PureNano™ Continuous Crystallizer: A Breakthrough in Crystallization Technology Enables Continuous Manufacturing of Non-soluble Drug Suspensions

Featuring a pharmaceutical case study for oncology drug formulation with improved bioavailability and delivery capabilities

Abstract

Drug suspensions are of great interest because of their high bioavailability (the rate at which the active drug enters the systemic circulation) which significantly reduces the amount of drug that needs to be delivered into a patient as compared to drug emulsions. However, the particle size of the solid API plays a crucial role in 1) the stability of the suspension and 2) the safe delivery of the drug into the circulatory system.

This paper describes a novel manufacturing technology, the PureNano™ Continuous Crystallizer, which enables pharmaceutical and biotechnology companies to overcome both issues. PureNano combines a unique high shear processor with expert process consulting to achieve breakthrough formulation results on the nano-scale. A pharmaceutical case study featuring successful processing of an oncology drug is profiled.

Background

Estimates suggest that each year roughly half of all newly formulated drugs having potentially high pharmacological value will have little chance to make it beyond the laboratory and into marketplace. Drug and vaccine formulations exist basically as either emulsions or suspensions, the latter consisting of non-water soluble (hydrophobic) active pharmaceutical ingredients (APIs) suspended in a liquid. Drug suspensions are of great interest because of their high bioavailability (the rate at which the active drug enters the systemic circulation) which significantly reduces the amount of drug that needs to be delivered into a patient as compared to drug emulsions. However, the particle size of the solid API plays a crucial role in 1) the stability of the suspension and 2) the safe delivery of the drug into the circulatory system. A recent breakthrough in continuous crystallization technology now enables pharmaceutical and biotechnology companies to overcome both issues.

PureNano Continuous Crystallizer technology is a novel manufacturing technology based upon Microfluidics' globally patent-pending Microfluidics Reaction Technology™ (MRT) platform. PureNano takes on an important role in the formulation and the continuous manufacturing of high purity stable nano-suspensions[1] which is not always achievable with conventional particle size reduction methods.

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[1] Nano-suspensions consist of uniform size nano-particles which are defined as particles that are less than 100 nanometers or, one billionth of a meter in size.

Other crystallization processing technologies claiming to produce stable nano-particles are mainly experimental. However, a closer look at two such offerings reveals the shortcomings of each which the PureNano Crystallizer overcomes. As an example, low pressure impinging jet technology[1] is characterized by low flow rates, low jet velocities, and therefore low energy. The jet velocities of the low pressure impinging jet technologies are over two orders of magnitude lower than velocities used in PureNano. Low pressures and low energy levels are associated with large particles and inability of the technology to handle high solid loadings without plugging or fouling.

Another example is use of a supercritical carbon dioxide (CO_2) spray processing technology[2]. With this technology, liquid CO_2 is used to dissolve a drug. The liquid CO_2 is then sprayed vaporizing the CO_2 and leaving the drug in the form of small particles. The technology has been proven to be impractical for manufacturing because it is not scalable and is highly energy intensive.

The PureNano Crystallizer, which incorporates a scalable mixing chamber, is an energy-efficient method which offers a pathway for the continuous processing of numerous drugs and vaccines that could not otherwise be formulated or efficaciously administered in the past. It may be noted here that the pharmaceutical manufacturing industry continuous to rapidly move from the decades-old “tried and true” batch processing to continuous processing. Continuous processing in manufacturing offers lower cost and higher quality. Additionally, continuous processing allows a manufacturing plant to increase production rates with little or no new investment in capital equipment.

A case study presented below demonstrates the success of the PureNano Crystallizer in formulating a nano-suspension cancer drug that conventional particle size reduction methods were unable to achieve.

Nano-suspensions by Continuous Crystallization

Continuous crystallization is not new to the pharmaceutical industry. It is a process by which crystals are grown from individual molecules. It is used primarily for the production of a desired API from the starting raw materials and is the culmination of multiple operations and processes to produce the desired API in solid form consisting of small particles with a narrow size distribution.

The PureNano Crystallizer is an advancement of the continuous crystallization process for pharmaceuticals in that it provides the next step in the production of nano-suspensions of non-soluble APIs. With the PureNano Crystallizer, crystallization takes place as a continuous process within a patented mixing chamber.

Principal of Operation

Applications best suited for the PureNano Crystallizer are dependent upon the length of time for crystallization to occur. These “resident” times are critical to the crystallization process and are determined by the API involved. Candidate APIs may have residence times that range from a few hundred microseconds to several hundred milliseconds. To accommodate this range of times, the PureNano Crystallizer employs either of two basic system configurations with each configuration utilizing the proprietary mixing chamber.

Configuration A: No Pre-mix

The principal of operation of this PureNano Crystallizer configuration is depicted in Fig 1 below. The API is first dissolved in a predetermined solvent. The resulting solution, Solution 1, is placed in one of the two inlet reservoirs. Solution 2, the "anti-solvent," which in many cases may be water, is placed in the second reservoir as shown. The anti-solvent enables crystallization to occur upon contact with Solution 1.

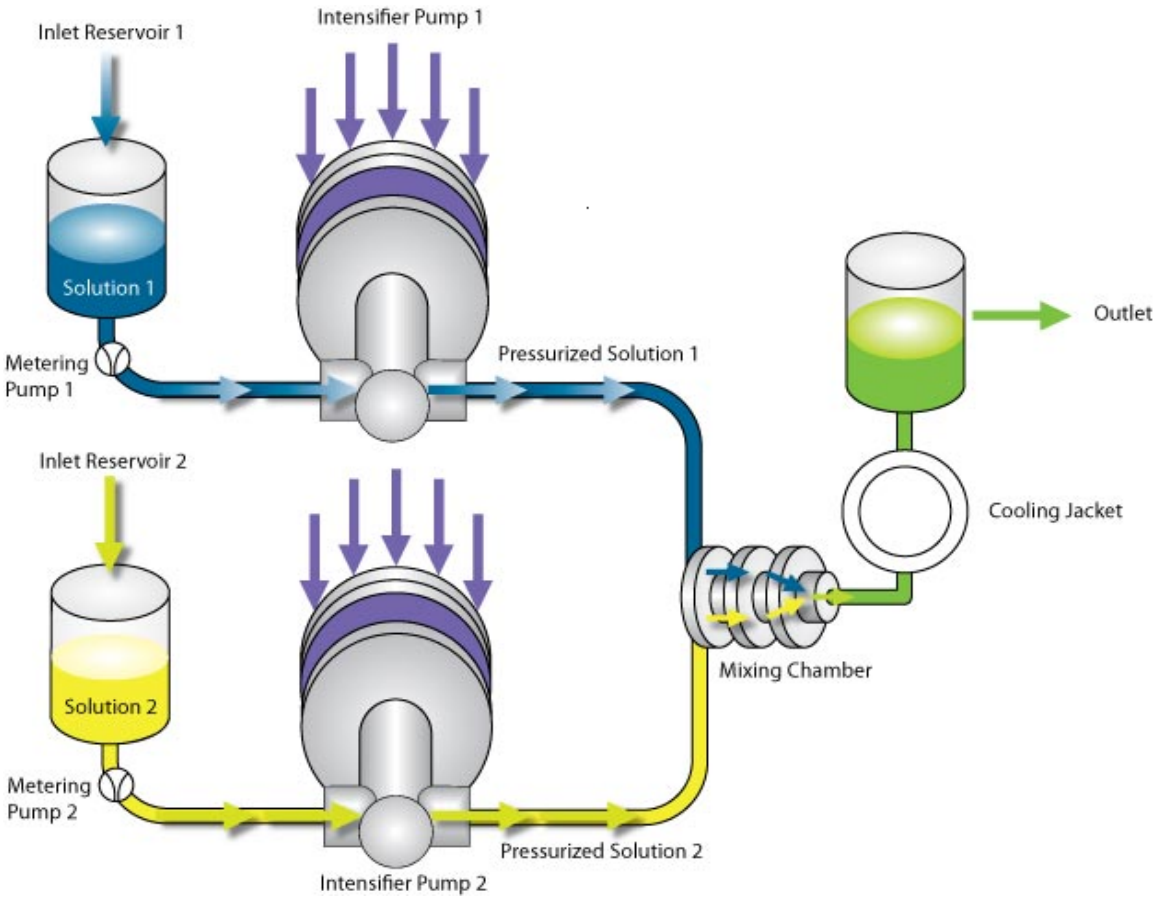


Figure 1. Principal of operation of the PureNano Crystallizer

The streams of Solutions 1 and 2 are then individually pressurized to achieve high velocities and subsequently collide "head-on" within the mixing chamber. This forces Solutions 1 and 2 to interact at a nano-scale level resulting in a continuous output flow of a stable high purity nano-suspension. The high purity of the resulting nano-suspension is a direct result of an extremely fast crystallization time within the mixing chamber.

Key components of this system include: an intensifier pump for high pressure generation of the solution streams, a metering pump with each of the solution streams for the precise control of their flow rates, a network of feedback sensors and actuating valves and a programmable logic controller (PLC). The PLC is the central control system and is programmed to maintain the continuous flow rates and the precise mixing ratios of the solvent/anti-solvent streams. It is important to note that mixing ratios are controlled

within ±1% accuracy to ensure the proper stoichiometry within the mixing chamber and that of the final product – a stable dispersion. Also, this control strategy enables a broad range of mixing ratios from 1:1 up to 1:40 for the solvent and anti-solvent solutions. This is a key factor in accommodating a wide selection of APIs.

In contrast, the conventional particle size reduction methods mechanically break larger particles into smaller and uniform particle sizes. These methods include wet-milling, homogenization, and micronization. Although these methods create high pressures and intense shear rates, they are unable to produce enough energy to break through nature's barrier to reduce particles smaller than the primary crystal size which varies with each material of interest. This limitation was the impetus for Microfluidics to embark upon their internally funded MRT program.

Figure 1 discussed above is the PureNano Crystallizer configuration for very fast crystallization times. It is designed to prevent the reactant steams from coming in contact prior to entering the mixing chamber which is essential.

Configuration B: Pre-mix for Extended Residence Times

For crystallization requiring longer residence times, which comprise the majority of applications that Microfluidics researchers have encountered, the PureNano Crystallizer is configured with a "coaxial feed" to allow the controlled pre-mixing of the two streams of Solutions 1 and 2 within a "macro-mixing" zone prior to entering the mixing chamber as depicted in Fig 2.

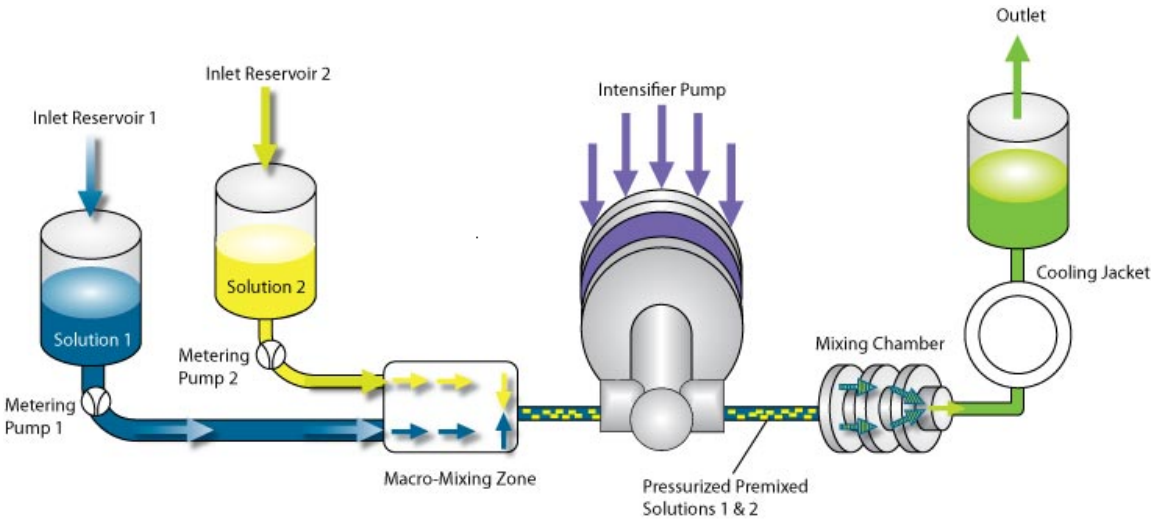


Figure 2. The PureNano Crystallizer configured with coaxial feed for longer residence times to accommodate a slower crystallization process

Pre- mixing of Solutions 1 and 2 occurs for a predetermined period of time within the macro-mixing zone, usually in the order of several milliseconds, creating a small amount of microcrystalline product nuclei for "seeding" prior to the pre-mixed solutions entering in the mixing chamber. The feed rates, solution ratios and mixing intensities within the coaxial feed are precisely controlled with a metering pump.

The pre-mixed Solutions 1 and 2 subsequently enter the mixing chamber as a single stream, split into two streams internal to the mixing chamber and subsequently collide "head on" resulting in a continuous output flow of the desired nano-suspension.

In both PureNano Crystallizer configurations, post processing may be necessary to prevent crystal growth or to alter crystal shape (length/diameter ratios of needle-shaped crystals, for example). Agglomeration is a natural post-crystallization event that can be minimized by dilution of the product stream or, alternatively, the product can be re-dispersed at a later time.

Nano-suspensions Development Roadmap

Microfluidics has developed an effective three step process in development of a pharmaceutical nano-suspension:

1. For candidate APIs, conduct screening experiments to determine the best solvent, anti-solvent and surfactant systems, considering issues such as solubility, toxicity and compatibility for the particular application. Analysis are conducted to aid in the selection the most suitable materials and to optimize the concentrations.

2. Produce nano-suspensions with the PureNano Crystallizer to determine the optimal processing parameters, such as feed rates of each solution, mixing ratios, process pressure, super-saturation ratio, and number of passes.

3. If required, purify the resulting nano-suspension using existing methods such as centrifuging, filtering, rinsing, and lyophilizing.

As previously reported by Microfluidics, the PureNano Crystallizer has been successful in producing stable nano-suspensions in the laboratory[3,4,5,6,7] where conventional particle size reduction methods were proven to be unsuccessful.

Microfluidics has since made laboratory model PureNano Crystallizers available to the marketplace (Fig 3 below) and in doing so, have established an installed base within pharmaceutical and biotechnology companies who have been, up to now, unable to produce new and important drug suspensions.

Figure 3. The PureNano Crystallizer Laboratory Model

Featured Case Study: **Pharmaceutical Oncology Drug**

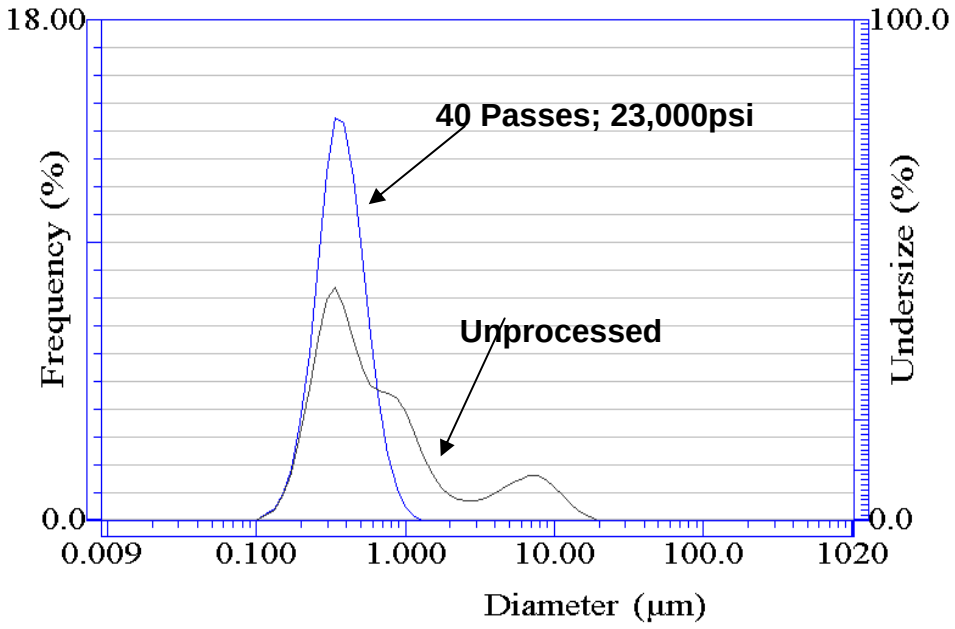
At one of the above mentioned beta sites Microfluidics has been involved in an ongoing collaborative effort with a well known pharmaceutical company[8] in an effort to successfully formulate a cancer drug known here as Compound V.[9] Several formulation options were considered for this poorly water-soluble drug. To increase bioavailability, it was determined that the drug needed to be delivered intravenously in the form of a nano-emulsion or a nano-dispersion. However, the option of nano-emulsion formulations would involve injecting several liters of a formulation into the patient, and therefore that was not a practical solution. The only other alternative was the formulation of the drug in the form of a nano-suspension.

Microfluidics conventional "top down" particle size reduction technology and PureNano were used for the production of the nano-suspension. The required particle size was a median size less than 0.200 microns.

Using the Microfluidics top down method, a suspension of the drug in water was prepared and processed using a Model 110EH-30 Microfluidizer processor. After 40 passes through the processor, the mean particle size of the API was reduced from 1.401 microns to 0.401 microns with no further particle size reduction resulting with additional passes (Fig 4). It was determined that the resulting suspension was unacceptable in that it did not meet the stability requirements.

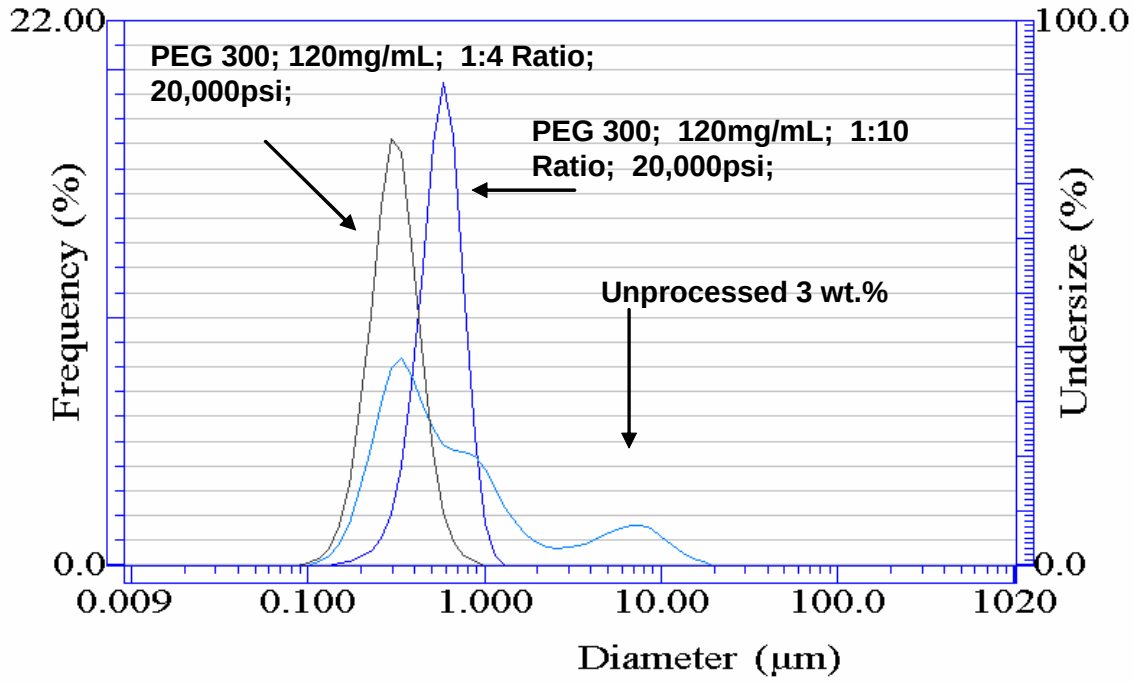
Using a PureNano Crystallizer in conjunction with the aforementioned "Nano-suspensions Development Roadmap", a continuous crystallization process was developed. Compound V was dissolved in a solvent, polyethylene glycol (PEG), at various concentrations (Fig. 5). The solution stream was mixed in with the antisolvent stream (water) at the appropriate proportions using a PureNano Crystallizer processor. The drug concentrations in the solvent stream were in the range of 20-120mg/ml, which the ratio of the solvent to antisolvent stream varied from 1:4 to 1:10.

Tests conducted with PureNano technology resulted in a stable nano-suspension with a median particle size of 0.102 microns which was achieved in a single pass. The particle size distribution was well within the specifications.



Passes	Particle Size (microns)			
	d10	d50	d95	Mean
Unprocessed	0.220	0.470	7.283	1.401
40	0.227	0.379	0.734	0.410

Figure 4. Results with conventional particle size reduction method



Concentration (mg/mL)	Ratio (Sol:Anti)	Particle Size (microns)			
		d10	d50	d95	Mean
20 mg/mL	1:10	0.109	0.177	0.329	0.257
50 mg/mL	1:10	0.058	0.102	0.277	0.126
120 mg/mL	1:10	0.350	0.529	0.812	0.539
120 mg/mL	1:4	0.188	0.287	0.489	0.302

Figure 5. Results with the PureNano Crystallizer

Looking Forward

The introduction of the PureNano Crystallizer to the marketplace is a major breakthrough for pharmaceutical and biotechnology companies. In addition to offering them a capability to produce difficult-to-formulate drug suspensions, continuous processing is now being adopted for new pharmaceutical manufacturing facilities. It has proven to dramatically lower costs compared to the age-old batch processing method for producing drugs. As noted by M.J. Mollan et al[10]; *"Continuous processing technologies provide one possible path forward for the industry to reduce the cost of manufacturing, with the objective to convert selected unit operations and processes from batch to continuous mode along with appropriate real time characterization using state of the art process analytical technologies".* It may be added that continuous manufacturing of drugs is expected to reduce the size of overall physical manufacturing plants combined with a significant reductions in capital equipment needs.

Notes and References:

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8. *Note - Because of confidentiality agreements currently in place with Microfluidics, the name of the subject pharmaceutical company cannot be used at this time.*
9. *Note - Because of confidentiality agreements currently in place with Microfluidics, the name or detailed description of the subject cancer drug cannot be used at this time.*
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