Tailoring of High-Order Multiple Emulsions by the Liquid-Liquid Phase Separation of Ternary Mixtures

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Abstract

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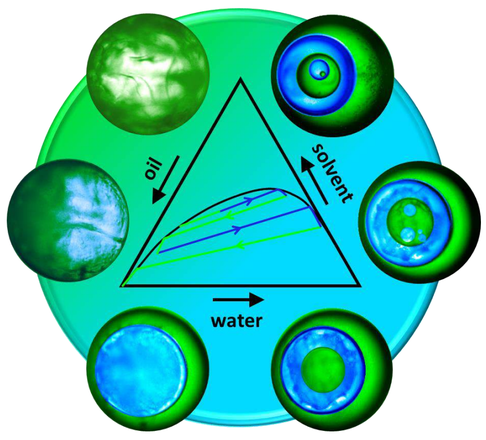
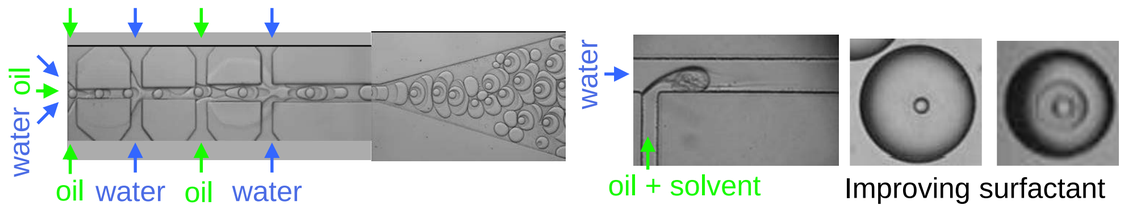


Multiple emulsions with an "onion" topology are useful vehicles for drug delivery, biochemical assays, and templating materials. They can be assembled by ternary liquid phase separation by microfluidics, but the control over their design is limited because the mechanism for their creation is unknown. Herein we show that phase separation occurs through self-similar cycles of mass transfer, spinodal decomposition or nucleation, and coalescence into multiple layers. Mapping out the phase diagram shows a linear relationship between the diameters of concentric layers, the slope of which depends on the initial ternary composition and the molecular weight of the surfactant. These general rules quantitatively predict the number of droplet layers (multiplicity), which we used to devise self-assembly routes for polymer capsules and liposomes. Moreover, we extended the technique to the assembly of lipid-stabilized droplets with ordered internal structures.

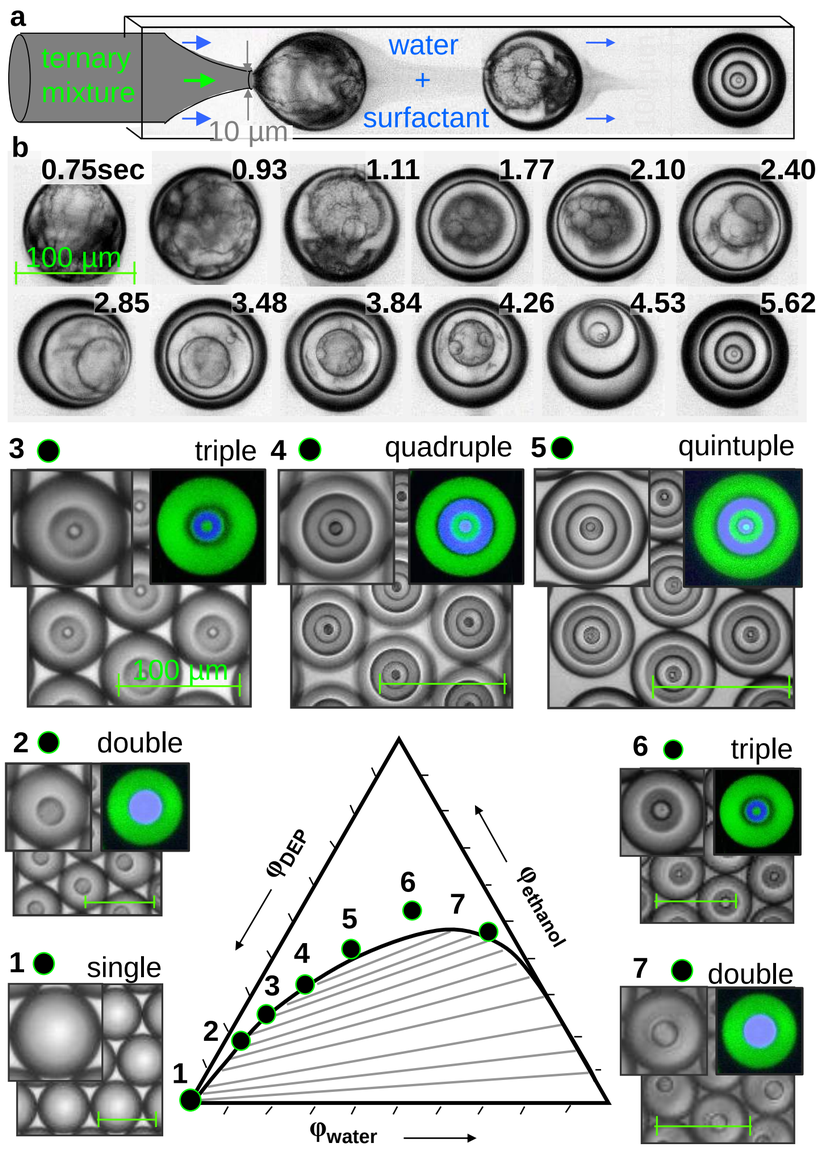
Literature: Making multiple emulsion droplets

Mechanical Formation Kim, 2011, Angew. Chem. **By phase separation** Zhao, 2009, Angew. Chem.



- Mechanical formation requires synchronization of multiple streams, wettability modifications of channel walls and is susceptible to interferences
- Formation by phase separation requires only two liquid flows, but control over design is limited since mechanism for creation is unknown

1. Phenomenon: Ternary phase separation in drops



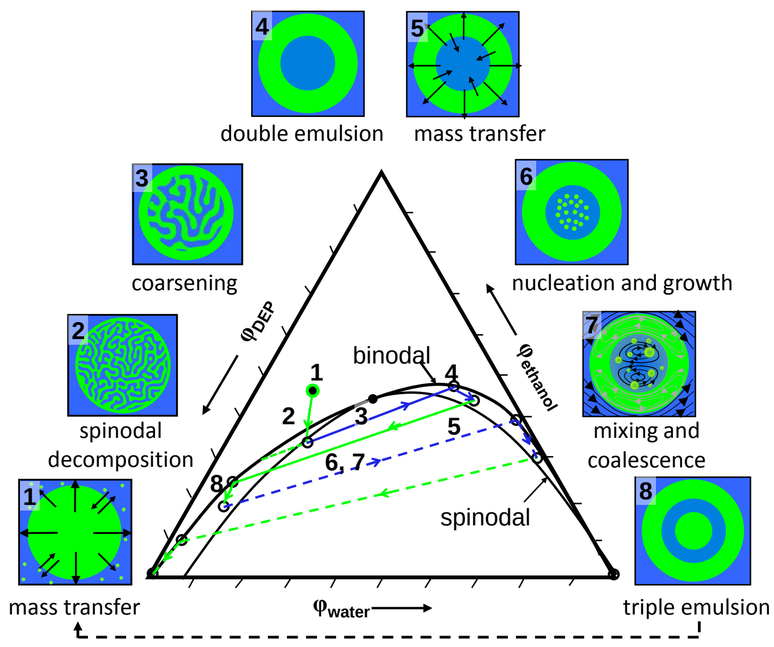
Sequential phase separation events:

- Tapered cylindrical glass capillary in square glass capillary
- Injection of a ternary liquid mixture of oil/solvent/water into a water stream
- Following the resulting droplet along its flow trajectory shows sequential phase separation events

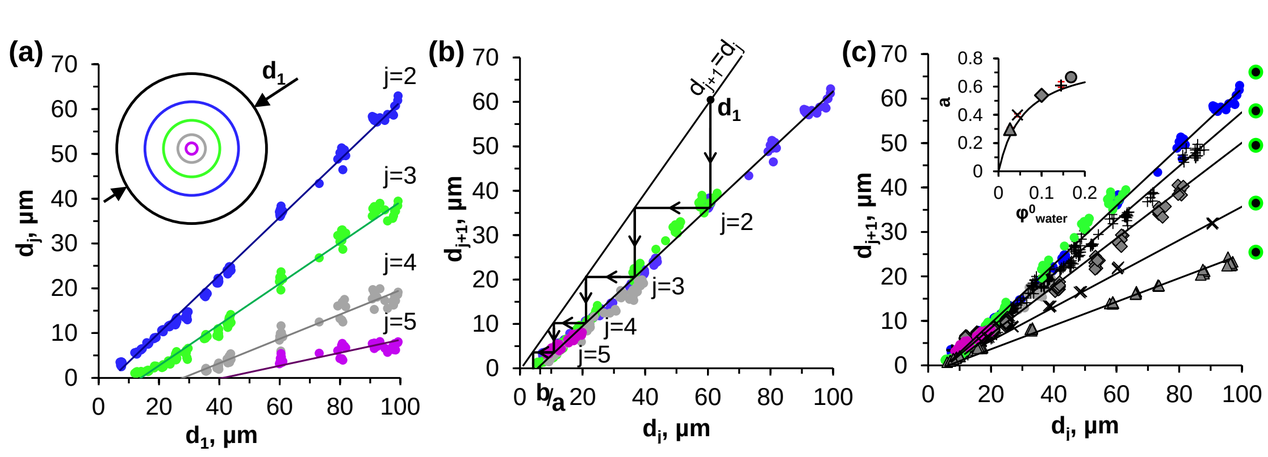
Multiplicity dependence on initial composition:

- Monophasic initial compositions along the binodal line are selected
- **Increasing the initial alcohol and water concentration → increasing emulsion multiplicity (1 - 5)**
- A maximum of five layers (quintuple) is found close to the critical point of the phase diagram
- Increasing the initial water and ethanol concentration beyond the critical point decreases the droplet multiplicity.

2. Analysis of mechanism: Zig-zag trajectory through the ternary phase space and self similarity



- Contacting the ternary droplet with the continuous water phase initiates the mass transfer of ethanol **(1)**
- Droplet composition is shifted into the immiscible region. Water rich inner droplet is formed by phase separation **(2 – 4)**
- Oil rich droplets phase separate inside and the resulting third layer **(5 – 8)** undergoes the next cycle upon mass transfer
- The sequential process can be described by multiple tie lines
- **The higher up in the ternary diagram the starting composition, the more tie lines can be crossed, resulting in more droplet layers**



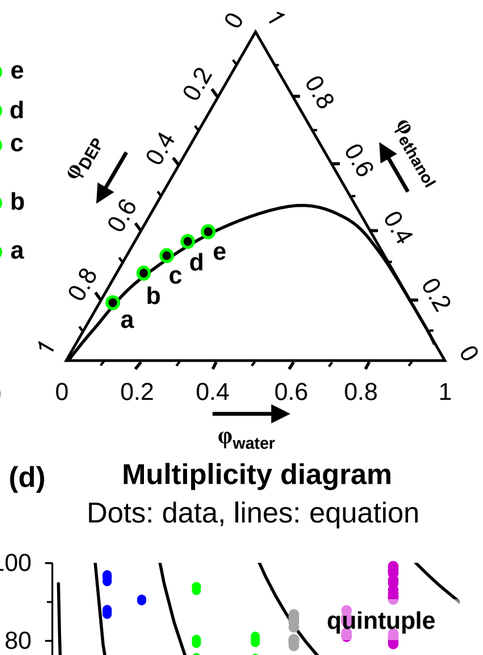
- Diameters of sequential layers are proportional to outermost diameter d_1 **(a)**
- Mastercurve is obtained by plotting consecutive diameters against each other **(b)**
- For given d_1, number of staircase steps j between mastercurve $d_{j+1} = a\, d_j + b$ and $d_{j+1} = d_j$ until hitting the x-axis gives the multiplicity **(b)**:

$$d_j = d_1 \cdot a^{j-1} + b \cdot a^{j-2} \cdot \sum_{m=0}^{j-2} a^{-m} = 0 \quad \xrightarrow{\sum_{m=0}^{j-2} a^{-m} = \left(\frac{1-a^{-(j-1)}}{1-a^{-1}}\right)} \quad j = 1 + \log_a \frac{b}{(a-1)\cdot d_1 + b}$$

- Mastercurve slope a depends on initial water content φ^0_{water}, intercept b is constant **(c)**
- Derivation of phase diagram $j = f(d_1,\ \varphi^0_{water})$ **(d)** with boundaries between different multiplicity regions

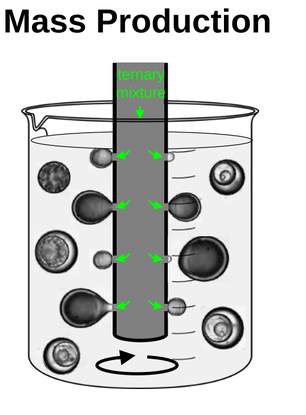
$$a = \frac{0.84 \cdot \varphi^0_{water}}{0.065 + \varphi^0_{water}} \qquad b = -3.7\mu m$$

$$\xrightarrow{j = 1 + \log_a \frac{b}{(a-1)\cdot d_1 + b}} \qquad d_1 = -\frac{3.7}{\frac{0.84 \cdot \varphi^0_{water}}{0.065 + \varphi^0_{water}} - 1} \cdot \left(\left(\frac{0.84 \cdot \varphi^0_{water}}{0.065 + \varphi^0_{water}} \right)^{1-j} - 1 \right)$$



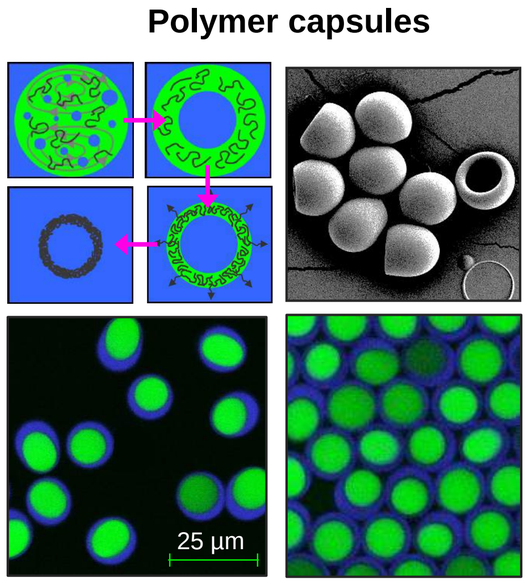
3. Applications derived from multiple emulsions formed by ternary phase separation

Mass Production



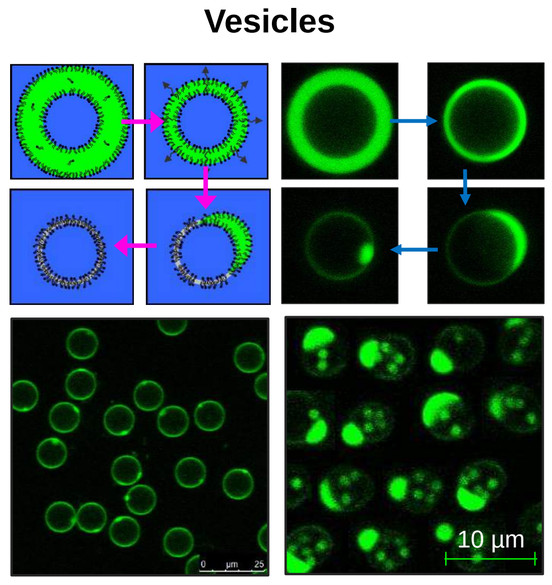
Using a membrane emulsifier to inject the ternary liquid mixture into a stirred water bath results in polydisperse multiple emulsion droplets

Polymer capsules



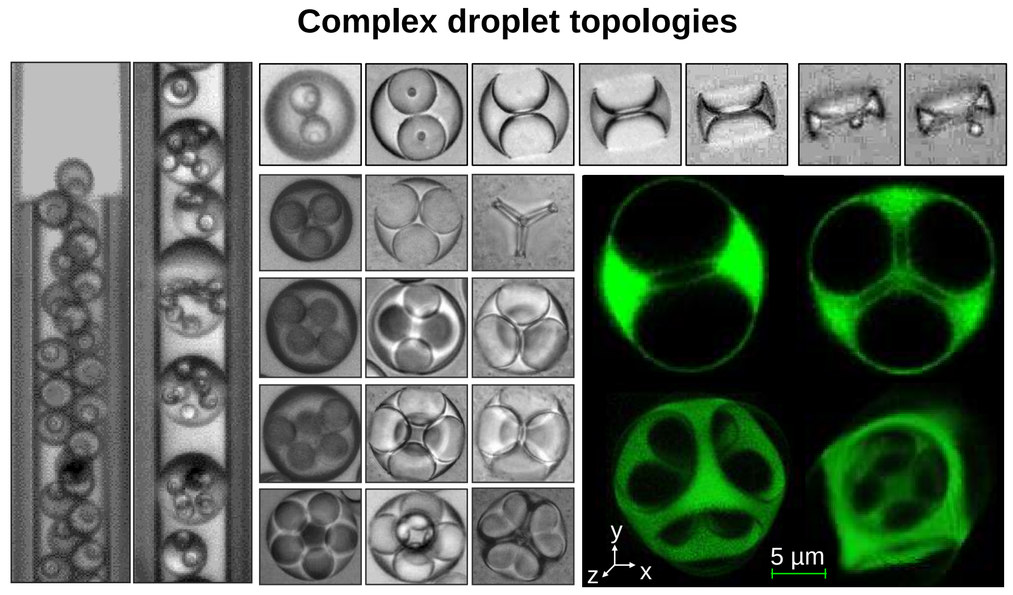
- Quaternary mixture of butylacetate, ethanol, water and polymethylmethacrylate phase separates into a double emulsion
- Evaporation of butylacetate → formation of a polymer capsule
- Hydrophobic (blue) and hydrophilic (green) fluorescent dyes can be encapsulated

Vesicles



- Quarternary mixture of butylacetate, ethanol, water and lipids (DOPC) phase separates into a double emulsion
- Evaporation of butylacetate → dewetting transition → bilayer membrane
- Monodisperse vesicles
- Encapsulation of colloids into vesicles

Complex droplet topologies



- Controlled coalescence yields multiple emulsion drops with several spatially separated inner droplets
- Evaporation of the oil phase results in the formation of complex lipid bilayer scaffolds
- Complex droplet topologies with ordered internal structures useful for self assembly applications or as compartmentalized biomimetic structures (e.g. neighboring cells)

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