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PURPOSE

Appropriate and adequate physicochemical characterization of complex formulations is crucial to ensure product sameness of a generic product to a reference listed drug (RLD). This is particularly important if the product has complex structures that are sensitive to manufacturing process changes. Most current analytical techniques cover rather well on particle size, particle concentration, or in vitro drug release. However, limited information is available on existence of the morphological variations in a complex formulation, and more importantly the impact of morphological changes on product performance. Our previous work on propofol emulsions revealed some unique structures were present in the products, such as hybrid structures of oil droplets/lipid vesicles.

OBJECTIVES

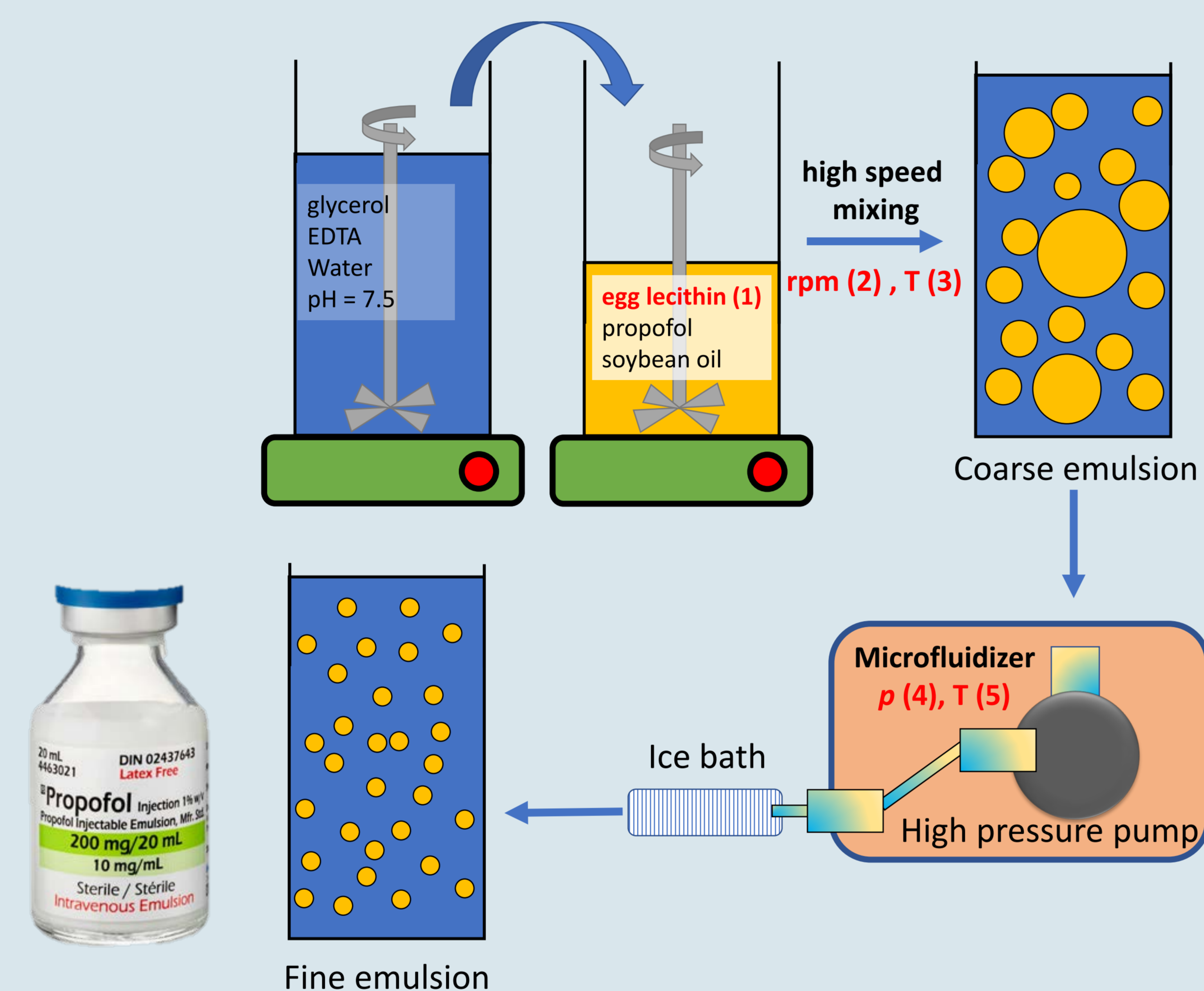
We are focused on understanding the impact of manufacturing process changes on particle size and morphology in a complex formulation such as propofol emulsion.

METHODS

In-house manufacturing of propofol emulsions involves two-step processing: The generation of a coarse emulsion, followed by homogenization using a microfluidizer. The coarse emulsion was prepared by mixing the oil phase (soybean oil) with the aqueous phase at various mixing speeds (500 and 1000 rpm) and temperatures (55, 65 and 75 °C). The coarse emulsion was then subjected to microfluidization to reduce the particle size. During this step, various combinations of microfluidization pressures (10000, 20000 and 30000 psi) and temperatures (10, 20, and 30 °C) were evaluated. In addition, the effect of the amount of emulsifier (6, 12, or 24 g of egg lecithin) on particle size and morphology was investigated. Particle size and particle concentration were measured by dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA), respectively. Cryogenic transmission electron microscopy (cryo-TEM) was used to confirm particle size and determine particle morphology.

RESULTS

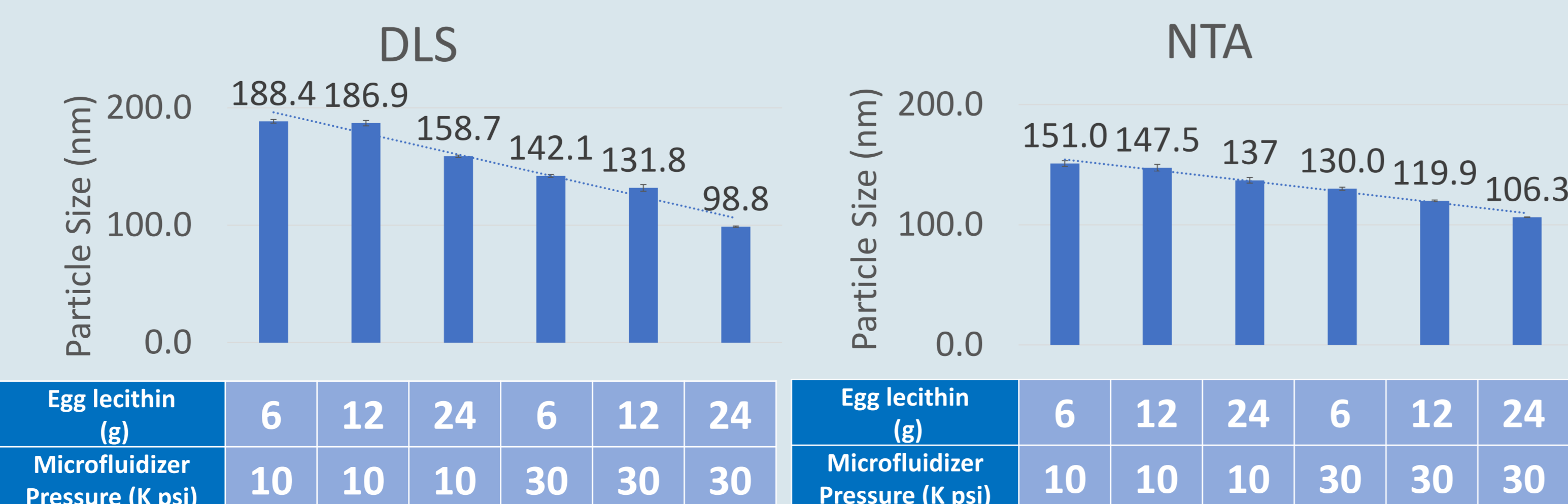
Propofol Emulsion: Manufacture Process and Parameters of Interest



Experimental Design

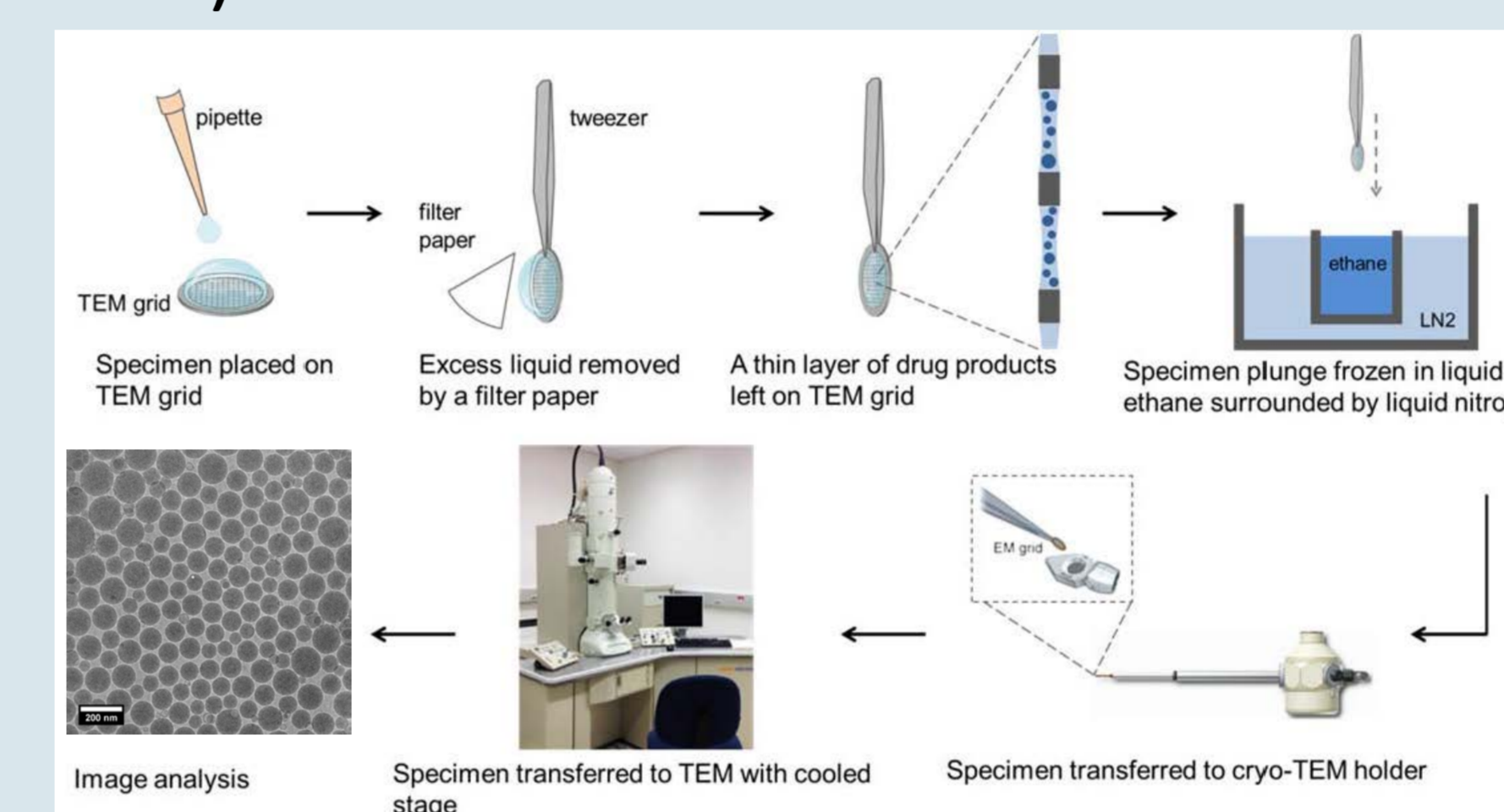
Formulation	Mixing		Microfluidizer		Egg Lecithin (g)
	Speed (rpm)	Temperature (°C)	Temperature (°C)	Pressure (psi)	
1	500	65	20	10000	12
2	500	65	20	30000	12
3	1000	55	30	10000	12
4	1000	55	10	30000	12
5	1000	75	30	10000	12
6	1000	75	10	10000	12
7	1000	55	20	10000	12
8	1000	75	20	10000	12
9	1000	65	20	10000	6
10	1000	65	20	30000	6
11	1000	65	20	10000	12
12	1000	65	20	30000	12
13	1000	65	20	10000	24
14	1000	65	20	30000	24

Particle Size of Propofol Emulsions

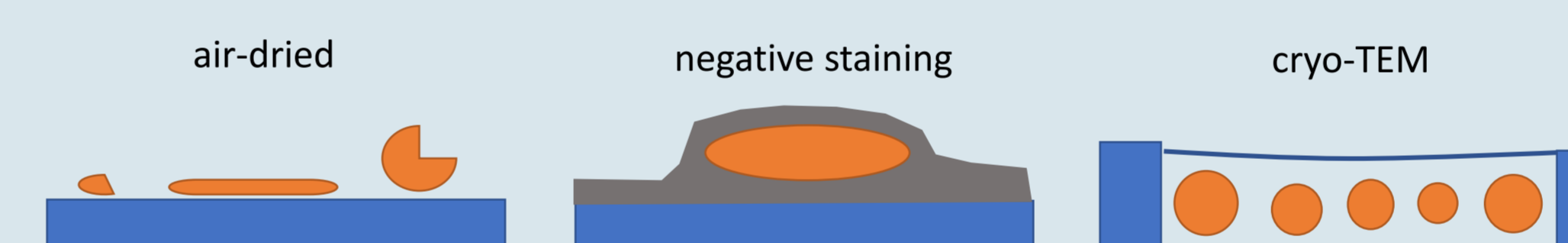


DLS and NTA cannot provide morphology information related to shape or internal structure. But Cryo-TEM can!

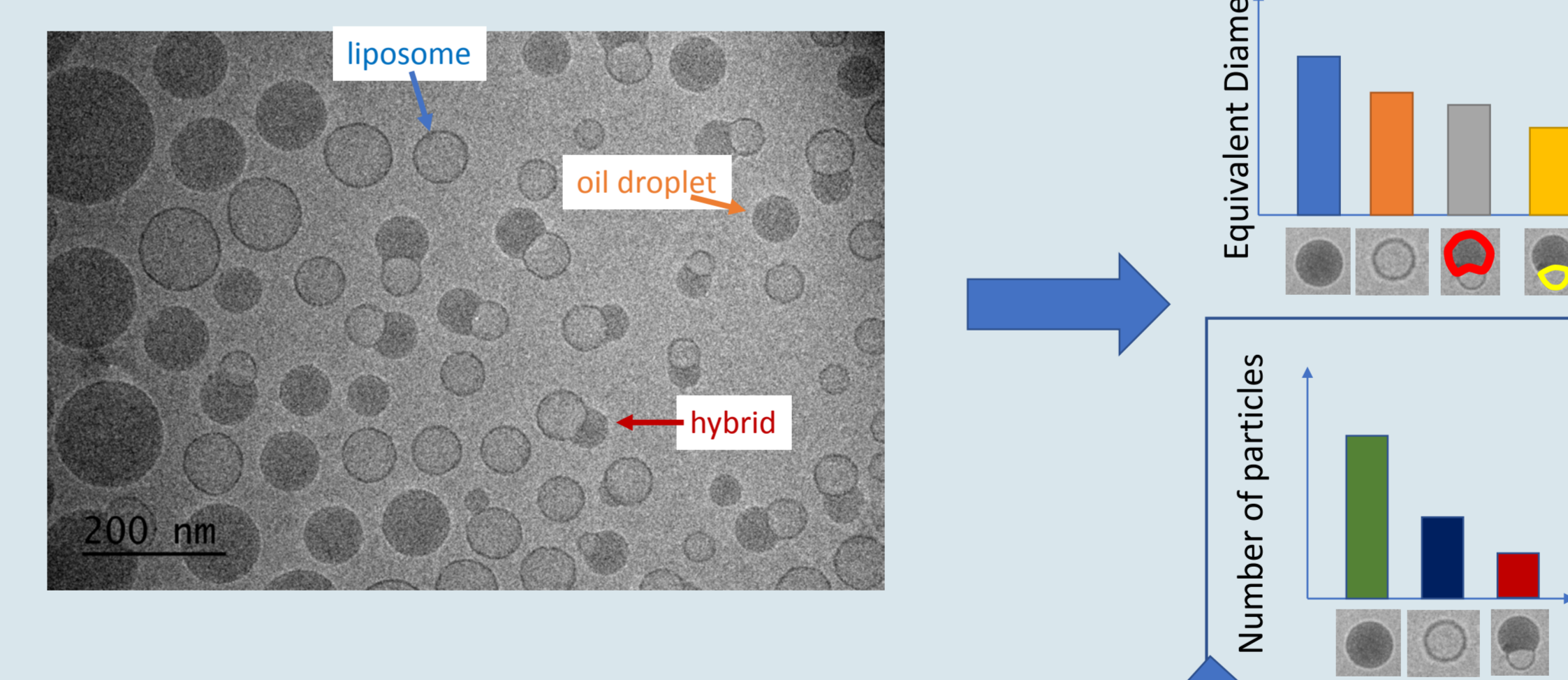
Cryogenic Transmission Electron Microscopy (cryo-TEM)



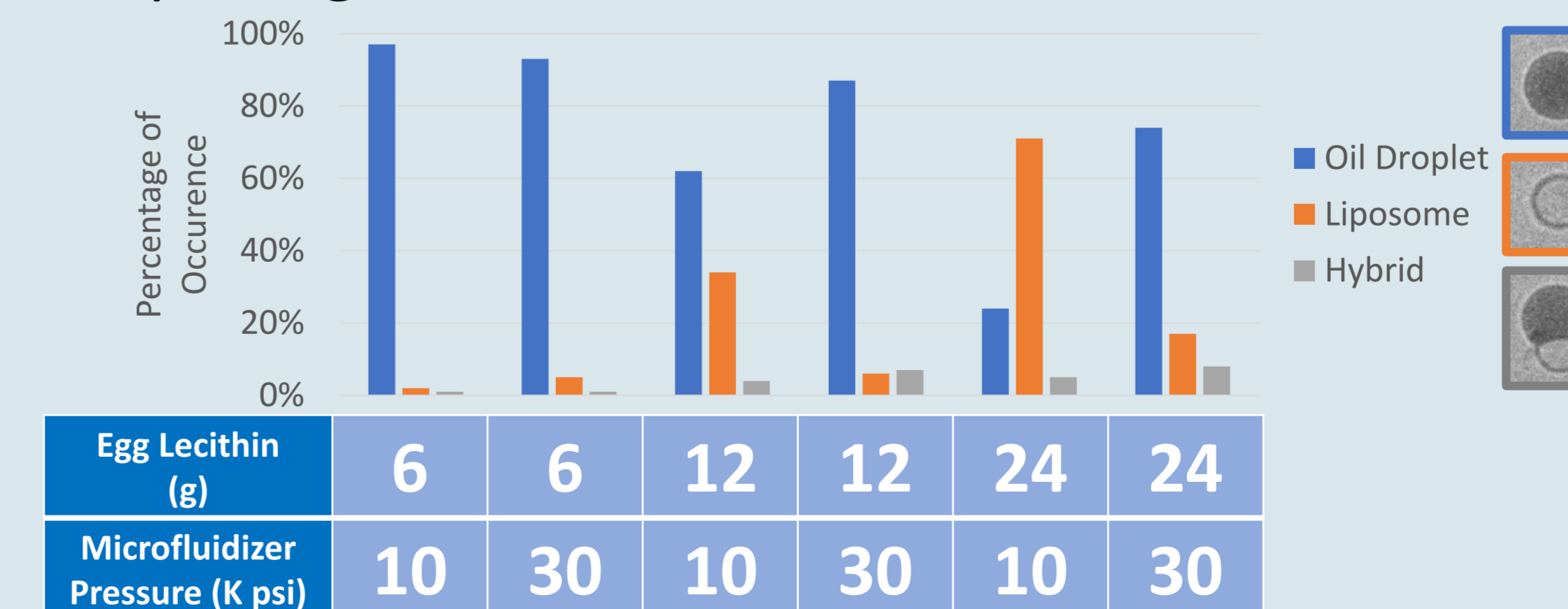
Ideal for Nanoscale Soft Nanomaterial Imaging



Cryo-TEM Imaging and Analysis



Morphological Variation



Both parameters affected the morphology composition. Their effects were interdependent:

- When the amount of egg lecithin is low, microfluidizer pressure has minimal impact;
- When egg lecithin is in excess, increasing microfluidizer pressure results in a decrease in liposome percentage.

CONCLUSIONS

Physicochemical Properties	Mixing		Microfluidizer			Egg Lecithin (g)	
	Speed (rpm)	Temp. (°C)	Pressure (psi)	Temp. (°C)	10000 psi	30000 psi	
Particle Size	DLS	↓	↓	↓	↓	↓	
	NTA	↓	---	↓	---	↓	
Particle Concentration (NTA)	---	---	↑	---	↑/---	↑/---	
Particle Morphology (Cryo-TEM)	Oil Droplet	---	↓	↑	↓	↓/---	
	Liposome	---	↑	↓	---	↑/---	
	Hybrid	---	---	---	---	---	

- Manufacturing process parameters were observed to have marked effects on the size, concentration and morphology of particles in propofol complex formulations:
 - All studied process parameters affected particle size.
 - Mixing temperature, microfluidizer pressure and egg lecithin also affected the particle morphology.
 - The effect of emulsifier is interdependent on the specific microfluidization conditions.
- Cryo-TEM is the only technique capable of discerning the particle morphology, and the relative ratio of different structures (e.g. oil droplets and lipid vesicles).
- Future work will focus on understanding how process-induced structural variations affect the drug release characteristics.

ACKNOWLEDGEMENT

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DISCLAIMER

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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