Chemistry and Formulation Guidelines of Traditional Binary and Tertiary Emulsions

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February 9, 2017

CoastSouthwest™

Outline

- What is an emulsion
- Factors that form emulsions
- Characterizing emulsions
- Multiple phase systems

What is an emulsion

- In the traditional definition a distinct oil and water phase – Never the two shall meet, unless you have a little help
- Physical attributes: continuous and non-continuous phase – What do you mean?

Attributes

- Water in oil, oil in water, multi-phase

Factors to consider when making emulsions

- Stability of the active ingredient
- Visual appearance, color, odor (development of pungent odor/loss of fragrance)
- Viscosity, extrudability
- Loss of water and other volatile vehicle components w/Si
- Concentration of emulsifier
- Order of addition of ingredients
- Particle size distribution of dispersed phases
- pH where water is the continuous phase
- Temperature of emulsification

Factors to consider when making emulsions

- Type of equipment
- Method and rate of cooling
- Texture and aesthetics
- Microbial contamination/sterility (in the unopened container and under conditions of use)
- Release/bioavailability (absorption vs adsorption)
- Phase distribution, phase inversion (homogeneity/ phase separation, bleeding)

Things that affect systems

Factors

- Solubility, polarity, molecular weight,
- Functional groups (attachments – alkyl or organic)

Attributes

- Water in oil (silicone), oil in water, multi-phase

Stokes Law and Sedimentation Rate

-
  - Low sed rate - What can you actually affect?
    - The erythrocyte **sedimentation rate** (**ESR**) is the **rate** at which red blood cells sediment in a period of one hour. It is a common hematology test, and is a non-specific measure of inflammation. The red cells form stacks called 'rouleaux‘, which settle faster due to their increased density.
    - V = $\frac{2}{9}\frac{(\rho 1 - \rho 2)}{\mu} g\ R^2$

      Stokes Law of a sphere falling through a fluid

What can you affect

- Emulsifier choice
- Thickeners in the phase
- Powder load – impact on the phase more than aesthetic
- Facial tension – secondary emulsifiers and emollients
    - Pigment treatment
    - Solvent interactions/wetting

Water in Si or oil

Factors to consider in stabilizing a water in oil emulsion

- From an energy point of view, w/Si or w/o are not stable. Why?
  - Diffusion gradient
  - Freeze point – Huh?
  - Solubility of preservative choice
  - Order of addition – efficacy of the emulsifiers
  - Particle size – what you can do to minimize it
    - Surface to volume ratio
    - Proportion of water to oil phase

Water in silicone

Chemistry: The Force Awakens

- When combining water into oil, a protective shield of adsorbed nonionic surfactant forms at the interphase. When enough energy (i.e., a collision) is applied it disrupts the droplet and the droplet is repulsed by the release of free energy
- Another thought is droplet formation by repulsion at the surface of the adsorbed layer (o/w)
- Either way, you have to provide enough energy to overcome the particles from contacting each other leading to coalescence/instability

Water in silicone

Emulsifier choice

- HLB applies well but not enough
- Choose oils and silicones that are flexible and not stearically hindered. The glass temperature is an indicator of flexibility (think of the truck and trailer analogy)
  - PDMS – lowest glass temp (best choice)

Phase ratio

- If the density difference between the two phases is great enough, creaming and syneresis

Water in silicone

Phase inversion

- Polarity of the oil phase in w/o – nonionic
- The electrolyte used
- NaCl, MgSO4 7H20,Sodium Citrate
- They reduce the particle size of the emulsion
- MOA – PDMS forms permeable layers to gas
- A little salt is a good thing

Water in silicone

Processing

- Add emulsifiers, preferably nonionic, last. Consider all the sources of solvent (i.e., elastomers, secondary emulsifiers), and if they are silicone based (e.g., Dimethiconol in silicone systems)
- When initially adding water to oil, monitor the rate of addition and how much shear is imparted

Water in silicone

Processing

- Meter in the dose of water and monitor the time taken to add. Don’t have the water float on the surface
- Remember, preservatives and extracts (phospholipids) can act as emulsifiers
- Batch size!

Water in silicone

Mixing

- Particle size
  - Without adequate processing, the emulsion will have a broad distribution
  - High shearing in the initial formation of w/o systems is bad. In o/w its not a problem
  - Mix for the time taken to add the water phase in a metered dose
  - Depending on the emulsifier, do you need a final finishing step (batch size mismatch, beware of low shear)?

Water in oil in water

- Tertiary emulsions behave as if the external phase is fluid
- At least in a binary system, you had a defined phase
- Your external phase is looking for equilibrium

Advantages:

- Sustained drug delivery, enhanced absorption of the said active
- Vaccine adjuvants/enzyme immobilization

Water in oil in water

- Use actives that would react with each other

<u>**Disadvantages:**</u>

- Unstable thermodynamically unless modified. Time consuming from process and formulating. Disruption of the oil membrane and droplets
- Require a second shear process. Why? Either high or low NOT HIGH AND HIGHER!

3 Phase emulsions

- Don’t follow some of the laws such as Bancroft's Rule
- Isolate difficult to formulate additives – Ascorbic Acid and Niacinamide
- Emulsion stability is dependent on keeping a low density difference between the discrete phases
- Do not expose these emulsions to a great deal of shear since they behave like an inverse emulsion

Head scratchers

Applications – Things that make you go Hmmm?

- Drug overdose – remove barbiturates and salicylates in the GI tract where in the inner basic phase they are converted to an inactive/insoluble anion
- Some emulsions have been designed to deliver cytotoxic agents

Head scratchers

- Some emulsions have been designed to deliver cytotoxic agents
- In cosmetics – deliver actives like Vit C and E which do not do well in external phase exposure
- w/o/w emulsion that was proposed as part Flu virus vaccine which would carry the Flu virus surface antigen

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Revision date: 02/06/2017

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