From the Lab to Commercial Production: The Challenge of Scaling Up Homogenization Processes

After successfully creating new formulations in a controlled laboratory environment, innovators in the pharmaceutical, biotechnology, chemical, personal care, and food industries often face significant challenges in scaling up production to commercial quantities.

Unfortunately, instruments designed for the laboratory setting can differ significantly from the equipment required to produce large volumes and withstand the rigors of the manufacturing environment. For certain processes, it is difficult or impossible to adjust and modify production-scale equipment to precisely match the formulations created in the laboratory.

The transition from laboratory to manufacturing can be particularly challenging for the homogenization processes used for cell disruption, particle size reduction, and emulsification. Scaling up conventional homogenization can be as much art as science — a trial-and-error process that can be time consuming and expensive — with results that are difficult to predict and too often fail to achieve the identical product as produced in the lab.

UNPREDICTABLE SCALABILITY OF CONVENTIONAL HOMOGENIZATION

The conventional homogenization process was originally designed for processing milk and other dairy products. Auguste Gaulin received a patent in 1899 for a milk homogenization mechanism that reduced the size of fat globules in order to prevent the formation of a cream layer. It is a mechanical process that forces milk under high pressure through a tiny orifice.

Today, a two-stage homogenization process is typically used for dairy products. The first stage operates at a pressure of 2500 psi and reduces the fat globules to a mean size of 0.5 micrometers (with actual size ranging from 0.2–2.0 μm). Because of a tendency for clumping and clustering of the reduced fat globules, a second stage of homogenization is employed. The second stage valve does not reduce the size, but it does separate the clusters into individual fat globules that are less likely to form cream during two or three weeks of shelf life.

Over the past century, more than 100 additional patents have been awarded for improvements on Gaulin's original design, producing smaller average particle size and achieving higher levels of precision than traditionally required by the dairy industry. For advanced products, conventional homogenizers can be designed to perform a variety of cell disruption, particle size reduction, and emulsification operations by selecting or creating a particular orifice size and valve geometry and by adjusting the pressure.

However, for conventional homogenizers, the orifice size, valve geometry, and pressure settings apply only to a specific flow rate. When scaling up from a laboratory-size homogenizer to a pilot system and from a pilot system to a full-scale production system, completely different valves are used and the pressure may need to be raised or lowered considerably. Sometimes several iterations of equipment design must be tested before an acceptable product is produced, or until the specified flowrate is achieved.

FIXED GEOMETRY OF HIGH SHEAR FLUID PROCESSING

An alternative method of homogenization, high shear fluid processing, is favored by many

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companies developing new formulations because production volumes can be seamlessly increased from the laboratory to full commercial manufacturing, while utilizing the same processes and turning out identical product.

High shear fluid processing systems contain an electric-hydraulic system providing power to one or two single-acting intensifier pumps. The pump amplifies the hydraulic pressure to the selected level which, in turn, imparts that pressure to the product stream. Process pressures range from 2,500 to 40,000 psi, resulting in high velocity, high shear process streams.

The intensifier pump supplies the desired pressure at a constant rate to the product stream. As the pump travels through its pressure stroke, it drives the product through precisely defined fixed-geometry microchannels within the interaction chamber. At the end of the power stroke, the intensifier pump reverses direction, and the new volume of product is drawn in. The intensifier pump again reverses direction and pressurizes the new volume of product, repeating the process.

As a result, the product stream accelerates to high velocities, creating shear rates within the product stream that are orders of magnitude greater than any other conventional means. The entire product experiences identical processing conditions, producing the desired results, which include uniform particle and droplet size reduction, deagglomeration, and high-yield cell disruption.

The fixed geometry of the microchannels not only ensures that the processing conditions are identical for all product passing through a single machine but that the processing conditions are also identical for all machines using a particular interaction chamber design and pressure setting, regardless of flow-rate capacity.

Therefore, once a high shear fluid processor achieves a successful result with a small laboratory system producing only a few hundred milliliters per minute, then the same interaction chamber and pressure specifications can be used in the design of a full-scale production system that produces tens of gallons per minute. Because of the ability to scale-up production seamlessly, many users of high shear fluid processors skip the usual pilot stage and move directly from the laboratory to full-scale commercial production capacity.

PRECISION HOMOGENIZATION APPLICATIONS

High shear fluid processors are widely used in two broad categories of applications that require precision processing. The first category is particle reduction and emulsification. For example, drug manufacturers use high shear fluid processors to make emulsions with high energy lipids that can be administered intravenously, with uniform droplet sizes well below one micron — smaller than the diameter of the capillaries in the human body — all but eliminating the risk of thrombosis.

In the chemical industry, the effectiveness and appeal of high-end coatings for aerospace and automotive applications increase as droplet size decreases and particles become more uniformly dispersed. Manufacturers of the resins, extenders, and additives that are integrated with these coatings use high shear fluid processors to achieve high color strength and gloss. The makers of high quality digital inks use a similar process to ensure that all pigment particles are sufficiently small to avoid clogging tiny ink-jet print nozzles.

The pharmaceutical and cosmetics industries also rely on high shear fluid processors for creating the time-released and depth-released characteristics of lotions and creams. Through uniform micro-encapsulation of active ingredients in liposomes, these products can live up to their promise of delivering benefits to specific sites at controlled and predictable rates.

In addition, the food industry is using liposomes in nutraceuticals to enable the slow release of nutrients that can be more easily ingested. High shear fluid processors enable many other enhancements to the nutritional value, color, taste, and texture of foods and beverages. For example, tiny particles of fiber are added to soymilk and many foods without effecting taste or texture.

The second category of applications requiring the precession of high shear fluid processors is cell disruption for the biotechnology industry: precisely-controlled amounts of shear force are applied to bacteria and other cell structures to safely extract high yields of intact proteins and nano-sized particles. These compounds need to be extracted from the living organisms quickly and without damage or contamination.

Conventional homogenization has served the needs of the dairy industry for over a century. However, the development of advanced products utilizing particle reduction, emulsification, and cell disruption applications now requires a level of precision, uniformity, and predictability that is best achieved with high shear fluid processing.

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