Phytonadione Injectables: Understanding Dosage Form and Formulation Processes

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Purpose

Phytonadione injection contains an oil-like immiscible drug substance, which is mixed with surfactant, then further dispersed in an aqueous phase. Depending on the ratios of these ingredients and manufacturing conditions used, the final product may exist as a two-phase oil and water system, emulsion, or microemulsion. Consequently, these different dosage forms have inherently different physicochemical properties and thus necessitate different characterization and criteria for demonstrating equivalence. The impact of manufacturing process conditions (e.g., stir rate, shear, mixing equipment, directionality) on formulation dispersion state and particle size distribution (PSD) were examined. The objective of this study was to compare how different sources of surfactant and manufacturing processes impact the formulation dispersion state, PSD, and the determination of product dosage form.

Methods

Three formulations were produced in-house maintaining the same formulation composition with the exception of the type of surfactant (i.e., PEG-30-castor oil, PEG-35-castor oil and PEG-40-castor oil). Each formulation was mixed under varying processing conditions, ranging from low shear (via magnetic stirrer) to high shear mixing (via homogenizer) as well as differing mixing directionality, either dispersed oil phase into continuous aqueous phase (**O2A**) or continuous aqueous phase into dispersed oil phase (**A2O**). PSD of formulations were measured by batch mode dynamic light scattering (DLS) (Wyatt Technology, DynaPro Plate Reader II) and compared to PSD as determined by asymmetrical flow field-flow fractionation with online multiangle light scattering (AF4-MALS) and online DLS (Wyatt Technology, Eclipse). A commercially available phytonadione injection product was used for PSD comparison. Three different polyethylene glycol (PEG)-n castor oil surfactants were used for formulation comparison (n = 30, 35, and 40). Formulation PSD was measured via DLS (DynaPro Plate Reader II, Wyatt Technologies, Santa Barbara, CA) as a function of time, including immediately following preparation and after 4 and 24 hours. In addition, surface tension of formulations and placebo sample (i.e., micelles formed from three types of surfactant and without API) were determined using drop shape analyzer (Krüss DSA-100, Hamburg, Germany, fitted with an oscillating drop module). Analysis of surface tension over a range of surfactant concentrations were used to determine the surfactant critical micelle concentration (CMC).

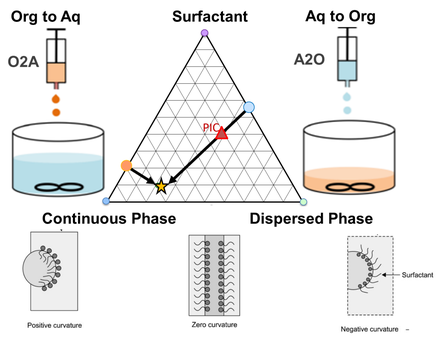

Figure 1. Diagram of formulation directionality, O2A represents the dilution and solubilization of the surfactant-API stock in the dispersant. While during processing in the A2O direction the mixture passes through a phase inversion composition (PIC) where the interface rearranges from water-in-oil (W/O) to oil-in-water (O/W) dispersion, the resultant PSD is strongly influenced by processing conditions (temperature, shear of mixing, etc.) during phase rearrangement.

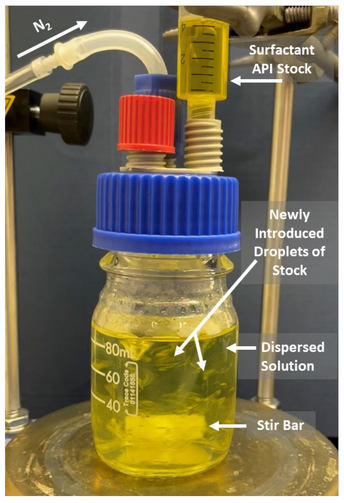

Figure 2. Experimental setup for preparation of phytonadione injections at ambient temperature and under low shear in the O2A mixing direction.

Results

Both the manufacturing process (i.e., mixing, temperature, etc.) and formulation composition (i.e., surfactant to oil ratio) can affect the initial dispersion state of the formulation, producing macro-, nano-, or micro- emulsions. Notably, both appearance (turbidity) and more quantitatively PSD were found to be useful surrogates for distinguishing nanoemulsions (broad PSD, turbid) from microemulsions (monodispersed PSD, translucent). For the formulation composition of phytonadione injection, varying processing conditions produced a spectrum of initial dispersion states (Figure 3). Comparison of number-based and intensity-based particle size distributions, form AF4 and batch DLS respectively, helped to correlate formulation conditions for nanoemulsion formation and the observed onset of turbidity. All subsequent data presented here is for formulations using PEG-35-caster oil.

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Results: Composition Effects

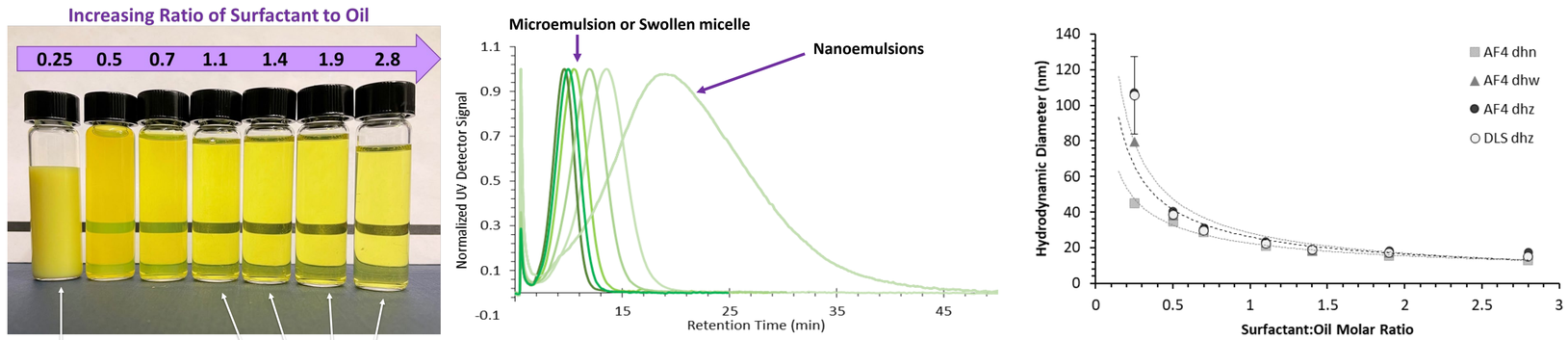

Figure 3. a) Formulations prepared at differing ratios of surfactant to oil, showing the transition of dispersion state from translucent to turbid. b) AF4 fractograms overlaying UV-Vis detector signals, showing a change in size and PDI as oil content is increased and the system transitions from a microemulsion to nanoemulsion. c) Overlay of particle hydrodynamic diameter as determined via either batch DLS and AF4-MALS-DLS, with number (n), weight (w), and intensity (z) averages from AF4 distribution. **Error bars: standard deviations (n=5)*

Results: Mixing Directionality Effects

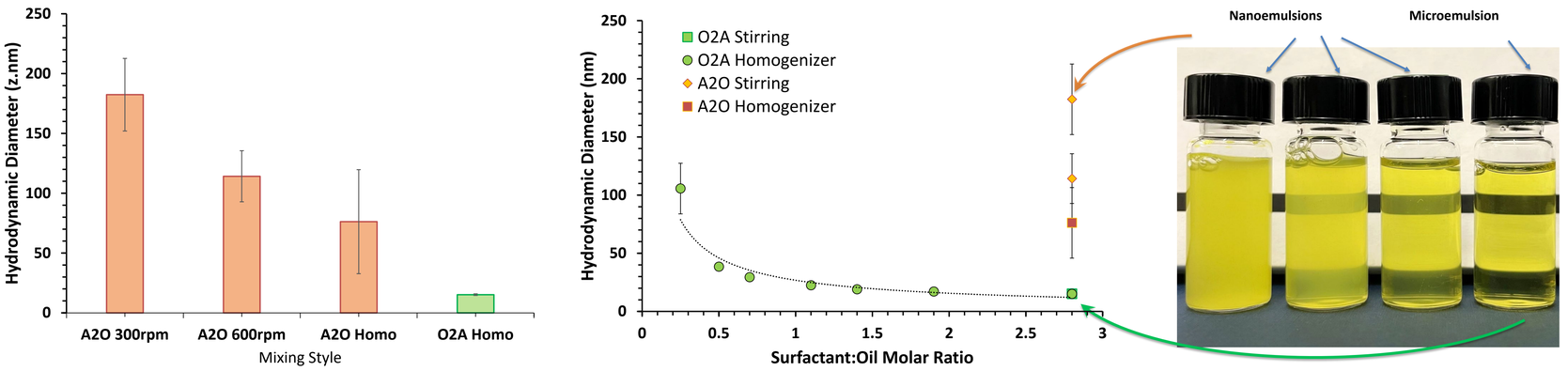

Figure 4. a) Particle sizes for formulations prepared at equivalent composition (surfactant to oil ratio, S:O = 2.8) using different formulation directionality and mixing procedures, b) overlaid with Figure 2 batch particle sizes from DLS, with c) accompanying representative images. **Error bars: standard deviations (n=5)*

Results: Thermodynamic vs Kinetic Stability

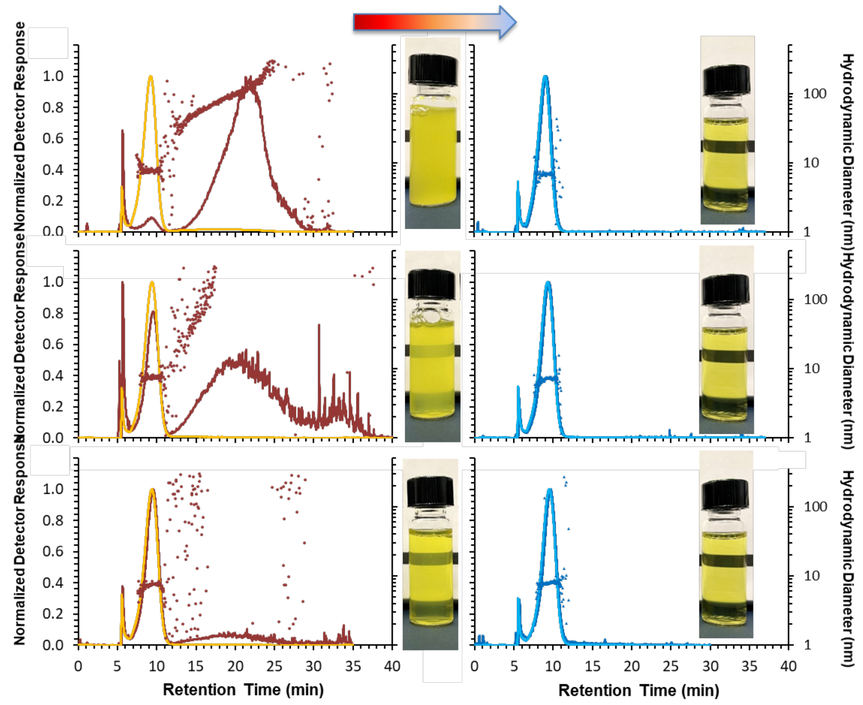

Figure 5. AF4 fractograms for formulation from Figure 4 before and after incubation at 70°C for 30 minutes. UV-Vis detector response (yellow and light blue) with light scattering intensity at 90° from MALS (brown and dark blue) are overlaid with hydrodynamic radius from online DLS (scatter). Insets: Still images of formulations before (left) and after (right). Particle sizes summarized in Table 1.

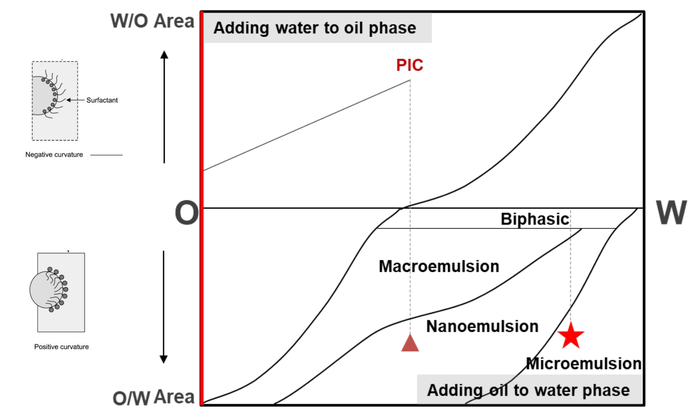

Figure 6. Binary phase diagram for a fixed surfactant to oil ratio. Y-axis incorporates the magnitude of interfacial area generated during the mixing process. For each formulation composition such a diagram exists as a cut-plane through a traditional pseudo-ternary phase diagram, extending the diagram into a third dimension. Construction of an interface directed pseudo-ternary phase diagram can aid in the explanation of variations observed during formulation process. In the A2O direction as the formulation passes through the PIC the amount of shear experienced during interface rearrangement dictates the resultant particle size distribution.

Table1. Heating Stability Comparison

ID	DLS $(d_h)_z$	AF4 $(d_h)_z$	AF4 $(d_h)_n$	AF4 $(d_h)_z$
1	182.4	171.8	15.8	15.4
2	114.2	93.4	15.4	16.1
3	76.2	70.8	14.2	14.0
	Before Heating			After

**Hydrodynamic diameter in nm.*

- Use of low shear conditions in the A2O direction produces larger particle sizes with high PDI.
- Use of high shear conditions in the A2O direction produces lower particle sizes and PDI.

Conclusions

For the phytonadione injection composition the nanoemulsion dispersion state represented a transient state for the system, which was limited by kinetic constraints like surfactant lability. With enough time and energy (thermal or mechanical) the phytonadione injection formulations reverted to the most energetically favored microemulsion dispersion state. Lastly, an interface directed pseudo-ternary phase diagram was constructed to elucidate the role of interfacial areas (e.g., via changes in manufacturing processes) on the dispersion states, which helped to explain the difference in the initial dispersion states of phytonadione formulations caused by switching the order of mixing continuous and dispersed phases. Based on the PSD of the in-house produced samples as well as the employed processing conditions, phytonadione formulation is unlikely to be a kinetically stabilized emulsion. Instead, it appeared that phytonadione formulation is a thermodynamically stabilized system, such as microemulsions or micelles.

Acknowledgements

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