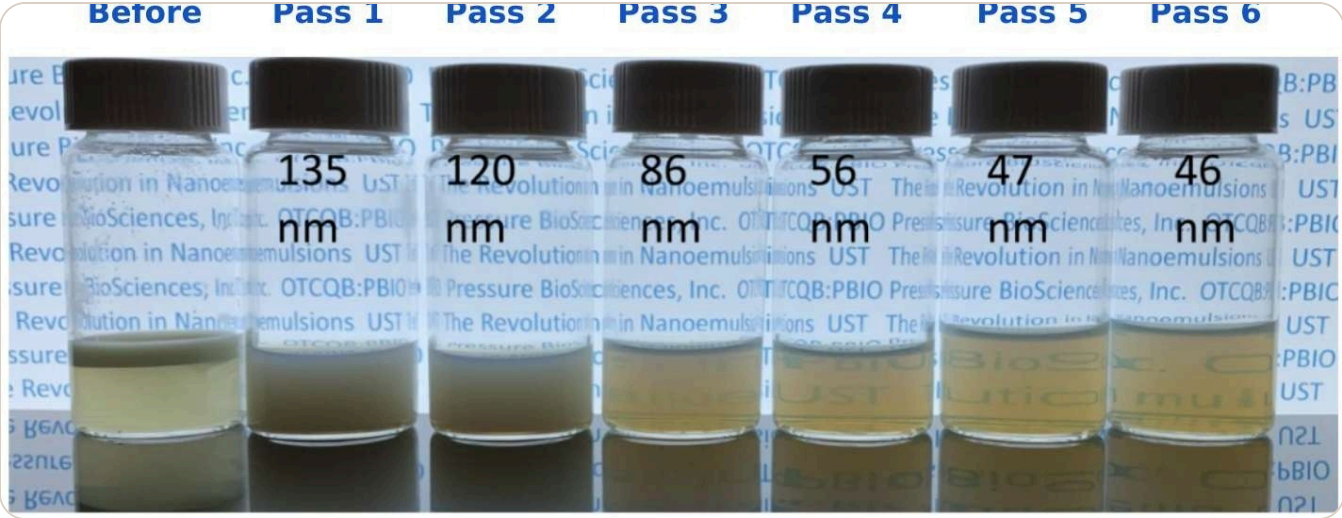
WHITE PAPER · ULTRASHEAR TECHNOLOGY

From droplet *to dose.*

Manufacturing nanoemulsions of lipophilic actives with UltraShear Technology: the mechanism, process data, the first peer-reviewed in-vivo evidence and its limits, and how to scale up in-house on the BaroShear™ NE-5 Gen 2.



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SHEAR SCIENCES

A DIVISION OF PRESSURE BIOSCIENCES, INC.

1 · Executive summary

- **The problem.** Many high-value actives (cannabinoids, carotenoids, coenzyme Q10, fat-soluble vitamins A, D, E and K, omega-3, astaxanthin) are lipophilic and thus poorly water-soluble. For cannabidiol, absolute oral bioavailability in fasted humans is estimated at about 6%, rising roughly fourfold with a high-fat meal [1].
- **The lever.** For a fixed oil volume, the interfacial area scales as 6/d. Reducing droplets from 1 µm to 50 nm increases the oil–water interface twentyfold, which speeds lipolysis and micellar solubilization and changes how the dose is presented to the gut.
- **The process.** UltraShear Technology (UST) drives a coarse starting emulsion at up to 30,000 psi (≈2,068 bar) through a patented, self-throttling Nano-Gap™ valve [6,7,9]. In supplier process data, mean droplet diameter fell from 135 nm after one pass to 46 nm after six, with a matching gain in optical clarity (Section 5).
- **The evidence so far.** In a peer-reviewed rat study of a ≈60 nm UST CBD nanoemulsion (n = 4 oral, n = 3 IV), parent-CBD bioavailability relative to dose-adjusted IV was 18.6% at 6 h and 25.4% at 24 h [2]. The study was small and had no matched oral control; Section 6 sets out what it does and does not show.
- **The platform.** The BaroShear™ NE-5 Gen 2 brings the nanoemulsification process in-house: this patented machine offers, among other assets, working pressures of 10,000–30,000 psi, a flow rate of up to 0.8 L/minute, two 10 L jacketed tanks, and a chiller. The machine uniquely uses the UST platform to reduce oil droplet sizes to 20–200+ nm, depending on formulation, parameters, and the number of passes [10].

2 · The delivery problem

A lipophilic active dosed in an oil reaches the circulation only after several steps. Pancreatic lipase must act at the oil–water interface to digest the carrier lipids. The products, fatty acids and monoglycerides, combine with bile salts into mixed micelles, which carry the active across the unstirred water layer to the enterocyte [11]. Most absorbed drug then enters the portal blood and undergoes first-pass metabolism in the liver.

Highly lipophilic compounds can also be incorporated into chylomicrons and exported into the intestinal lymph, which reaches the systemic circulation without a first pass through the liver. In rats, dietary lipids and lipid excipients substantially increased systemic exposure to orally dosed cannabinoids, consistent with a lymphatic contribution [3]. The large food effect seen with CBD in humans [1,8] points the same way: absorption depends heavily on how the molecule is presented to the gut.

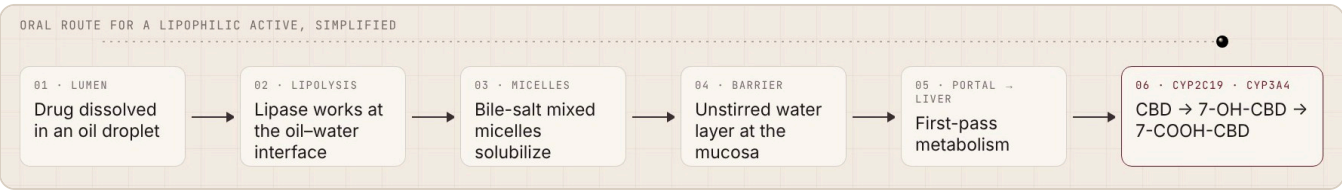


Figure 1. Simplified oral route for a lipophilic active, from oil droplet to first-pass metabolism.

3 · Why droplet size and uniformity matter

Interfacial area

For monodisperse spheres, the surface area per unit oil volume is $a = 6 / d$. Reducing the diameter from 1 µm to 50 nm therefore multiplies the oil–water interface available to lipase twentyfold at the same dose.

Stability and size distribution

A nanoemulsion is kinetically stable but thermodynamically unstable. A microemulsion, by contrast, forms spontaneously and is thermodynamically stable, but usually needs much more surfactant [4]. The main long-term failure mode of a nanoemulsion is Ostwald ripening: smaller droplets have a higher Laplace pressure, so oil diffuses from small droplets into large ones and the distribution coarsens. A narrow distribution slows this mechanism. For lipid-based delivery systems, a polydispersity index of 0.3 or below is generally considered acceptably homogeneous [5]. In the sub-100 nm range, Brownian motion outweighs gravity, so creaming slows dramatically.

Optics and filtration

Droplets comparable to the wavelength of visible light scatter strongly in the Mie regime, so coarse emulsions look milky. For droplets much smaller than the wavelength of light, scattering follows the Rayleigh regime, where scattered intensity scales as $I \propto d^6 / \lambda^4$. Halving the diameter cuts scattering about 64-fold, so the emulsion becomes translucent and then essentially clear. Small, uniform droplets can also pass a 0.22 µm sterilizing-grade membrane, which allows cold filtration of heat-sensitive active ingredients, where the formulation permits.

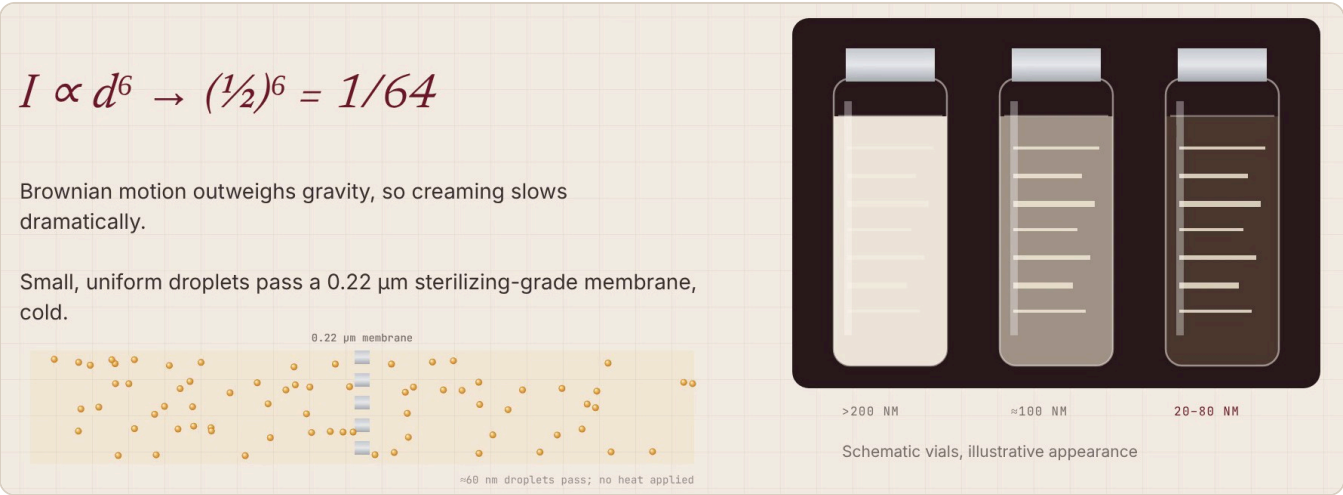


Figure 2. Schematic only: apparent clarity at three droplet-size ranges, and passage of ≈60 nm droplets through a 0.22 µm membrane. Not measured data.

4 · How UltraShear Technology (UST) works

A coarse starting emulsion is pressurized to as much as 30,000 psi (≈2,068 bar) and forced through an annular valve whose gap is in the nanometer range. The fluid accelerates through the gap and is subjected to intense, uniform shear in a continuous-flow process. The valve is self-throttling: its clearance adapts dynamically, which is designed to resist the clogging and erosion that limit fixed-orifice valves. Pressure, formulation, and the number of passes are the control variables. The valve and the processing system are covered by US

11,156,295 ("Ultrahigh pressure compact valve with throttling capability") and US 10,823,159 ("System for high pressure, high shear processing of fluids") [6,7]. Astaxanthin nanoemulsions produced on this valve design have been characterized in the peer-reviewed literature [9].

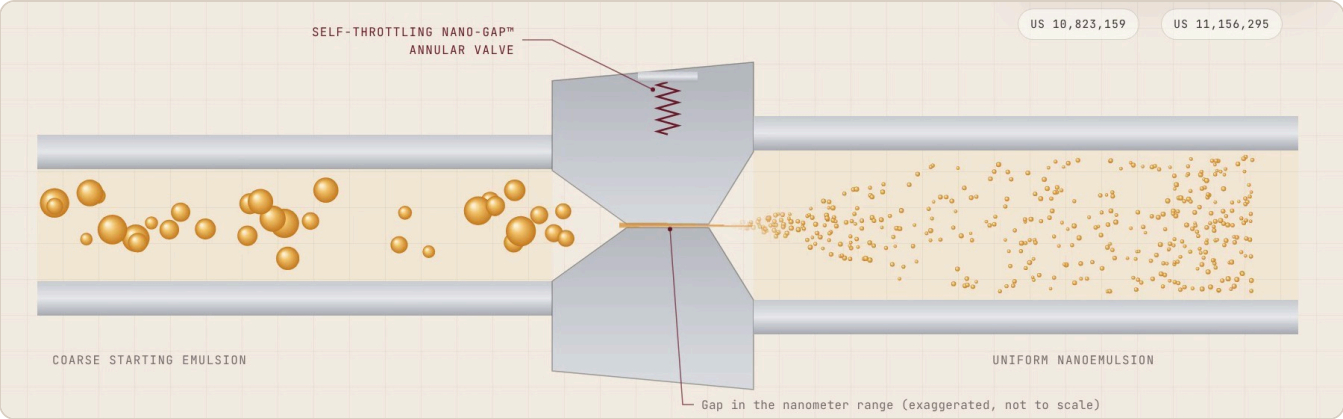


Figure 3. Schematic cross-section of the self-throttling annular valve (gap exaggerated, not to scale).

METHOD	TYPICAL LIMITATION	CONSEQUENCE
Rotor–stator	Limited energy density	Struggles to reach the sub-200 nm range
Ultrasonic	Uneven energy field; scale-up difficulty	Broad distributions that favour Ostwald ripening
Fixed-orifice high-pressure	Narrow fixed orifice	Reaches the nanoscale, but erodes and clogs
UltraShear (patented, self-throttling Nano-Gap™ valve)	Pressure, formulation, and pass count are tuned per product	Achieves reproducible, homogeneous 20 to 200+ nm droplets by design

Qualitative comparison for orientation.

5 · Process data: droplet size and clarity by pass

Pass count is the simplest lever on droplet size. Figure 4 shows one emulsion before processing and after each of six passes on the BaroShear NE-5 using the UST platform, with the mean droplet diameter measured after each pass. Size falls steeply over the first four passes and then levels off, and the sample clarifies with each ensuing pass, as the Rayleigh relationship in Section 3 predicts.

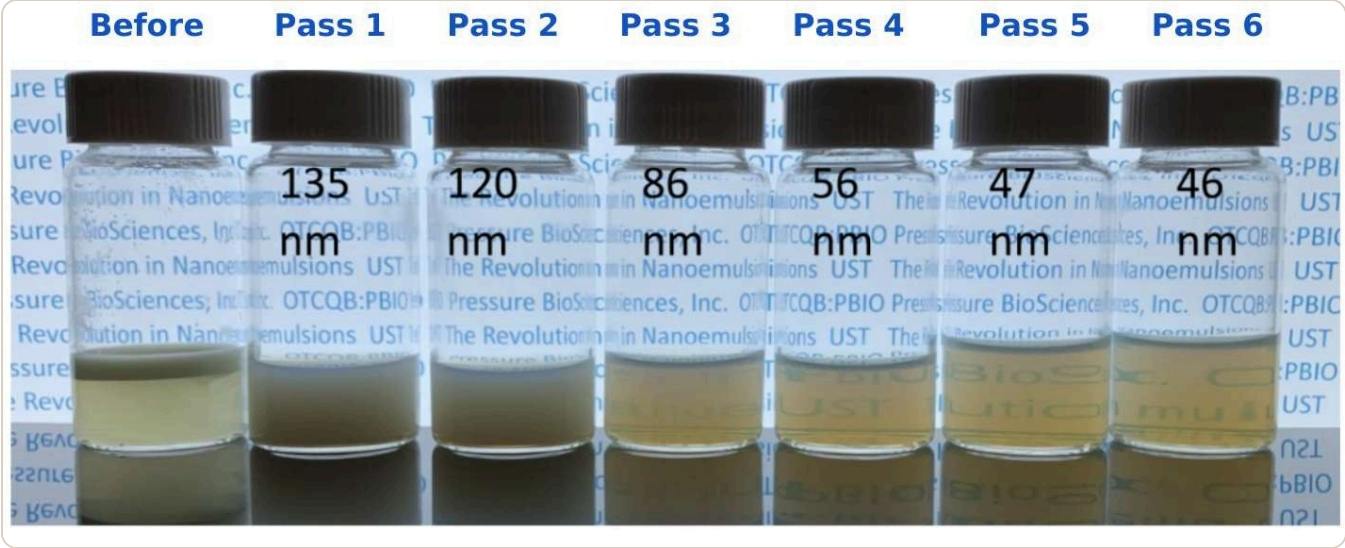


Figure 4. The same emulsion before processing and after passes 1–6, labelled with mean droplet diameter. Supplier photograph and data (Pressure BioSciences UST-Nano one-pager [12]).

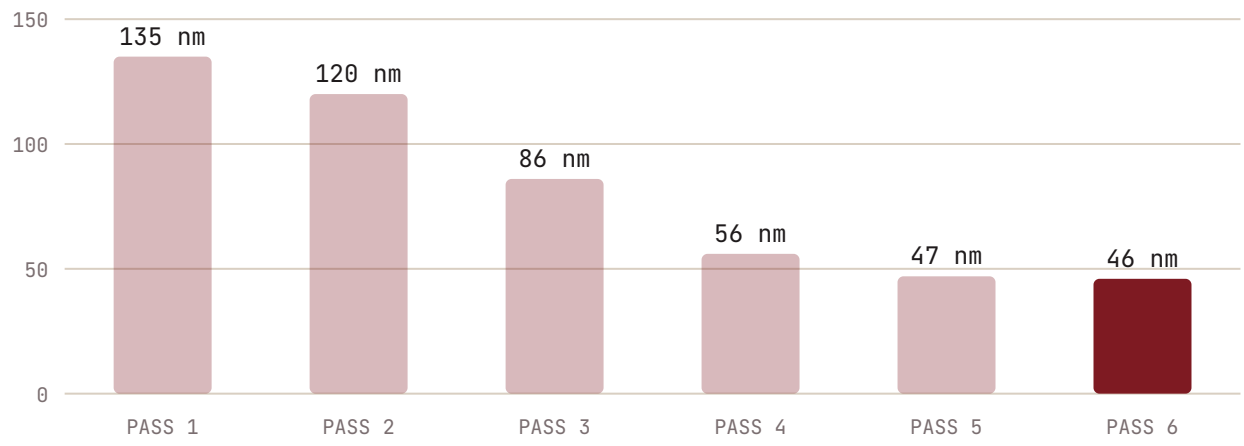


Figure 5. Mean droplet diameter by pass, from the labels in Figure 4: 135, 120, 86, 56, 47 and 46 nm. Supplier data [12]; results depend on formulation and processing conditions.

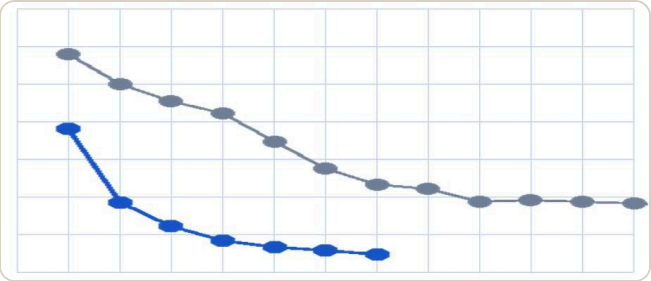


Figure 6. Optical transmittance by pass, UST-Nano versus a conventional high-pressure homogenizer, as published by the supplier [12]. The comparator instrument and its settings are not identified in the source; we show the chart as reported.

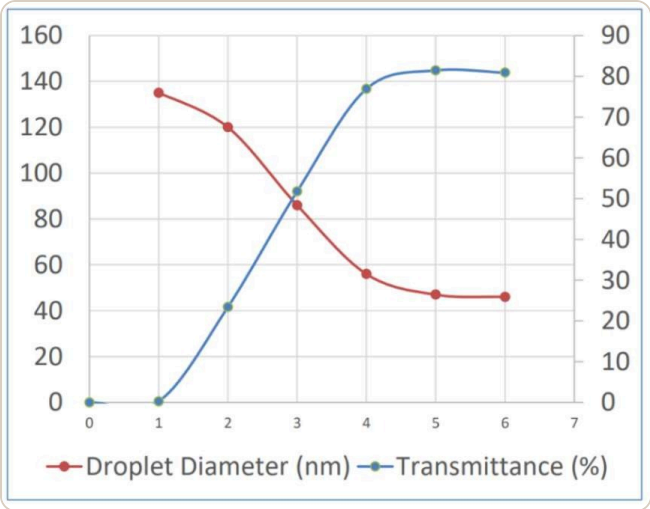


Figure 7. Droplet diameter (red, left axis, nm) and transmittance (blue, right axis, %) by pass for the series in Figure 4, as published by the supplier [12].

What a reviewer will ask: the formulation (oil phase, surfactant and loading), the pressure used, the sizing method and its polydispersity, and replicate runs. These details are available on request and are a natural first item for a feasibility discussion.

6 · The first in-vivo data, and its limits

ElSohly, Shahzadi and Gul (2023) evaluated a UST-processed CBD nanoemulsion in rats [2]. The article is open access (CC BY-NC 4.0). The authors report that the formulation was provided by Pressure BioSciences and that the study was partially supported by the company. They declared no conflicts of interest.

PARAMETER	AS REPORTED
Formulation	20 mg/mL CBD (isolate >98%), 10% virgin hempseed oil, 10% glycerol, 9% polysorbate 80, water
Process	Rotor–stator pre-blend, then 6 passes on a BaroShear Mini benchtop homogenizer
Droplets	Mean ≈60 nm, PDI 0.22 (dynamic light scattering)
Animals and dosing	Male Sprague-Dawley rats, jugular-cannulated, fasted. Oral gavage 5 mg (n = 4); IV 1 mg (n = 3) in ethanol : Kolliphor ELP : water (1:1:8)
Analytes	CBD, 7-OH-CBD, 7-COOH-CBD by LC-MS/MS to 24 h; metabolites expressed as CBD-equivalents

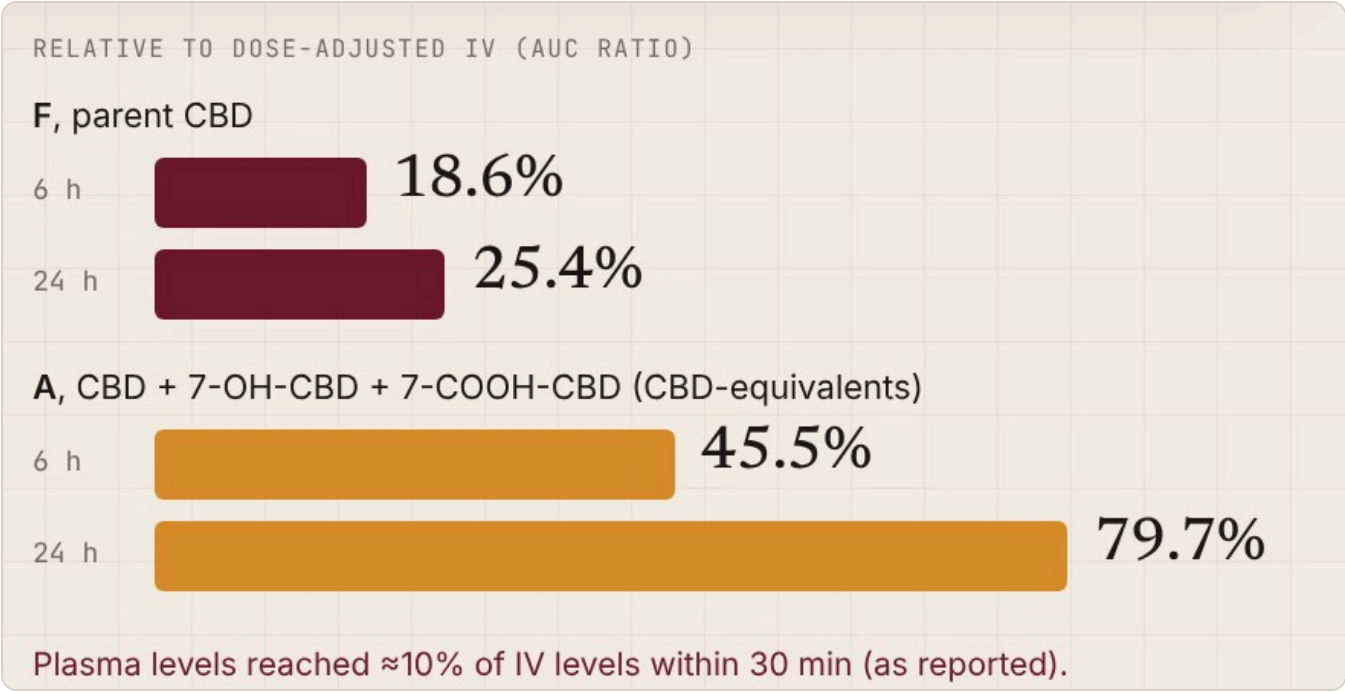


Figure 8. Relative bioavailability F (parent CBD) and total relative absorption A (CBD plus two metabolites, CBD-equivalents) versus dose-adjusted IV AUC, as reported in [2].

MEASURE (RELATIVE TO DOSE-ADJUSTED IV)	6 H	24 H
F, parent CBD	18.6%	25.4%
A, CBD + 7-OH-CBD + 7-COOH-CBD (CBD-equivalents)	45.5%	79.7%
Half-life, oral vs IV		5.3 ± 1.5 h vs 4.4 ± 0.9 h
Early exposure	≈10% of IV levels within 30 min (as stated in the abstract)	

Limitations a reviewer will raise

- Very small groups (n = 4 oral, n = 3 IV); the authors note SD and %CV are of limited use at this n.
- Route and vehicle are confounded: the IV arm used ethanol/Kolliphor, not the nanoemulsion.
- No matched oral oil control in the same study. The widely quoted "3–4×" advantage compares rat F (25.4%) with a human literature estimate (~6%, fasted) [1]; species and conditions differ.
- The 24-h IV value for one animal was missing and gap-filled with zero for the AUC calculation, which may lower the 24-h IV reference and raise 24-h ratios.
- Only three analytes were measured; total-absorption estimates depend on metabolite coverage and molecular-weight correction.
- The formulation was made on the BaroShear Mini benchtop system, not on the NE-5. Equivalent droplet size on the NE-5 should be confirmed for each formulation.

7 · Bringing UltraShear in-house: the BaroShear™ NE-5 Gen 2



The BaroShear NE-5 Generation 2 is a medium-sized, floor-model ultra-high-pressure homogenizer system designed specifically for manufacturing oil-in-water nanoemulsions with the UST platform. It runs at up to 30,000 psi with a sustained flow of up to 0.8 L/min at maximum pressure, and produces droplet sizes from above 200 nm to approximately 20 nm depending on formulation, operating parameters, and the number of passes [10].

The system ships with stainless-steel heat-exchange coils, two 10 L jacketed pre- and post-process tanks, and a chiller. All non-consumable parts, plus travel and labor, are covered by a one-year warranty [10].

The manufacturer expects future upgrades to raise the maximum operating pressure above 30,000 psi and notes potential applications in lipid nanoparticles and stable dispersions of nano-solids. These are forward-looking statements, not current specifications [10].

PARAMETER	SPECIFICATION [10]
Working pressure range	10,000–30,000 psi (optimum setting 30,000 psi)
Maximum flow rate	0.8 L/minute per pass
Holding tanks	2 × 10 L, jacketed, pre- and post-process
Temperature control	Stainless-steel heat-exchange coils; chiller included
System power and electrical	5 HP; 208–240 V AC, 1-phase, 50/60 Hz, 30 A
Size and weight	48 × 30 × 30 in; ≤ 350 lb (estimated)
Enclosure	Stainless steel, IP-54 or better
Operating space	8 × 8 ft minimum
Warranty	1 year on non-consumable parts, travel and labor

Planning throughput

Rated flow is per pass, so net throughput depends on how many passes a formulation needs. The arithmetic below uses the maximum rated flow; actual flow depends on pressure and formulation, and the figures exclude set-up, cleaning and changeover.

PASSES REQUIRED	NET THROUGHPUT	PER 8-HOUR RUN	ONE 10 L TANK
1	48 L/h	384 L	12.5 min
2	24 L/h	192 L	25 min
4	12 L/h	96 L	50 min
6	8 L/h	64 L	75 min

Site requirements

The customer provides site infrastructure: deionized and potable water supply, drainage, any additional heat-exchange equipment, filter-sterilization cassettes and consumables. Pressure BioSciences advises on the type and specification of this equipment on request [10].

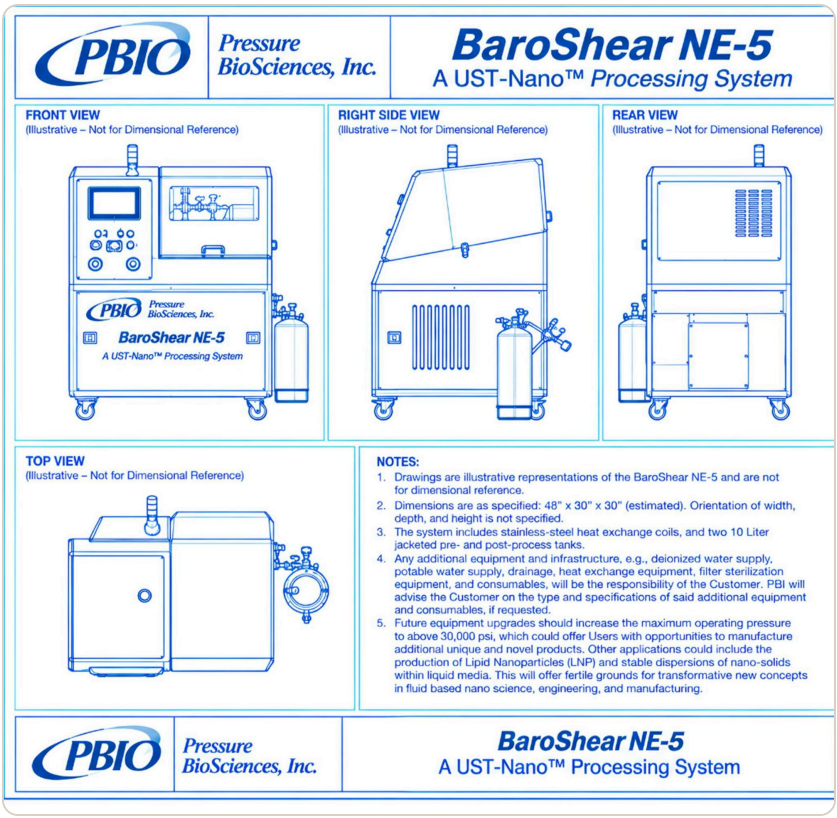


Figure 9. General arrangement, front, side, rear and top views. Illustrative; not for dimensional reference [10].

8 · Applications by industry

The physics in Sections 3–5 applies to any lipophilic active ingredient carried in an oil phase. The table lists candidate applications and the readouts that matter for each. Formulation performance depends on composition and processing conditions, and each product should be evaluated on its own data.

SECTOR	TYPICAL ACTIVES OR SYSTEMS	FORMULATION GOAL	READOUTS TO PLAN FOR
Pharmaceutical R&D	Poorly water-soluble APIs, lipid-based oral and topical systems	Smaller, narrower droplets; sterile filtration where possible; bioavailability to be tested in matched-control designs	Size and PDI, stability, PK in matched-control designs
Nutraceuticals and supplements	Carotenoids, CoQ10, curcumin, vitamins D/E/K, omega-3 oils	Clear, stable liquid formats; lower surfactant; higher bioavailability	Size and PDI over shelf life, clarity, taste, label claims review
Cannabinoids and botanical extracts	CBD, minor cannabinoids, hemp and botanical oils	Water-compatible beverages, sprays and drops; faster onset	Potency recovery, size stability, regulatory status by jurisdiction
Food and beverage	Flavor oils, colors, fortificants	Clear beverages, emulsion stability, cold processing, enhanced flavor	Turbidity, creaming, sensory, food-grade compliance
Cosmetics and personal care	Oils, vitamins, botanical actives	Light, clear serums and sprays; skin delivery to be tested per product	Appearance, stability, skin feel
Agrochemical and industrial fluids	Oil-soluble actives and adjuvants	Stable, dilutable, bioavailable concentrates	Dilution stability, droplet size on dilution

Candidate applications for evaluation. Formulation goals are what development teams aim for, not measured results; each must be confirmed with data for the specific product. No therapeutic, health or efficacy claim is made for any product.

9 · How to evaluate UltraShear for your formulation

STEP 1

Discovery call

Discuss your active ingredient, oil phase, current process, and target format with a Pressure BioSciences scientist.

STEP 2

Formulation review

Surfactant, loading, and pass strategy; what the data say about similar active ingredients and systems.

STEP 3

Feasibility processing

Under certain circumstances, it may be possible to process a sample of your formulation and report size, PDI, and appearance by pass. There may be a reasonable charge for this service.

STEP 4

Decision

Purchase terms and availability available upon request.

To begin, contact Ric Schumacher at rschumacher@pressurebiosciences.com, (508) 230-1828 (office) or (508) 801-1031 (mobile), or use the inquiry form on the Shear Sciences BaroShear NE-5 page.

10 · References

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