# Mass Transfer in the Dissolution of a Multicomponent Liquid Droplet in an Immiscible Liquid Environment

Jonathan T. Su and David Needham*

Department of Mechanical Engineering and Materials Science, Duke University, Durham, North Carolina 27708-0300, United States

S *Supporting Information*

ABSTRACT: The Epstein−Plesset equation has recently been shown to predict accurately the dissolution of a pure liquid microdroplet into a second immiscible solvent, such as oil into water. Here, we present a series of new experiments and a modification to this equation to model the dissolution of a two-component oil-mixture microdroplet into a second immiscible solvent in which the two materials of the droplet have different solubilities. The model is based on a reduced surface area approximation and the assumption of ideal homogeneous mixing [mass flux $\mathrm{d}_{m_i}/\mathrm{d}t = A_{\mathrm{frac}_i} D_i (c_i - c_s)\{(1/R) + (1/(\pi D_i t)^{1/2})\}$] where A_{frac_i} is the area fraction of component i, c_i and c_s are the initial and saturation concentrations of the droplet material in the surrounding medium, R is the radius of the droplet, t is time, and D_i is the coefficient of diffusion of component i in the surrounding medium. This new model has been tested by the use of a two-chamber micropipet-based method, which measured the dissolution of single individual microdroplets of mutually miscible liquid mixtures (ethyl acetate/butyl acetate and butyl acetate/amyl acetate) in water. We additionally measured the diffusion coefficient of the pure materials—ethyl acetate, butyl acetate, and amyl acetate—in water at 22 °C. Diffusion coefficients for the pure acetates in water were 8.65×10^{-6}, 7.61×10^{-6}, and 9.14×10^{-6} cm²/s, respectively. This model accurately predicts the dissolution of microdroplets for the ethyl acetate/butyl acetate and butyl acetate/amyl acetate systems given the solubility and diffusion coefficients of each of the individual components in water as well as the initial droplet radius. The average mean squared error was 8.96%. The dissolution of a spherical ideally mixed multicomponent droplet closely follows the modified Epstein−Plesset model presented here.

$$\frac{dm_i}{dt} = A\mathrm{frac}_i D_i (c_i - c_s)\left\{ \frac{1}{R} + \frac{1}{\sqrt{\pi D t}} \right\}$$
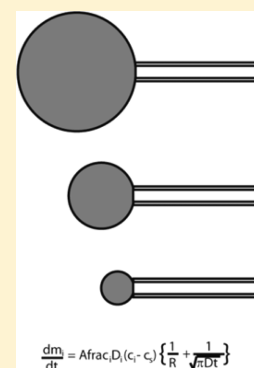
INTRODUCTION

Following the early work of Epstein and Plesset for gas microbubbles, the Needham laboratory has developed new experimental and theoretical models for the dissolution of single-component (gas[1] and oil[2]) and multicomponent (protein solution[3]) liquid droplets in a liquid environment. These models have been experimentally verified using a micropipet technique capable of forming and manipulating single microdroplets of one immiscible liquid in a second dissolving solvent. These single microdroplets have volumes on the order of tens of picoliters and are formed and manipulated in a 0.8 mL glass cuvette. They can therefore be considered to be in infinite dilution and well below their solubility limit. In this article, we present a new model based on the Epstein−Plesset equation for the mass transfer of a single component and two component mixtures of mutually miscible liquids (ethyl acetate, butyl acetate, and amyl acetate) from single liquid microdroplets diffusively dissolving into a second immiscible solvent (water) as well as experimental verification for this model. Additionally, we report three new values for diffusion coefficients of ethyl acetate, butyl acetate, and amyl acetate in water. These single microdroplet studies and accompanying models can now add to our knowledge of multicomponent mixing and mass transfer for multidroplet suspensions on the bulk scale.

In those earlier papers, we used the classic diffusion-based droplet dissolution model of Epstein and Plessett[4] to model the dissolution of air microbubbles in water[1] and then both aniline

droplets in water and water droplets in aniline.[2] Su et al.[5] used the dissolution of water droplets in n-alkanes (n-pentane to n-hexadecane) and n-alcohols (n-butanol to n-octanol) to measure the diffusion coefficients of water in these homologous series, finding that the diffusion coefficients of water in alcohols was some 25 times slower than in the same viscosity alkane. By using a microdroplet of protein solution in n-decanol, Rickard et al.[3] was able to show how, as water is lost, the protein solution concentrates to reduce the water of solution and even the water of hydration of a protein such as lysozyme to a density of 1100 mg/mL.[3] This process of "microglassification" is now forming the basis for new protein preservation and formulation studies.

The micropipet system, mounted on an inverted microscope, allows us to study any liquid−liquid system as long as it is immiscible, that is, as long as the droplet material forms an interface with the surrounding medium. Ethyl acetate, butyl acetate, and amyl acetate were chosen as a model homologous series because they are all soluble in water (Table 1) and are expected to mix ideally in their own liquid solution and each of these chemicals is immiscible with water (Table 1, Figure 4), as can be seen from their positive interfacial tension with water and the ability to form a microdroplet in an aqueous phase. As

Table 1. Solubility Values for Ethyl Acetate,[18] Solubility of Butyl Acetate,[19] Solubility of Amyl Acetate,[20] and Density Values[21]

chemical	density (g/cm^3)	solubility in water (g/cm^3)	interfacial tension with water (dyn/cm)
ethyl acetate	0.895	8×10^{-2}	6.8
butyl acetate	0.879	7.8×10^{-3}	14.5
amyl acetate	0.859	2.2×10^{-3}	15.2

shown schematically in Figure 1, ethyl, butyl, and amyl acetate are all molecules with the same polar acetate group and a
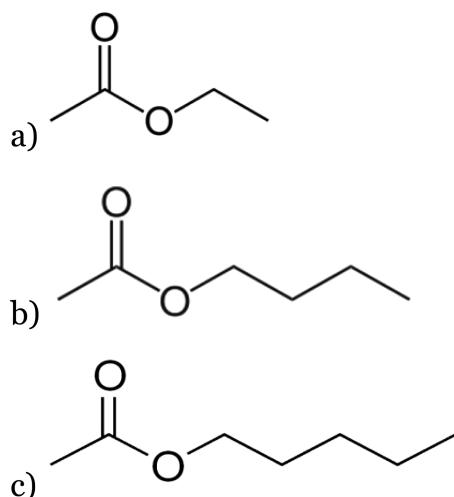
Figure 1. Chemical structures of (a) ethyl acetate, (b) butyl acetate, and (c) amyl acetate.

carbon chain. Ethyl, butyl, and amyl acetate differ only in the length of the carbon chain, with ethyl, butyl, and amyl acetates having two, four, and five carbon chains, respectively. In the model, it is assumed that because these molecules all have the same polar acetate group each molecule should have similar adsorption to the droplet interface with water and hence the same area per molecule normal to the interface. The longer carbon chain results in a lowered solubility in water as shown in Table 1. Because of this lowered solubility, we expect a longer carbon chain to correspond to a slower rate of mass transfer from the microdroplets into the surrounding aqueous medium.

Mass transfer in a system of many droplets is a common occurrence in liquid–liquid extraction processes. Liquid–liquid extraction processes have been used in analytical chemistry since 1892, when Rothe[6] described an extraction method based on the differing solubilities of ferric chloride (soluble) and manganous, nickelous, chromic, and aluminum chlorides (insoluble) in ether in the presence of hydrochloric acid. Since then, liquid–liquid extraction processes have been widely used for a large number of purposes, including the formation of polymer microspheres through solvent evaporation,[7−13] in uranium production,[14] and, in a new innovation from our laboratory, the formation of dehydrated, glassified protein microspheres.[3] Mass transfer in these systems, however, is difficult to model en masse for multiparticle systems. Understanding the mass transfer in a single-droplet system can improve models of more thermodynamically and kinetically complex, multiparticle systems. Nauman,[15] for example,

proposed a simple model for micromixing based on the idea that the mixing of one liquid into another can be modeled by the dissolution of a large number of uniform spherical droplets diffusing into a liquid with a suitable average concentration. Rys[16] proposed a simple mixing-reaction model based on the idea that a liquid mixed into another can be thought of as forming spherical constant-radius liquid elements.

Previous studies of the dissolution of two-component droplets in another liquid have been primarily focused on interfacial turbulence that can rapidly increase mass transfer.[17] Because of the greater interest in the literature in this spontaneous interfacial turbulence, which does not occur in our static system, the purely diffusive dissolution of droplets of a liquid mixture in another liquid remains relatively unexplored and is one motivation for addressing it in this article. In principle, single-particle studies could also explore the interfacial turbulence, which will be addressed in future studies.

We present a new model, based upon a modification of the Epstein−Plesset equation, for diffusive single-particle dissolution of a multicomponent droplet. This model approximates this amount by assuming ideal homogeneous mixing both in the internal volume of the microdroplet and at its interface. Our model has been tested for single microdroplets of short-chain alkyl acetate liquid mixtures by using our signature micropipet-based method. Because this model assumes diffusive dissolution and ideal mixing, it cannot be applied for systems where core−shell structures may form at the microdroplet boundary or when micelles in the bathing medium are involved in diffusive transport. These phenomena are also currently under study and are accessible, one particle at a time, using the micropipet technique.

■ MODEL DEVELOPMENT: DROPLETS COMPOSED OF A MIXTURE OF TWO MUTUALLY MISCIBLE LIQUIDS DISSOLVING IN A SECOND IMMISCIBLE SOLVENT

The Epstein−Plesset (EP) equation[4] was originally derived by Epstein and Plesset to describe the dissolution of a gas bubble due to diffusive mass transfer into an undersaturated liquid−gas solution as well as the rate of growth of a bubble in an oversaturated liquid−gas solution. Duncan and Needham[1] tested this equation for the dissolution of single air micro-bubbles. Although the EP model had remained difficult to test on millimeter-sized bubbles because of their relatively long dissolution time, the micropipet technique allowed them to form single microbubbles. That is, by taking advantage of the scaling ($x^2 = 2Dt$) in the micrometer range, dissolution could occur and be measured accurately in a laboratory time frame of just a few seconds. They could therefore show that the EP model was indeed a very good model for gas microbubble dissolution. Because air is relatively hydrophobic, they then hypothesized that this model might also predict the dissolution of organic liquids into water. They then applied this equation to the dissolution of a liquid droplet (aniline or water) in another liquid (water or aniline)[2] where mutual diffusion coefficients and solubilities of aniline and water were already known from the literature and showed again that the Epstein−Plesset model predicted liquid-in-liquid dissolution.

Upon the basis of the concentration gradient at the edge of the droplet and the diffusion coefficient of the droplet material in the surrounding medium, an expression can be derived for

the mass flow out of the droplet, which can then be related to the change in the dimensions of the droplet via its density.

The detailed derivation of the Epstein–Plesset equation is available in the original paper by Epstein and Plesset.[4] The mass-transfer expression obtained from the Epstein–Plesset equation is

$$\frac{dm}{dt} = D(c_0 - c_s)\left\{\frac{1}{R} + \frac{1}{\sqrt{\pi D t}}\right\} \tag{1}$$

where D is the diffusion coefficient of the droplet material in the surrounding medium, R is the radius of the droplet, t is the time, c_0 is the initial concentration of the droplet material in the surrounding medium, and c_s is the saturation concentration of the droplet material in the surrounding medium. Because what is measured in the single-microdroplet micropipet experiment[1,2,5] is the diameter of the microdroplet over time, this expression can be turned into the equivalent expression for the change in radius R over time, including fractional saturation, through the definition of density as mass per volume

$$\frac{dR}{dt} = \frac{Dc_s(1-f)}{\rho}\left\{\frac{1}{R} + \frac{1}{\sqrt{\pi D t}}\right\} \tag{2}$$

where f is the ratio of the initial concentration of the droplet material in the surrounding medium c_0 over the saturation concentration of the droplet material in the surrounding material c_s (i.e., c_0/c_s), and ρ is the density of the dissolving liquid. This is the Epstein–Plesset equation as used by Duncan and Needham[2] for single-component droplets (e.g., either an aniline droplet dissolving in water or a water droplet dissolving in aniline) and by Su et al.[5] for water droplets dissolving in alkanes and alcohols.

To accommodate a mixture of liquids in the droplet, it is now assumed that two miscible liquids in a droplet mix ideally and are homogenously distributed throughout the droplet, including at its interface (i.e., the area per molecule at the interface and indeed at any radial circumference throughout the droplet) reflecting the ideal mixing of the two components. According to the Epstein–Plesset equation, mass transfer due to diffusion from of a pure droplet is related to the concentration gradient at the boundary and the surface area through which mass is transferred. It can therefore be assumed that the surface area available to each component of the droplet is in proportion to the volume fraction that each component occupies in the droplet.

The total mass flux into the surrounding area, J_{total}, will be equal to $J_{total} = J_{liquid1} + J_{liquid2}$, where $J_{liquid1}$ and $J_{liquid2}$ are the mass flux of each component of the droplet. From the Epstein–Plesset derivation, the concentration gradient at the edge of the droplet is given by

$$\left(\frac{\partial c}{\partial r}\right)_R = (c_i - c_s)\left\{\frac{1}{R} + \frac{1}{\sqrt{\pi D t}}\right\} \tag{3}$$

where c_i and c_s are the initial and saturation concentrations of the droplet material in the surrounding medium, respectively.

Furthermore, from Fick's first law, the mass flux from the droplet is proportional to the concentration gradient via the diffusion coefficient. The mass transferred by this mass flux is, in turn, proportional to the surface area through which the flux occurs, which is assumed to be proportional to the volume fraction of the components. Hence, the mass flux of each component i is

$$\frac{dm_i}{dt} = A_{frac_i} D_i(c_i - c_s)\left\{\frac{1}{R} + \frac{1}{\sqrt{\pi D_i t}}\right\} \tag{4}$$

where A_{frac_i} is the area fraction of component i and D_i is the coefficient of diffusion of component i in the surrounding medium. These mass fluxes can be related to volume changes via the density of each component, which can in turn be related to the radius of a spherical droplet, which is what we measure (diameter) in the single-microdroplet dissolution experiment. Naturally, for the case in which a single liquid comprises the entirety of the droplet, this collapses back to the original Epstein–Plesset equation. Thus, this equation effectively tests for ideality of mixing in the droplet and, importantly, the ideality of adsorption (surface excess concentration) at the interface. It is this equation that is now compared to the experimental data for the dissolution of single-droplet mixtures.

■ DIFFUSION COEFFICIENT MEASUREMENT

To use this model, diffusion coefficients of pure ethyl, butyl, and amyl acetate in water were first measured using the technique of Su et al.[5] This technique is based on measuring the radius versus time profile of a dissolving pure spherical droplet of solvent in water. Because the solubility of these acetates is known from the literature (Table 1), diffusion coefficients can be obtained from a curve fit of the Epstein–Plesset equation (eq 2) to the experimental data. The results are summarized in Table 2.

Table 2. Diffusion Coefficients as Measured Using the Method of Su et al.[5]

| chemical	D in water (cm^2/s)
ethyl acetate	8.65×10^{-6} $(\pm 9 \times 10^{-7})$
butyl acetate	7.61×10^{-6} $(\pm 4 \times 10^{-7})$
amyl acetate	9.14×10^{-6} $(\pm 6 \times 10^{-7})$

■ MATERIALS AND METHODS

Materials. Butyl acetate (CAS no. 123-86-4, 99.5% pure) was obtained from Sigma-Aldrich (St. Louis, MO). Ethyl acetate (CAS no. 141-78-6, 99.9% pure) and amyl acetate (CAS no. 628-63-7, 99.5% pure) were purchased from Mallinckrodt (St. Louis, MO). Deionized water was purified through a Branstead Nanopure Life Sciences (UV/UF) ultrapure water system.

Method. The two-chamber technique (Figure 2), previously described in Su et al.,[5] was used for these experiments. This technique uses two 0.8 mL cuvettes that are mounted side by side on a microscope slide, as shown in Figure 2. Briefly, two chambers were
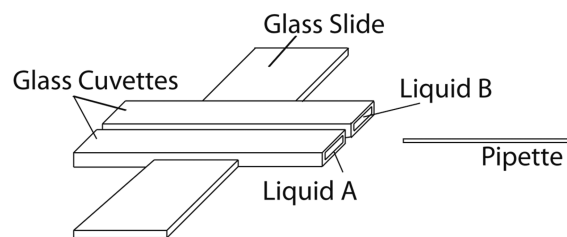
Figure 2. Illustration of the two-chamber method. The pipet is inserted into the chamber containing the test liquid, A. Liquid is drawn into the pipet, which is then withdrawn from the microchamber and placed into liquid B. A droplet of liquid A may then be blown into the microchamber containing liquid B, the test solvent for A dissolution.

employed. One chamber contained the liquid that will make the droplets. The other chamber contained both the surrounding liquid that the droplets will be formed in and a small amount of a relatively inert plug material (Figure 3) (water saturated with the respective
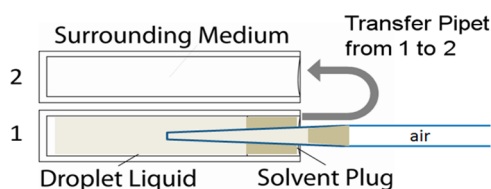
Figure 3. Two cuvettes, side by side, illustrating the use of immiscible solvent plugs. Because the droplet liquid must be kept at a constant concentration and the droplet liquid may be volatile, a saturated solvent plug (in this case, water saturated with the respective solvents) is first drawn into the micropipet, followed by the desired droplet liquid to avoid evaporation. The loaded pipet is then simply transferred from chamber 1 to chamber 2, and the droplet is blown out into the desired surrounding immiscible liquid. The same immiscible solvent plug is also used in the entrance to the microchamber to prevent any loss into the laboratory air environment.

solvents) that separates the droplet material from the rest of the pipet volume. By inserting the micropipet into the cuvettes in the correct order, a certain amount (∼10 pL) of plug material was drawn into the micropipet, followed by 20−30 pL of droplet material. This plug material prevented the evaporation of the droplet material out of the rear of the (air-filled) micropipet. After we moved this front-filled micropipet to the adjacent cuvette, the droplet material was gently blown into the cuvette containing the surrounding medium, retained on the end of the pipet, and the dissolution of this droplet was observed through the microscope. Droplet diameter versus time was measured on a recording of the experiment using calibrated video calipers. An image of a microdroplet formed and isolated on the end of a micropipet is shown in Figure 4.

The concentration of the droplet material is clearly constant for pure liquid droplets containing a single component. The same is not
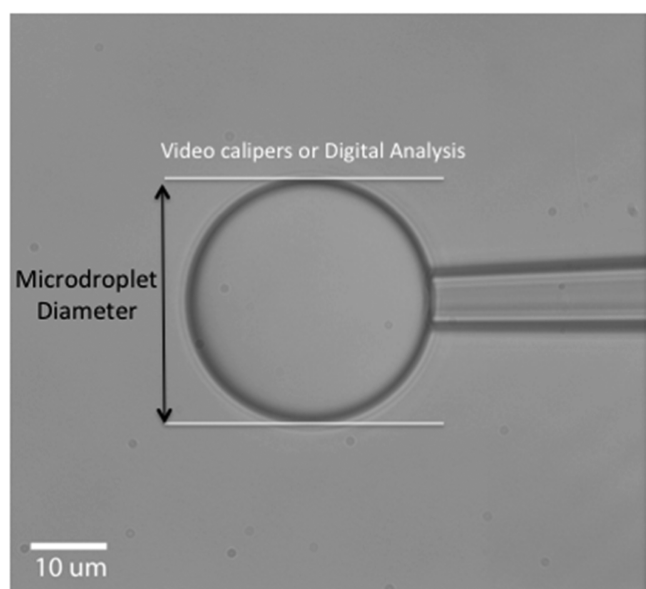
Figure 4. Ethyl acetate droplet in water (diameter = 42 μm) formed and isolated on the end of a micropipet. Despite its relatively high solubility in water of 8×10^{-2} g/cm^3, ethyl acetate has a positive surface tension (as do butyl and amyl acetates) ansd is immiscible with water and so forms a clear, measurable interface. The diameter was measured using video calipers.

true, however, for droplets that contain more than one component. In this case, all mass-transfer processes occurring throughout the experiment must be carefully accounted for, including experimental errors due to evaporation of the droplet and the surrounding media (and therefore a change in the concentration of the solutions) during all phases of the experiment, including any time a bottled sample of an organic mixture is not stoppered. Although this is not a problem for pure systems or for liquids that are not particularly volatile, problems arise when studying systems that are more volatile and will evaporate into the surrounding air environment, such as is the case for solution mixtures containing ethyl acetate.

To eliminate this source of error in both the chamber and the pipet, the nonvolatile plug of water saturated with the respective solvents is placed at the entrance to the cuvette that contains the droplet material, as shown in Figure 3. This aqueous plug is saturated with the droplet material. This greatly slows the transfer of mass from the cuvette to the surrounding environment and for all intents and purposes eliminates it as an experimental variable. Although some plug material may diffuse into the cuvette, on a case-by-case basis, the selection of the appropriate material should ensure that this quantity is minimal, as shown in Figure 3a.

■ RESULTS AND DISCUSSION

Formation and Dissolution of a Single Droplet. The two-chamber technique allows droplets to be created, by expelling the already drawn-in liquid from the micropipet tip, in 0.1−0.5 s. The time needed to form a microdroplet is relatively short in comparison to the overall lifetime of the droplet during its dissolution phase, which in these experiments ranges anywhere from ∼100 to ∼400 s. However, appreciable mass transfer can still occur during this droplet creation, or "blowing-out" phase, especially when one component is extremely soluble in the surrounding medium (such as ethyl acetate in water).

We therefore estimated the quantity of mass transfer into the aqueous phase that occurs during this 0.1−0.5 s droplet-formation (blowing-out) process. The quantity of lost material is estimated by applying the multicomponent droplet model developed in this paper. This involves obtaining a value for the mass lost at each time point by measuring the radius of the droplet during the blowing-out process every 0.1 s, finding the total surface area available, and applying eq 4. The amount of the correction will be highly dependent on both the composition of the system and the size of the droplet. As an example, a droplet formed in 0.27 s containing 3 parts ethyl acetate to 1 part butyl acetate may, in fact, be estimated to contain 2.97 parts ethyl acetate to 1 part butyl acetate once the droplet is completely formed, having lost this 0.03 part ethyl acetate even during the 0.27 s of droplet formation.

Figures 5 and 6 include the droplet radius measurements made during this initial droplet-formation process. This process is completed within 0.1−0.5 s, in comparison to the tens to hundreds of seconds of our droplet lifetime. This difference in time scales may cause these data points to appear to fall on the y (radius) axis.

Droplet Mixtures. Droplets consisting of mixtures of either ethyl acetate/butyl acetate or butyl acetate/amyl acetate were formed from the micropipet in water. Ethyl acetate, butyl acetate, and amyl acetate are soluble in water, with solubilities of between 8×10^{-2} to 0.2×10^{-2} g/cm^3 (Table 1).[19]

Theoretical comparisons to the experimental data (EtAc−ButAc and ButAc−AmylAc at 100:0, 75:25, 50:50, 25:75, 0:100 mol %/mol %) are shown in Figures 5 and 6. Because the droplets are perfectly spherical, measurements of droplet diameter are simply converted to radius and plotted versus
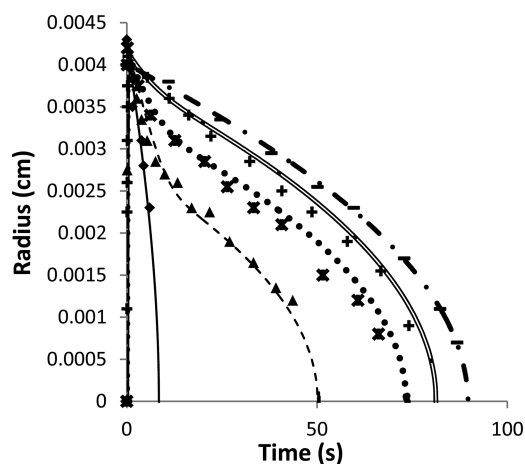
Figure 5. For microdroplets that are all about the same size (40−43 μm radius), here the experimental ethyl acetate/butyl acetate droplet dissolution is compared to model predictions in order of increasing amount of butyl acetate. Experimental data points (from left to right): pure ethyl acetate droplet (♦), 3:1 ethyl acetate/butyl acetate (▲), 1:1 ethyl acetate/butyl acetate (*), 1:3 ethyl acetate/butyl acetate (+), and pure butyl acetate (−).
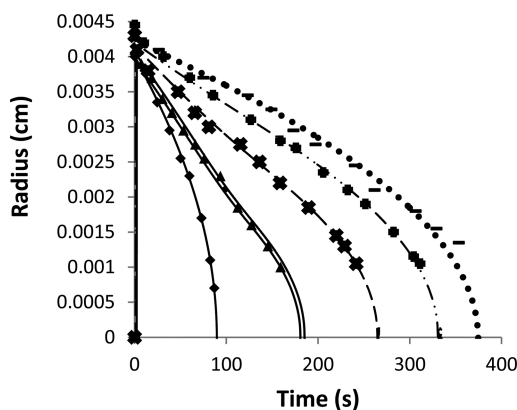
Figure 6. For microdroplets that are all about the same size (40−45 μm radius), here the experimental butyl acetate/amyl acetate droplet dissolution is compared to model predictions in order of increasing amount of amyl acetate. Experimental data points (from left to right): pure butyl acetate droplet (♦), 3:1 butyl acetate/amyl acetate (▲), 1:1 butyl acetate/amyl acetate (✕), 1:3 butyl acetate/amyl acetate (+), and pure amyl acetate (−).

time. Our plots show the time rate of change of droplet size due to loss of material into the surrounding water and the characteristically increasing droplet dissolution rate predicted by the modified Epstein−Plesset model. As shown in Figure 5, microdroplets of about the same size (40−43 μm radius) dissolved increasingly more slowly as the droplet composition was changed from pure ethyl acetate to pure butyl acetate. Similarly, for the series from butyl to amyl (Figure 6), microdroplets (40−45 μm radius) dissolved increasingly more slowly with increasing fraction of amyl acetate. A comparison of the data to the modified Epstein−Plesset model shows that both components of the droplet begin to diffuse from the droplet as soon as the droplet is formed in the second solvent medium.

We have included in our Supporting Information theoretical comparisons to the experimental data, where the model matches the single-microdroplet experimental observations.

As expected, droplets containing a mixture of ethyl acetate and butyl acetate (Figure 6) dissolve more slowly than a droplet of pure ethyl acetate and more quickly than a droplet of pure butyl acetate (Figure 5) Similarly, droplets containing a mixture of butyl acetate and amyl acetate dissolve more slowly than a droplet of pure butyl acetate and more quickly than a droplet of pure amyl acetate (Figure 6). Interestingly the individual S-shaped dissolution curve (most prominent in the ethyl acetate−butyl acetate mixture) is well represented by the model as the more soluble smaller component leaves first and the less soluble component concentrates and leaves last.

To evaluate the closeness of fit (solubilities were known and diffusion coefficients were fitted), we calculated the mean squared error (MSE) for our theoretical model prediction versus experimental results for each of our droplets. To give a feel for the size of this difference between our theoretical values and our results, we calculated the mean squared error as a percentage of the initial droplet diameter. As can be seen in Table 3, the average mean squared error for the droplets ranged

Table 3. Mean Standard Error of the Model Compared to the Experimental Measurements for Each System[a]

% ethyl acetate	% butyl acetate	average mean standard error (%)
75	25	8.01
50	50	8.11
25	75	3.40

% butyl acetate	% amyl acetate	average mean standard error (%)
75	25	15.56
50	50	7.90
25	75	10.08
overall average mean standard error (%)		8.96

[a]The average mean standard error for the droplets ranged from 3.40% (25% ethyl acetate, 75% butyl acetate) to 15.56% (75% butyl acetate, 25% amyl acetate). Overall, the average mean standard error was 8.96% for all systems evaluated.

from 3.40% (25% ethyl acetate, 75% butyl acetate) to 15.56% (75% butyl acetate, 25% amyl acetate). Overall, our model had an average mean squared error of 8.96% for all systems evaluated, which shows that our model is a good fit for the data.

Figure 7 shows the time for dissolution of 45-μm-radius microdroplets dissolving in water versus the whole range of
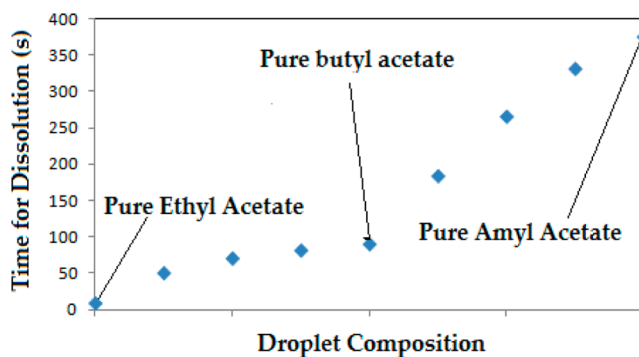
Figure 7. Time of dissolution for (R = 45 um) droplets dissolving in water for each droplet composition. From left to right: pure ethyl acetate, 3:1 ethyl acetate/butyl acetate, 1:1 ethyl acetate/butyl acetate, 1:3 ethyl acetate/butyl acetate, pure butyl acetate, and 3:1 butyl acetate/amyl acetate.

droplet composition. It is clear that the dissolution time is a function of the composition of the droplet. For a given droplet size, the droplet mixtures have a dissolution time between the dissolution time of the pure fastest-dissolving droplet and the pure slowest-dissolving droplet. For example, a droplet containing a mixture of ethyl and butyl acetates has a dissolution time between that of pure ethyl acetate and pure butyl acetate. The more butyl acetate a droplet contains, the more similar its dissolution time to that of pure butyl acetate. Similarly, the more ethyl acetate a droplet contains, the faster its dissolution time.

The underlying assumption of this model is that each component of the droplet leaves in accordance with the proportion of the droplet surface area that the homogenously mixed component occupies. Because this model successfully reflects our experimental findings, the droplet components must indeed mix homogenously. Deviation from this model may, in the future, be used as an indicator of inhomogeneous mixing, surface accumulation, and even shell formation.

The micropipet technique allows the measurement of the dissolution of a single spherical microdroplet of pure and mixed compositions. The developed theoretical model and single-microdroplet experiments represent, to the best of our knowledge, the first model and experimental verification of the diffusive dissolution of a multicomponent spherical droplet containing two ideally mixed components. The model is particularly relevant to our understanding of liquid−liquid extraction processes in which one, more soluble, component is extracted from a mixture. By understanding how this process proceeds in this idealized purely diffusive spherical dissolution system, a solid foundation can be established that can contribute to the understanding of more complicated systems, such as is the case for bulk suspension systems of many particles or when mixing and stirring occur. Understanding the dissolution of a microdroplet on a single-particle scale can also guide the scale-up of these processes.

CONCLUSIONS

A modification of the Epstein−Plesset equation based upon a reduced surface area approximation has been presented and evaluated experimentally. This modified equation models the dissolution of a liquid droplet mixture in a liquid environment in which both components of the droplet are soluble in the aqueous phase. With fast diffusive equilibration within the microdroplet, it assumes that their fractional volume in the microdroplet solution mixture represents the fractional surface coverage by each component at any moment in time during the dissolution process. Additionally, a modification to the two-chamber method, as previously laid out in Su et al.,[5] is presented that allows for the study of multicomponent droplets while overcomeing the challenge of working with relatively more volatile materials.

This model has been shown to predict accurately the dissolution of microdroplets for the ethyl acetate/butyl acetate and butyl acetate/amyl acetate systems given the solubility and diffusion coefficients of each of the pure components in water as well as the initial droplet radius. Care should be taken, however, in applying the model to systems where the assumption of homogeneous mixing does not hold true. In the case where there exists a surface excess of one component of the droplet, this model is expected to fail because the occupied fractional surface would not match the volume fraction as a result of surface excess concentrations that arise

from surface activity. In such cases, interest shifts to the time taken to form shells and their relative stability at droplet interfaces. Similarly, in any case where slow diffusion causes concentration gradients within the droplet, deviation from the model is expected, such as for large macromolecules. In this instance, it might be expected that they also could form insoluble shells.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental versus theoretical prediction data for this model. The data series are ethyl acetate/butyl acetate droplets in ratios of 3:1, 1:1, and 1:3 and butyl acetate/amyl acetate droplets in ratios of 3:1, 1:1, and 1:3. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: d.needham@duke.edu. Telephone: (919) 660-5355. Fax: (919) 660-8963.

Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Duncan, P. B.; Needham, D. Test of the Epstein-Plesset model for gas microparticle dissolution in aqueous media: effect of surface tension and gas undersaturation in solution. *Langmuir* **2004**, *20*, 2567−2578.

(2) Duncan, P. B.; Needham, D. Microdroplet dissolution into a second-phase solvent using a micropipet technique: test of the Epstein-Plesset model for an aniline-water system. *Langmuir* **2006**, *22*, 4190−4197.

(3) Rickart, D. L.; Duncan, B.; Needham, D. Hydration potential of lysozyme: protein dehydration using a single microparticle technique. *Biophys. J.* **2010**, *98*, 45a.

(4) Epstein, P. S.; Plesset, M. S. On the stability of gas bubbles in liquid-gas solutions. *J. Chem. Phys.* **1950**, *18*, 1505−1509.

(5) Su, J. T.; Duncan, P. B.; Momaya, A.; Jutila, A.; Needham, D. The effect of hydrogen bonding on the diffusion of water in n-alkanes and n-alcohols measured with a novel single microdroplet method. *J. Chem. Phys.* **2010**, *132*, 044506.

(6) Laby, T. The separation of iron from nickel and cobalt by lead oxide (Field's method). *Chem. News J. Ind. Sci.* **1904**, 89−90.

(7) ODonnell, P. B.; McGinity, J. W. Preparation of microspheres by the solvent evaporation technique. *Adv. Drug Delivery Rev.* **1997**, *28* (1), 25−42.

(8) Yuksel, N.; Baykara, T. Preparation of polymeric microspheres by the solvent evaporation method using sucrose stearate as a droplet stabilizer. *J. Microencapsulation* **1997**, *14*, 725−733.

(9) vanHamont, J. E., et al. Evaluation of Solvent Extraction and Solvent Evaporation Procedures for Production of Tobramycin-Releasing Microspheres. *23rd International Symposium on Controlled Release of Bioactive Materials*, 1996 Proceedings; Controlled Release Society: pp 365−366.

(10) Li, W. I.; Anderson, K. W.; DeLuca, P. P. Kinetic and thermodynamic modeling of the formation of polymeric microspheres using solvent extraction/evaporation method. *J. Controlled Release* **1995**, *37*, 187−198.

(11) Li, W.-I.; Anderson, K. W.; Mehta, R. C.; Deluca, P. P. Prediction of solvent removal profile and effect on properties for peptide-loaded PLGA microspheres prepared by solvent extraction/evaporation method. *J. Controlled Release* **1995**, *37*, 199−214.

(12) Iwata, M.; Mcginity, J. W. Preparation of multiphase microspheres of poly(D,L-lactic acid) and Poly(D,L-lactic-co-glycolic acid) containing a w/o emulsion by a multiple emulsion solvent evaporation technique. *J. Microencapsulation* **1992**, *9*, 201−214.

(13) Grandfils, C.; Flandroy, P.; Nihant, N.; Barbette, S.; Teyssié, Ph. Preparation of poly (D,L) lactide microspheres by emulsion solvent evaporation, and their clinical-applications as a convenient embolic material. *J. Biomed. Mater. Res.* **1992**, *26*, 467−479.

(14) Hanson, C. *Recent Advances in Liquid-Liquid Extraction*; Pergamon Press: Oxford, 1971

(15) Nauman, E. B. Droplet diffusion-model for micromixing. *Chem. Eng. Sci.* **1975**, *30*, 1135−1140.

(16) Rys, P. The selectivity of chemical reactions disguised by diffusion. Part I: chemical selectivity disguised by mixing. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 807−817.

(17) Hanson, C., Ed. *Recent Advances in Liquid-Liquid Extraction*; Pergamon Press: Oxford, U.K., 1971.

(18) Altshuller, A. P.; Everson, H. E. The solubility of ethyl acetate in water. *J. Am. Chem. Soc.* **1953**, *75*, 1727−1727.

(19) Liu, K.; Tong, Z.; Liu, L.; Feng, X. Separation of organic compounds from water by pervaporation in the production of n-butyl acetate via esterification by reactive distillation. *J. Membr. Sci.* **2005**, *256*, 193−201.

(20) Stephenson, R.; Stuart, J. Mutual binary solubilities - water alcohols and water esters. *J. Chem. Eng. Data* **1986**, *31*, 56−70.

(21) Flick, E. W. *Industrial Solvents Handbook*, 3rd ed.; Noyes Data Corporation: Park Ridge, NJ, 1985 .