

Propofol after multiple freeze-thaw cycles

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Abstract

Recent aggression in Ukraine has demonstrated the potential need for anesthesia in austere environments where temperature alternates above and below the freezing point of many anesthesia medications. A common anesthetic propofol comes in several formulations that all differ by the antimicrobial additive. One study to date demonstrated a difference in emulsion stability between two different formulations but this study has not been replicated for newer formulations.¹ Our research team studied the effects of multiple freeze thaw cycles on propofol with sodium metabisulfite vs Diprivan with EDTA. Our preliminary results indicate significant bottle-to-bottle variability in both formulations with the majority of molecules being less than 5µm but containing some globular formations as large as 100µm. Significant variability in the pH of propofol with sodium metabisulfite was noted and found to be outside of the manufacturer's stated pH.

Methods

1. Unexpired propofol and Diprivan bottles were obtained and assigned to one of the following categories: No Freeze/Thaw (F/T) cycles, 1 F/T cycle, & 3 F/T cycles.
2. After being subjected to the F/T cycles above, all samples were then subjected to the following tests: pH, microscopy, Zeta Potential, SPOS, and Laser diffraction.

Results

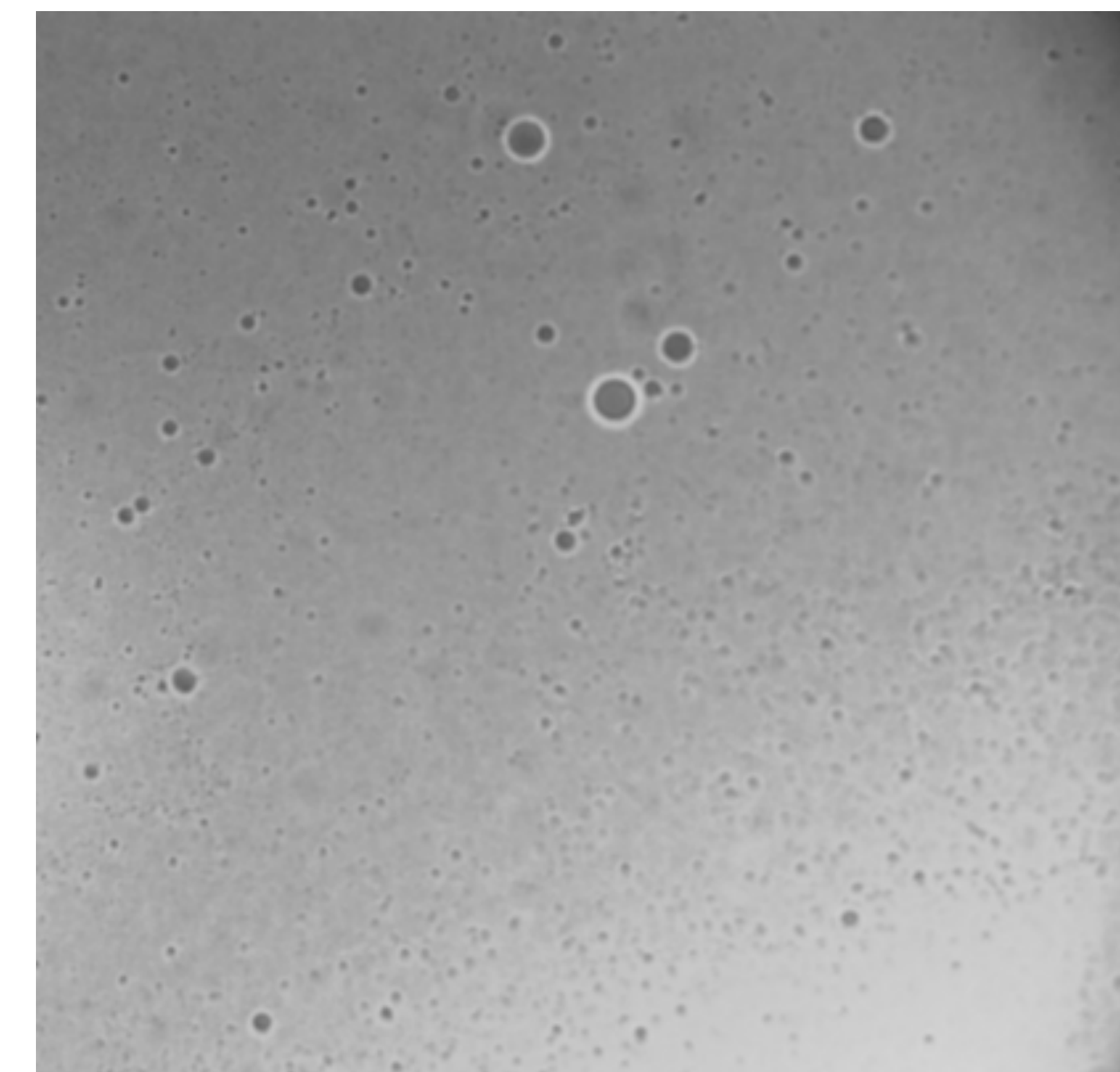
pH

Sample	No F/T	3 F/T
Diprivan	7.346	7.302
propofol	4.655	3.774

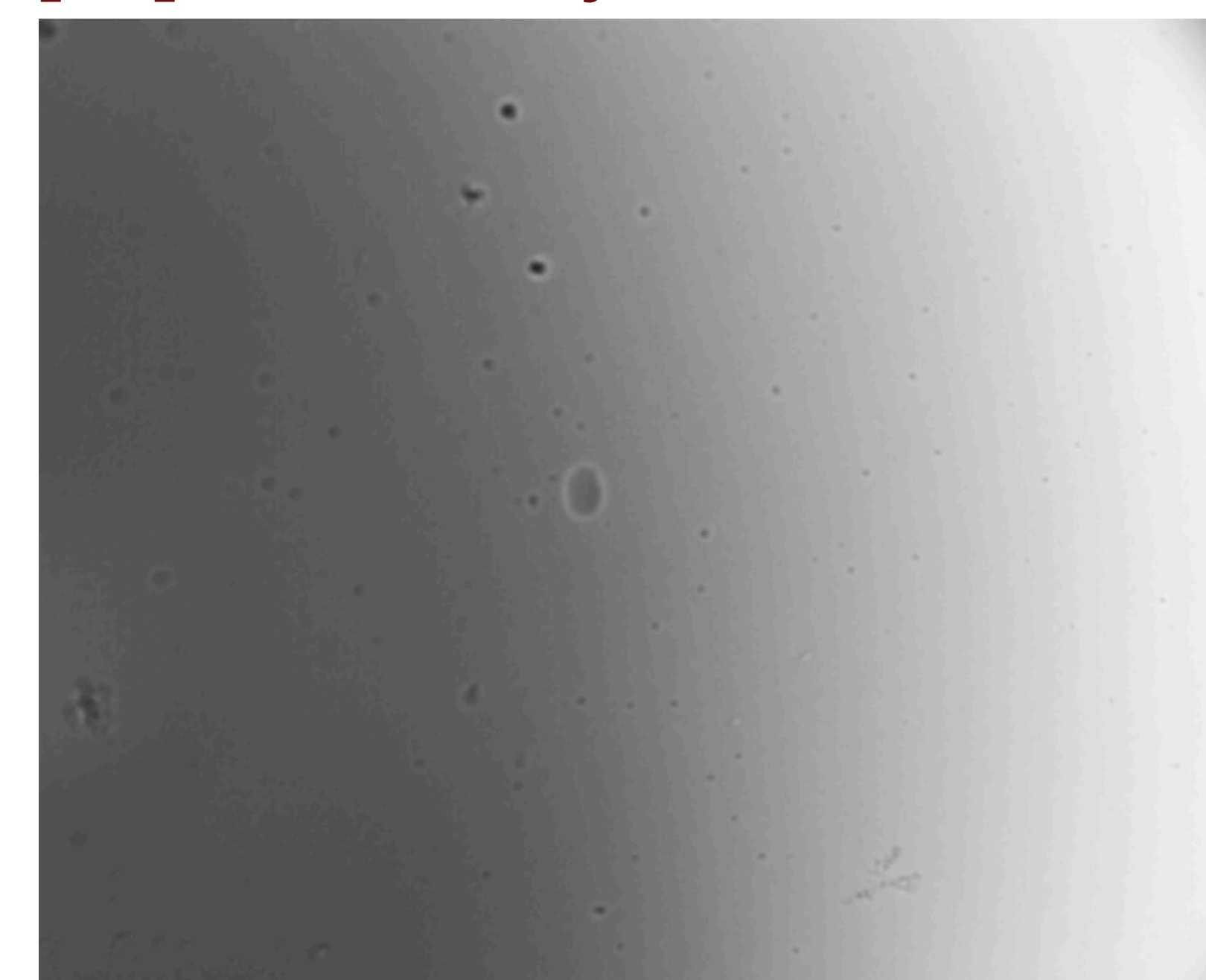
Marked variation in pH was noted for generic propofol and 1 sample was outside the manufacturer specified range.

Microscopy

Diprivan 3 F/T cycles



propofol 3 F/T cycles



Diprivan and propofol showed increased globular formation after **MULTIPLE** freeze-thaw cycles.

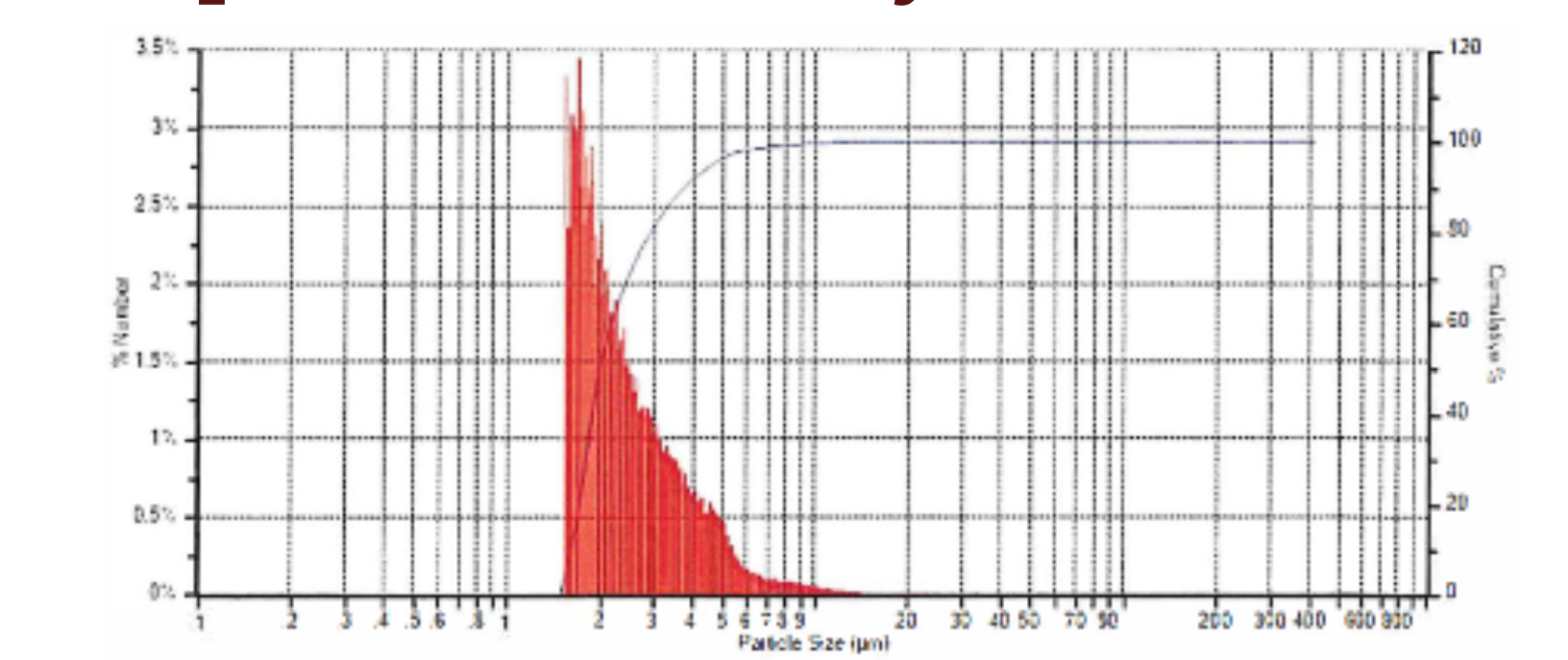
Propofol samples had pH values **outside** of manufacturer reported values



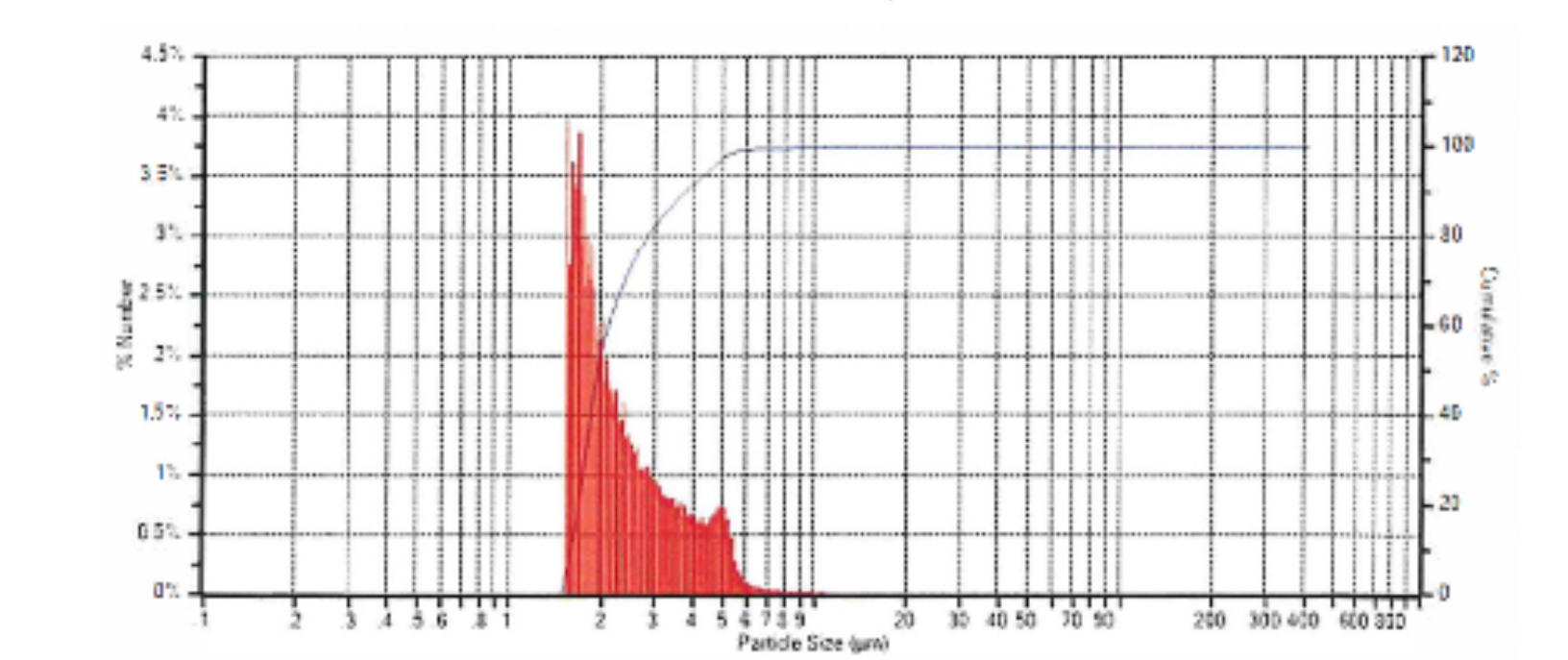
Sample distribution by SPOS

Sample	F/T Cycles	10th percentile (µm)	50th percentile (µm)	90th percentile (µm)	Mean (µm)	Largest (µm)
Diprivan 0		1.63	2	3.7	2.4	55
Diprivan 1		1.62	2	3.5	2.3	58
Diprivan 3		1.62	2	3.3	2.3	168
Propofol 0		1.62	2	3.9	2.4	49
Propofol 1		1.63	2	4	2.5	101
Propofol 3		1.64	2.1	3.8	2.5	71

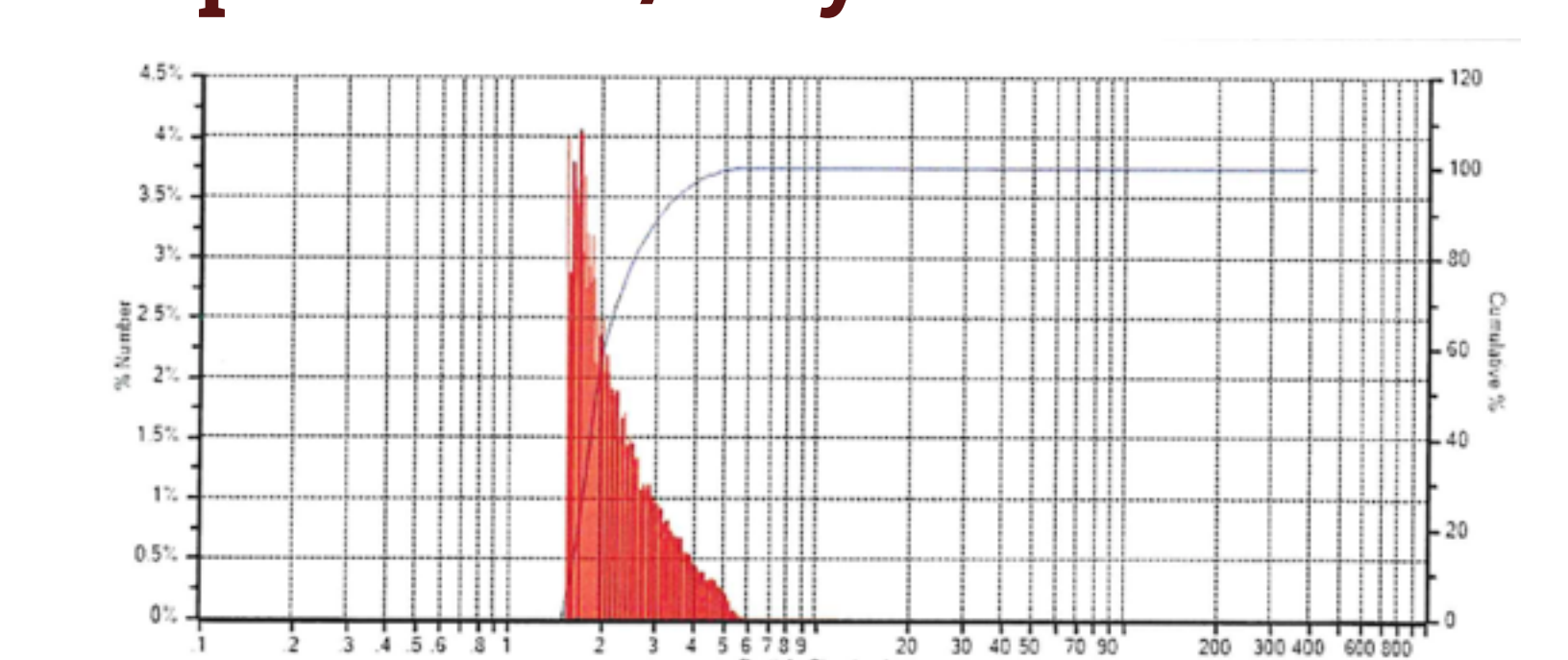
Diprivan No F/T cycles



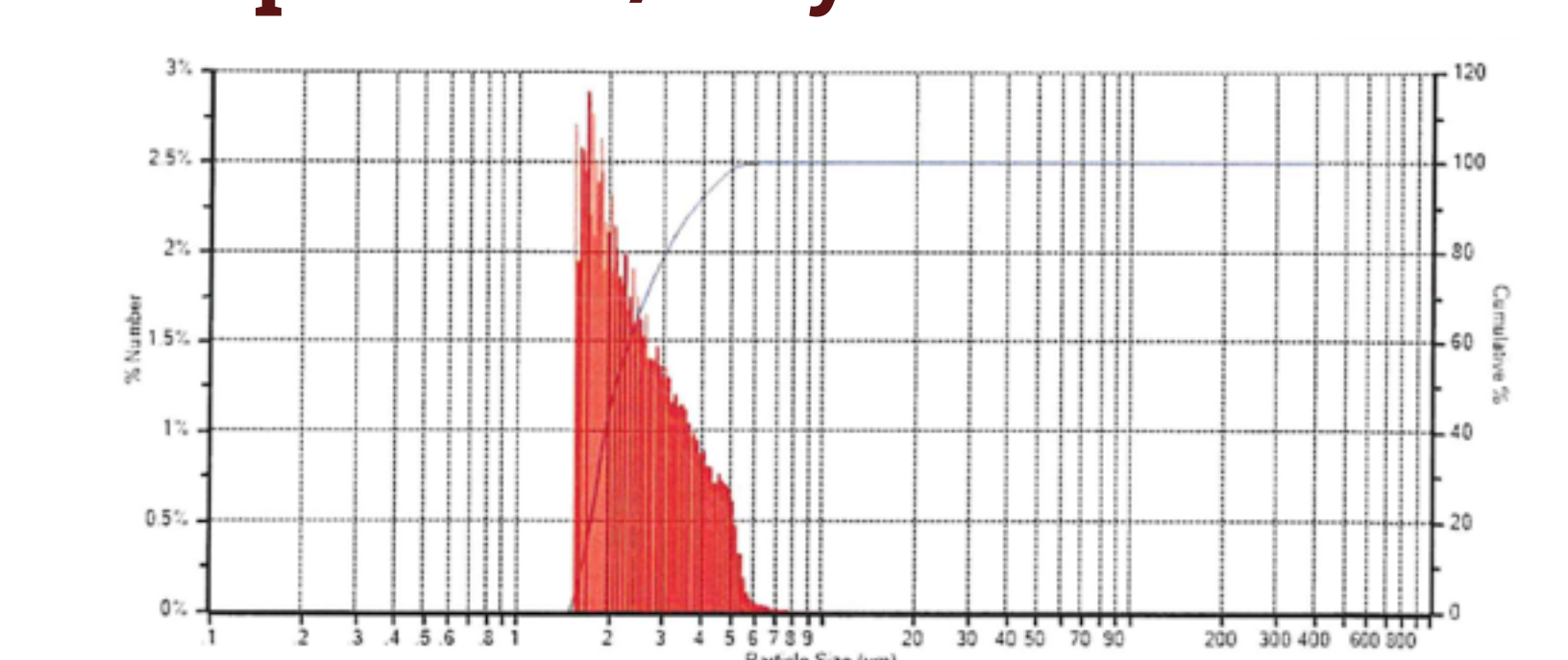
Propofol No F/T cycles



Diprivan 3 F/T cycles



Propofol 3 F/T cycles



Discussion

Large clumps of propofol > 5µm were noted in all samples including control samples of both Diprivan and generic propofol, but this only accounted for 3-5% of total molecules in the samples. Increases in globular formation size did occur with freeze/thaw cycles. Further testing is needed to determine if shaking the vial before administering or utilizing a filter needle will reduce or remove these large molecules to increase the safety profile for those at risk of lipid embolism.

Disclaimer

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References

1. Han J, Davis S, Washington C. Physical properties and stability of two emulsion formulations of propofol. *Int J Pharm.* 2001;11(215):207-220. doi:10.1016/s0378-5173(00)00692-x