HIGH ENERGY IMPINGING JET TECHNOLOGIES FOR CONTINUOUS CRYSTALLIZATION OF NON-WATER SOLUBLE DRUG NANOSUSPENSIONS

T. Panagiotou, R. J. Fisher[a], R. Bruno[b]

Microfluidics International, Newton, Massachusetts, USA (mimipi@mfics.com)
[a] Dept. of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA USA
[b] RP Bruno and Associates, Newton, MA, USA

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Presented here is a novel technology (PureNano™) for continuous crystallization and large scale production of drug mirco- or nano- particles with tailored properties, in a highly efficient matter. The technology allows for turbulent mixing of crystallization precursors (solvent, antisolvent, seeds, etc.), the formation of turbulence eddies in the range of 25-50nm, and therefore high spatial uniformity of supersaturation. In addition, PureNano™ allows for precise control of mixing times and intensity, and temperature history. Therefore it allows for precise control of the crystallization process. The energy for crystallization required by this method may be orders of magnitude lower than the energy demands of conventional methods for creating micro- and nano- suspensions, which involve breaking large crystals to smaller entities. In addition, crystallization times may be greatly reduced through minimizing of diffusion limitations.

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 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 which significantly reduces the amount of drug that needs to be delivered as compared to drug emulsions. However, formulation difficulties may still exist since 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.

Certain crystallization processing technologies claiming to produce stable nano-particles are mainly experimental and may have major shortcomings. As an example, low pressure impinging jet technology[1] is characterized by low flow rates, low jet velocities, and therefore low energy. These jet velocities 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 produce stable particles and handle high solid loadings without plugging or fouling. Another example is use of supercritical carbon dioxide spray processing technology. This technology has been proven to be impractical for manufacturing because it is not scalable and is highly energy intensive.

Recent breakthroughs in continuous crystallization technology now enable pharmaceutical and biotechnology companies to overcome issues related to stability and safe drug delivery. Microfluidics International Corporation is marketing this technology as their PureNano™ Continuous Crystallizer and associated process protocols. Consequently such systems take on an important role in the formulation and the continuous manufacturing of high purity stable nano-suspensions which is not always achievable with conventional particle size reduction methods.The PureNano™ Crystallizer, which incorporates a scalable mixing chamber, is an energy-efficient method. A case study is presented later that demonstrates the success of this system in formulating a nano-suspension cancer drug that conventional particle size reduction methods were unable to achieve.

Principal of Operation/Applications. 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 dependent upon the API involved, which may require residence times that range from a few hundred microseconds to several hundred milliseconds. To accommodate this range of times, multiple system configurations are available.

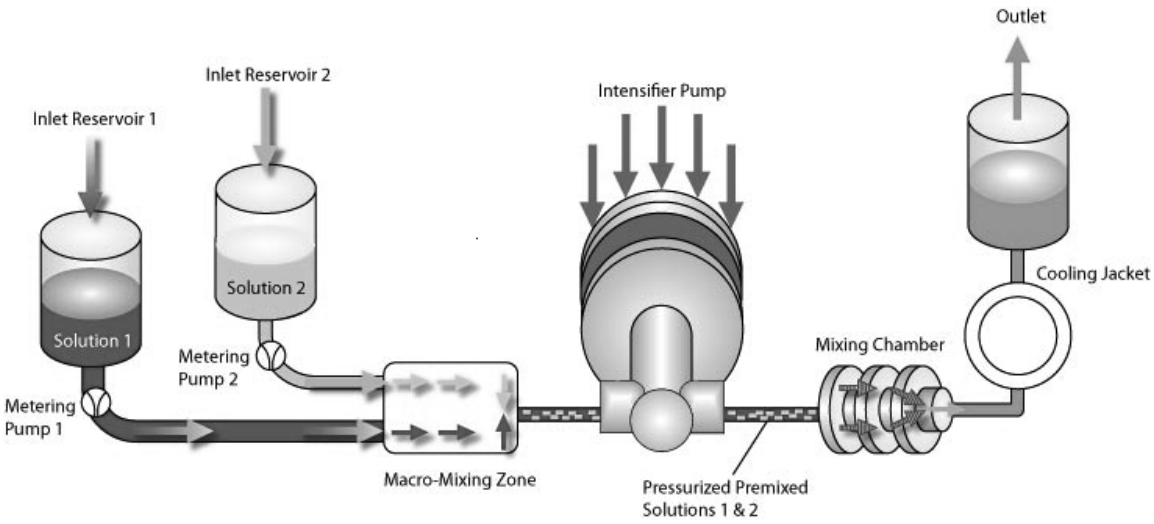


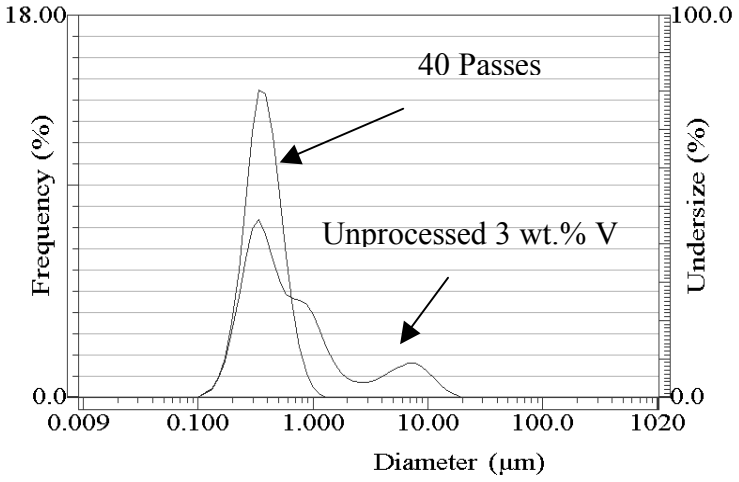
Figure 1. The PureNano Crystallizer configured with coaxial feed

To illustrate the principal of operation we selected the coaxial feed system as depicted in Fig 1. The API is first dissolved in a predetermined solvent, Solution 1, and 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. This feed configuration allows controlled pre-mixing of the two streams within a "macro-mixing" zone prior to entering the mixing chamber. This pre- mixing occurs for a predetermined period of time within the macro-mixing zone, usually in the order of several milliseconds, creating a small number of product nuclei for "seeding". The feed rates, solution ratios and mixing intensities within the coaxial feed are precisely controlled with metering pumps. This pre-mixed solution is then pressurized and subsequently enters the mixing

chamber as a single stream which is internally split into two jets that collide. This forces interact at the nano-scale resulting in a continuous output flow of a stable high purity nano-suspension.

As previously reported by Microfluidics, the PureNano™ Crystallizer has been successful in producing stable nano-suspensions in the laboratory[2,3] where conventional particle size reduction methods were proven to be unsuccessful. In all PureNano™ Crystallizer configurations, post processing may be necessary to prevent crystal growth or to alter crystal habit and/or morphology.

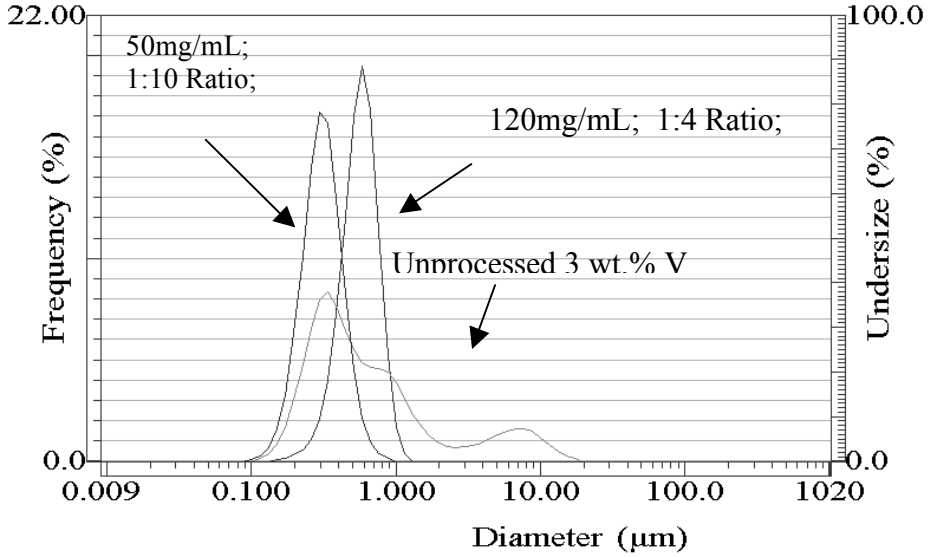
Case Study. Presented here are preliminary results from an ongoing collaborative effort with a well known pharmaceutical company in an effort to successfully formulate a cancer drug identified here as Compound V. To increase bioavailability, it was determined that the drug needed to be delivered intravenously in the form of a nano-dispersion. .



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 2. Results with conventional particle size reduction method

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 200 nanometers. Using the 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 401 nanometers with no further particle size reduction resulting with additional passes (Fig. 2). The resulting suspension was unacceptable; it did not meet the stability requirements.



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

Figure 3. Results with the PureNano Crystallizer

Using a PureNano™ Crystallizer in conjunction with our nano-suspensions development protocol, a continuous crystallization process was developed. Compound V was dissolved in a solvent, polyethylene glycol (PEG), at various concentrations (Fig. 3), in the range of 20-120mg/ml. This stream was mixed with the antisolvent stream (water) at the appropriate proportions using a PureNano™ Crystallizer processor. The ratio of the antisolvent to solvent streams varied from 1:4 to 1:10 producing various degrees of supersaturation. A stable nano-suspension with a median particle size of 102 nanometers was achieved in a single pass. The particle size distribution was well within specifications.

References:

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