comparing the release rate of multiple emulsions with that of simple emulsions, the release rate of simple emulsions is seen to be slow. This is contrary to the theoretical prediction indicating the half-life of simple emulsions is longer than that of multiple emulsions. But the reason lies in the fact that during the formation of multiple emulsion, a certain amount of solute is lost to the external phase. Once it is exposed to the external phase, the diffusion rate across dialysis membrane is faster for the multiple emulsion system, because of water-water interface diffusion as compared to oil-water interface diffusion for simple emulsions.

3. Anionic surfactants (SDS or sodium laurate) with alcohol as a secondary surfactant could not provide a rigid molecular packing to mass transfer resistance as seen in Fig. 4. The close packing of monolayer at the interface may not be sufficient to affect the overall release rate change. But the release rate is seen to decrease when using polymeric surfactant which can provide a significantly thick interfacial region around droplets in multiple emulsions.

4. As we increase the hydrophilic surfactant con-

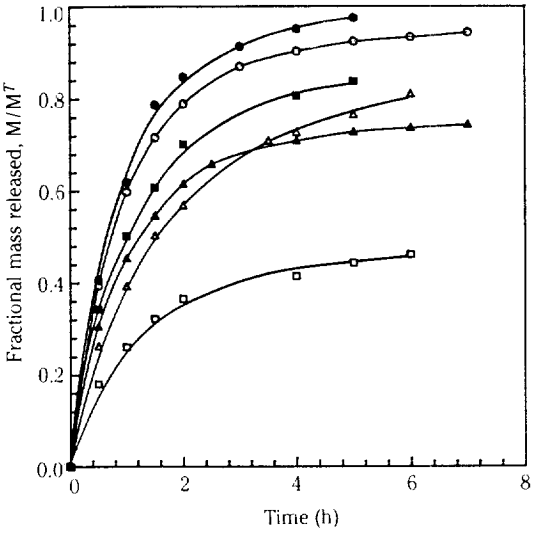

Fig. 4. Fractional amount of pyridine release for various multiple emulsion systems using a microemulsion as a primary emulsion.

- ● W/O microemulsion in 20 mM SDS + dodecanol solution
- ○ W/O microemulsion in 50 mM Sodium laurate + dodecanol solution
- ■ W/O microemulsion in 5% Tween 20 aqueous solution
- □ W/O microemulsion in 10% Tween 20 aqueous solution
- ▲ W/O microemulsion in 5% Pluronic F108 aqueous solution
- △ W/O microemulsion in 10% Pluronic F108 aqueous solution

centration in external aqueous phase, the release rate becomes slower (Fig. 4). Increasing the surfactant concentration will raise the multiple emulsion viscosity. Hence the mobility of multiple drops decreases and consequently drop breakdown will be reduced. But comparing the nonionic surfactant (Tween 20) with polymeric surfactant (Pluronic F108) in Fig. 4, although the viscosity of polymeric system is higher (Fig. 2), the release rate of 10% Tween 20 system is slower. One possibility might be due to the formation of the strong interfacial layer such as liquid crystalline structure, but this has not been confirmed.

5. The order of the overall release rate of multiple emulsions is not much different from that of simple dialysis diffusion in water. This indicates the dialysis membrane resistance is dominating over the emulsion resistance, and also indicates initial loss of the internal phase is quite high. If the initial loss is not significant, the time lag of release should be observed due to dialysis membrane resistance. The amount lost depends on processing conditions, such as the mixing speed and duration time, and these may be critical to the formation of multiple emulsions.

Table 2. Comparison of experimentally measured half-life for various multiple emulsions

Primary emulsion type	Secondary emulsifier	Half-life of multiple emulsion
W/O macroemulsion	Nonionic (Tween 20)	20 min
W/O microemulsion	Anionic (SDS + dodecanol)	20 min
	Nonionic (Tween 20)	40 min
	Polymeric (Pluronic F108)	60 min
Calculated value according to Eq. (7)		4 min-6 h

The overall mass transfer resistance, U, can be divided into two major contribution, one due to dialysis membrane and the other due to emulsion resistance.

$$1/U = 1/U_M + 1/U_E \tag{8}$$

where subscripts M and E denote membrane and emulsion, respectively.

Half-life of the system is inversely proportional to the overall mass transfer resistance, i.e., $t_{1/2} \propto 1/U$. Hence, the overall half-life is the sum of individual half-life.

$$t_{1/2} = (t_{1/2})_M + (t_{1/2})_E \tag{9}$$

From Fig. 3, the half-life of a dialysis membrane, $(t_{1/2})_M$, was 20 minutes. The overall system half-life can be measured from experiment, and the half-life due to emulsion resistance, $(t_{1/2})_E$, can be calculated from Eq. (9). Experimentally measured half-life due to emulsion resistance for different multiple emulsion systems is listed in Table 2. This is comparable to theoretical values for multiple emulsion as calculated in Table 1. Use of a microemulsion instead of a macroemulsion as a primary emulsion can increase the halflife of multiple emulsion from 20 minutes to 60 minutes, and the values are well within the theoretically predicted range. Although, the half-life of multiple emulsion can be increased by 2-3 times using a microemulsion as a primary emulsion, the values are still too small to be used as a drug carrier compared to the shelf-life of several months for pharmaceutical products.

CONCLUSIONS

The following conclusions are drawn from the results of this study;

1. The use of a microemulsion as a primary emulsion is introduced and the stability of multiple emulsion has been improved.

2. The molecular packing at the interface can be improved by appropriate combination of a straight chain surfactant with a long chain alcohol.

3. Dialysis technique can be applied to measure the interfacial mass transfer in multiple emulsions.

4. From the simple mass-diffusion model, half-life of multiple emulsions can be predicted, and the experimental observations are within the range of predicted value.

Further work is still required to delineate the factors affecting the stability of multiple emulsions, such as the method of preparation, selection of oil and surfactant, dispersed phase volume, droplet size, viscosity, etc. Once the problems of stability can overcome, multiple emulsions can be studied in more detail and may show their true potential as a new technology in separation system and controlled mass release system.

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