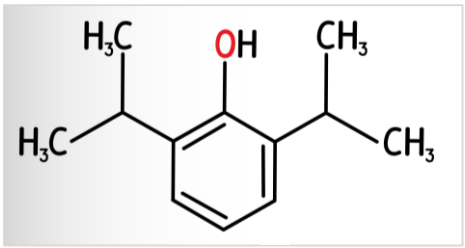
Microfluidics™

Application Note

Microfluidizer® Technology for producing Propofol emulsion



INTRODUCTION

Propofol is a potent intravenous anesthetic due to its rapid onset, short recovery time and minimal side effects. The use of propofol has expanded to include being a sedative hypnotic agent and as such is widely used for mechanically ventilated patients in intensive care units (ICU) and procedural sedation.

Propofol has come to the fore with the global coronavirus pandemic. Its usage has increased dramatically since COVID-19 patients often require prolonged periods of mechanical ventilation and treatment of related complications can also require the use of this product.

Due to the surge in propofol demand, it is currently on the FDA's drug shortage list[1] and they have also issued an Emergency Use of Authorization (EUA) for emergency use of a higher concentration formulation[2].

This Application Note looks at how Microfluidizer® Technology plays a vital role in safely producing this widely used drug.

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INTRODUCTION

Propofol is currently available under many different brand names worldwide, among them Diprivan® (marketed by Fresenius Kabi in the United States) is the well-known and widely used product. Propofol is used for the induction and maintenance of general anesthesia and sedation.

www.fresenius-kabi.com

Propofol is usually formulated as a lipid emulsion using either only soybean oil or a mixture of 1:1 ratio of soybean oil and medium chain triglycerides (MCT) oil as the carrier oil with 1% (10 mg/ml) strength.

One of the key challenges in manufacturing commercial intravenous emulsions is to be able to achieve target droplet sizes with a narrow distribution.

Emulsions delivered intravenously usually have droplets in the size range of 150–300 nm on average[3], and propofol emulsions are no exception. For example, Diprivan has an intensity based mean droplet diameter around 160–180 nm[4,5].

In addition to the small particle size, droplet uniformity or size distribution is also very important, especially for long term emulsion stability.

THE SOLUTION

Microfluidizer® technology is a well proven technology that effectively reduces liquid particle sizes to create nanoemulsions with homogeneous droplets.

The technology is reliable and scales up linearly from the lab to production. In addition, the Microfluidizer processors® comply with cGMP regulations which makes them the ideal solution for manufacturing commercial emulsions.

CASE STUDY

The ability of the Microfluidizer® technology to produce propofol emulsion is demonstrated on the next page.

In this study, a propofol formulation similar to Diprivan was processed with a Microfluidizer® processor.

The first goal was to replicate the reference particle size and size distribution by optimizing the process conditions.

The second goal was to subsequently scale up the process with a production scale Microfluidizer® processor.

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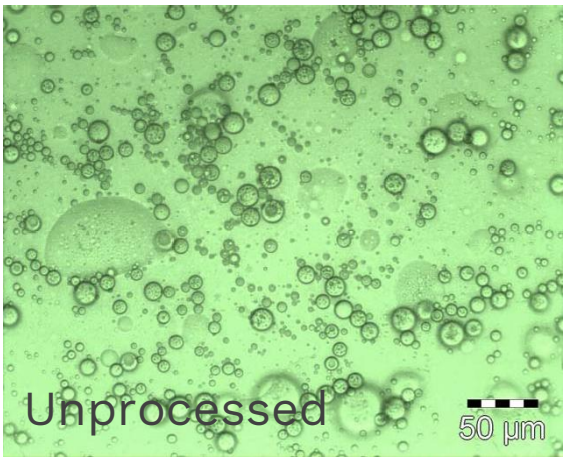
RESULTS

As shown in both microscopic images (figure 1) and the table of particle sizes, the droplets became very small and uniform after processing through the Microfluidizer® processor at just 20,000psi, compared to the unprocessed emulsion.

At this process pressure, the d50 particle size around 170 nanometers was achieved after just one pass, which was very close to the reference value. The particle size distribution, represented by the d10, d50 and d90 values, also agreed well with the reference. Additional pass further reduced the d50 particle size down to 140 nanometers.

PRESSURE (psi)	# OF PASSES	PARTICLE SIZE (microns)		
		d10	d50	d90
Reference	n/a	0.081	0.159	0.292
Unprocessed	0	2.313	3.831	6.137
20,000	1	0.096	0.171	0.286
20,000	2	0.084	0.141	0.223



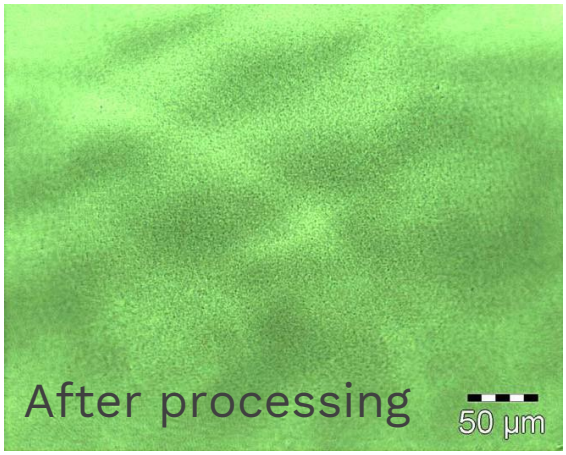


Figure 1 – Emulsion before and after being processed through a Microfluidizer® processor

As with all other parenteral/injectable drug products, propofol emulsion must be sterilized to destroy or remove any potential microbial contaminants.

Propofol is a stable drug at high temperatures, which means the emulsion can be autoclaved to achieve sterilization.

With the Microfluidizer® technology the d90 particle size indicates that the majority of droplets inside the processed emulsion are small and similar to the mean size of the sterile filters (220 nm), therefore this emulsion may be sterile filtered instead.

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SCALABILITY

The manufacturing process is truly scalable with the results achieved in the lab being assured in production scale.

The chart here shows how the results from the pilot scale M100EH model were replicated in the M7250-30 production model. Particle sizes after both 1 and 2 passes obtained on the production machine were very close to that obtained on the pilot machine.

The chart also shows how tight the particle size distribution (PSD) is that can be achieved.

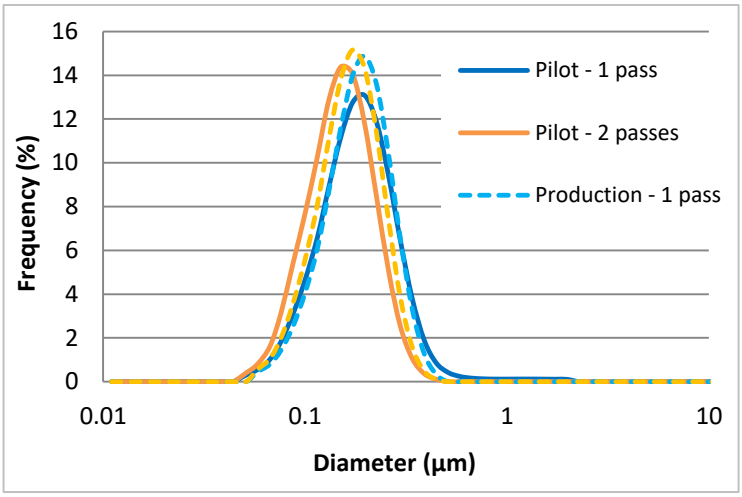

Figure 2 – Comparison of particle size distribution obtained from pilot scale and production scale Microfluidizer processors

REFERENCES

[1] https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Propofol%20Injectable%20Emulsion&st=c

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[3] M.T. Baker, et al., Anesthesiology, 2005; 103(4).

[4] R.F. Simoni, et al., Rev Bras Anestesiol, 2013; 63(1).

[5] N. Nilsson, et al., Pharm Technol Hosp Pharm, 2019; 4(2).