A Breakthrough in Microreactor Technology

New Technology Produces Nano -Suspensions with Continuous Flow Reactions

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Abstract

The PureNano***TM*** Continuous Flow Microreactor is a novel manufacturing technology that enables continuous flow chemical reactions[1] involving solids as reactants or products for the production of stable nano-suspensions. This new process is based upon Microfluidics' PureNano technology platform that is scalable – an all important factor for the successful implementation into the manufacturing environment. The key difference between the PureNano Microreactor and other existing technologies is that it is a high pressure process with the ability to process solids that exist either as the reactants, catalyst or the resulting products. Other microreactors offered today by companies such as Lonza, Velocys and Battelle are low pressure devices and are inherently limited to chemical reactions involving only liquids and gasses. Another difference is the mixing or turbulence level between such devices. PureNano is a high energy technology and creates highly turbulent conditions during the reactions. This results in reactant interactions which are faster and on a smaller scale compared to other technologies.

Background

In a 2005 study[2] it was reported that *"50% of all (chemical) reactions in the chemical/pharmaceutical industry could benefit from a continuous process based on microreactor technology. However, the frequent presence of a solid phase still hinders the widespread application of such a technology as a multipurpose solution".* Previous work by the same group[3] reported that: *"In more than 60% of the (chemical) reactions studied, a solid was present, whether as a reactant, catalyst or product. From our experience, the microreactors currently available can handle solids very poorly"*

This has been the case until scientists at Microfluidics recently announced that they have successfully demonstrated continuous flow chemical reactions involving solids with a new and revolutionary continuous flow microreactor. With its proven capability to produce stable nano-suspensions on a continuous basis, the PureNano Microreactor has the potential to expand the current number of candidate synthesized pharmaceutical and fine chemical products by an estimated 40%. This is of particular importance for the pharmaceutical industry where nano-suspensions are of great interest because of the high drug 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 standard formulations. Additionally, the nano-particle size plays a crucial role in both the stability of the suspension and the safe delivery of the drug orally or directly into the circulatory system. This new advancement in continuous flow microreactor technology will greatly assist pharmaceutical companies in overcoming solubility and permeability challenges that affect many new chemical entities.

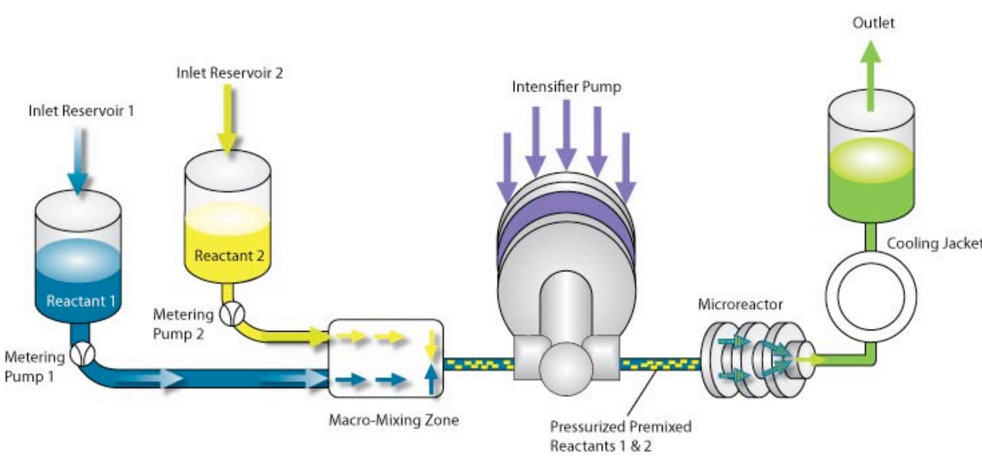
The PureNano Microreactor is based on a scalable technology. It has proven to be a safe and energy-efficient method that offers a pathway for the continuous processing of numerous nano-suspensions that could not otherwise be formulated. Additionally, it can be expected that a significant number of existing synthesized products that are currently produced using conventional batch processes will become candidates for continuous flow manufacturing thus offering existing manufacturing plants far greater efficiency, cost savings, higher quality and safety in the existing processing plants.

Principal of Operation

As shown in Fig.1 below, the streams of reactants 1 and 2 are individually pressurized to achieve high velocities enter a macro-mixing zone and subsequently collide “head-on” within the microreactor.

Pre- mixing of Reactants 1 and 2 occurs for a predetermined period of time within the macro-mixing zone, starting some of the chemical reactions and/or creating a small amount of microcrystalline product nuclei for “seeding” prior to the pre-mixed solutions entering in the microreactor. The feed rates, reactant ratios and mixing intensities are precisely controlled with a metering pump.

The pre-mixed Reactants 1 and 2 subsequently enter the microreactor as a single stream, splits into two streams internal to the microreactor and collide “head on” resulting in a continuous output flow of the desired nano-suspension.



<u>Figure 1.</u> Principal of Operation of the PureNano Continuous Flow Microreactor

Depending upon the reactants involved, pressures may range anywhere from 5,000 to 20,000 psi and higher. This permits the reactants to rapidly reach the requisite nano-scale mixing level for effective molecular interactions, i.e., for the reaction to proceed with minimal or no transport limitations. This results in a continuous output flow of a stable high purity nano-suspension.

Key components of this system include: an intensifier pump for high pressure generation of the reactant streams, a metering pump with each of the reactant 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 pre-set flow rates and the ratios of the reactant streams. This control strategy enables a broad range of mixing ratios from 1:1 up to 1:40 which is a key factor in accommodating a wide selection of reactants and in the control of reaction rates that are based on concentration levels. Mixing ratios are controlled within ±1% accuracy to ensure the proper stoichiometry within the microreactor and that of the end product.

High Purity Results

The high purity characteristics of the resulting nano-suspension are a direct result of a number of unique features of this technology which include:

- Controllable short residence times that prevent byproducts to form via slower and unwanted competitive reactions,

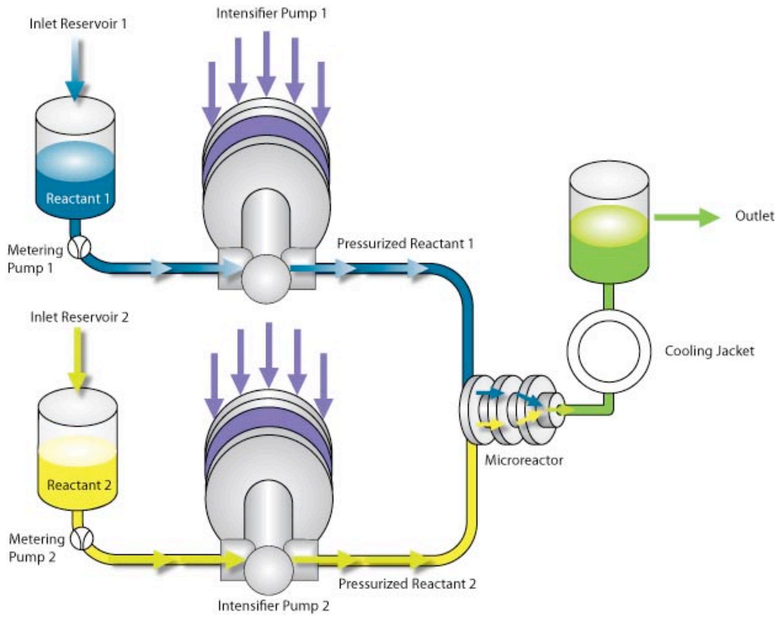
- Excellent mixing provides a uniform micro-environment and yields in narrow particle size distribution products

- Homogeneous distribution of the reactants prevents localized selectivity issues, such as favoring the rate of the undesired reactions in a multiple reaction network where extreme non-uniformity of concentration may exist.

Fast Reactions - No Residence Time

Applications best suited for the PureNano Microreactor are dependent upon a number of factors including the length of time for reactions to occur. For reactions requiring some amount of residence time, which comprise the majority of applications that Microfluidics researchers have encountered, the PureNano Microreactor is configured with a "coaxial feed" as discussed above and shown in Fig 1. This allows the controlled pre-mixing of the two streams of Reactants 1 and 2 within a "macro-mixing" zone prior to entering the microreactor.

There are cases where fast reactions occur and no premixing or residence time is required. To accommodate these types of reactions, the macro-mixing zone is removed (Fig 2) which prevents the reactant steams from coming in contact prior to entering the mixing chamber which is essential.



<u>Figure 2.</u> The PureNano Microreactor Configured to Accommodate Fast Reactions

In both PureNano Microreactor 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-reaction event that can be minimized by dilution of the product stream or, alternatively, the product can be re-dispersed at a later time.

<u>Continuous Flow Reactions – Some Examples</u>

The following four examples demonstrate the effectiveness of the PureNano Microreactor producing stable sub-micron suspensions on a continuous flow basis.

<u>*Zinc Omadine*</u>

The objective of this test was to create submicron particles of zinc omadine, which is used as an antimicrobial agent in personal care products such as shampoos. Submicron particles are required to avoid the formation of sediment at the bottom of the container and for improving the appearance of the product by increasing its clarity.

Zinc omadine was produced as a result of a chemical reaction and subsequent precipitation between a zinc salt and an omadine salt. This resulted in zinc omadine with narrow particle size distribution as shown in Figure 3.

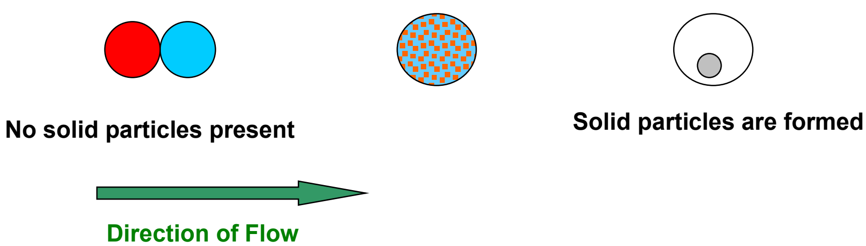
Organic zinc salt for cosmetics

Proposed Mechanism

(1) Each solution stream is reduced into submicron size entities

(2) Reaction occurs when such entities interact under conditions resembling those of a well mixed reactor

(3) The product precipitates and forms submicron particles with uniform size distribution



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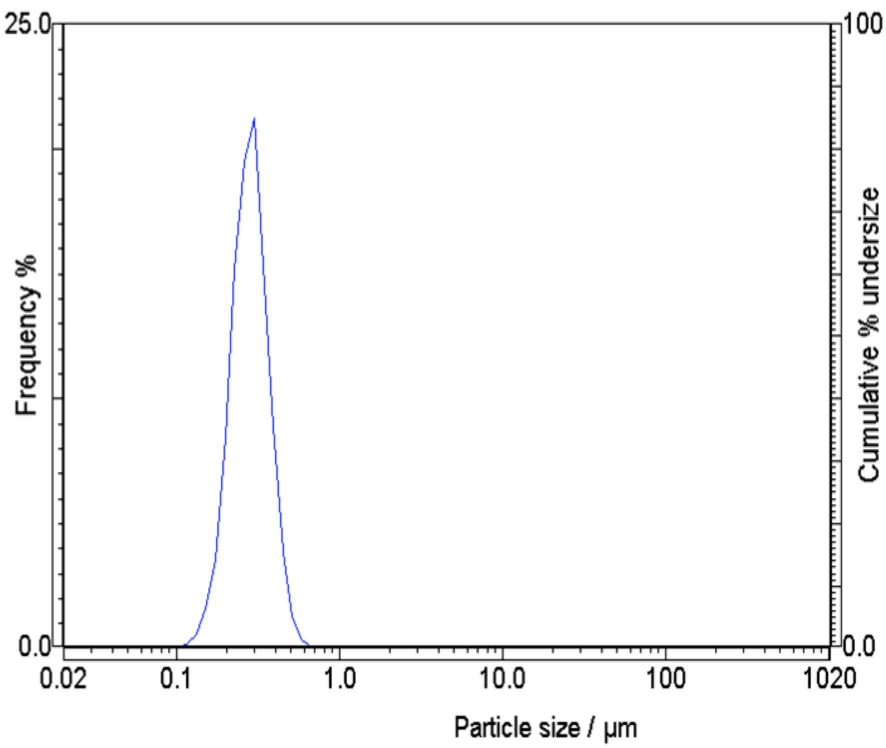


<u>Fig 3 Particle Size Distribution of Zinc Omadine Nano-suspension with Median Particle Size 263 nm.</u>

Calcium Stearate Nano-particles

The objective of this test was to create nano-particles of calcium stearate used for paper coatings. Calcium stearate is typically produced as a result of reaction between calcium hydroxide, a solid with limited solubility in water, and stearic acid, a waxy solid. Calcium hydroxide particles are suspended in water providing a continuous supply of that reactant in the water phase while stearic acid is melted to create an oil-like liquid. The two liquid streams are immiscible, so for the reaction to take place high intensity mixing is required.

Conventionally this reaction takes place in stirred tank over a period of several hours period. The resulting spherical particles are up to 10 microns in diameter; therefore substantial particle size reduction is required after the end of the reaction. However, since calcium stearate particles are fairly soft and waxy, particle size reduction may be difficult, since under shear stresses the particles have a tendency to fuse together.

In contrast, when PureNano was used the two liquid streams, the calcium hydroxide suspension and the molten stearic acid were fed continuously at specific flow rate ratios, to ensure proper stoichiometry during reaction. The reaction was complete after a single pass through the interaction chamber, The median particle size was 367 nm, see Figure 4 and the solid loading of the product stream was 38% solids.

Given the fact that the residence time inside the interaction chamber is about 1 ms, PureNano expedited the chemical reaction tremendously, and in addition it resulted in nano-particles that do need size reduction.

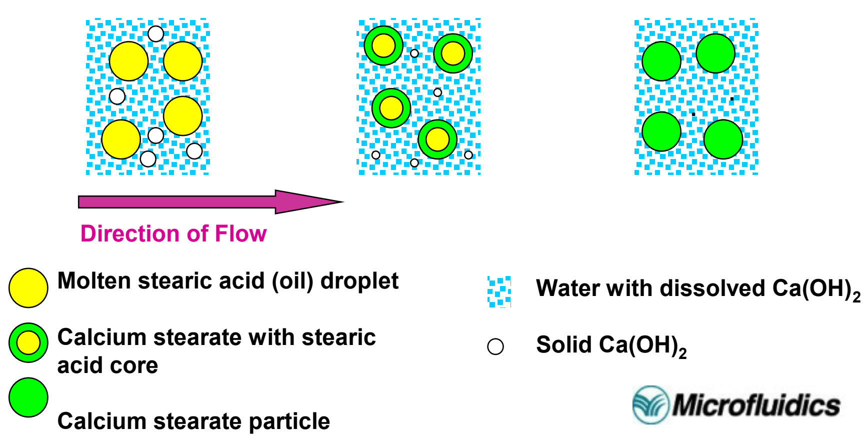
Calcium stearate sub-micron particles

Proposed mechanism

(1) An oil/water nano-emulsion forms

(2) The $Ca(OH)_2$ that is dissolved in water reacts with the oil droplet at the interface of water and oil

- As dissolved $Ca(OH)_2$ is consumed, more dissolves in water and reacts until the reaction is complete



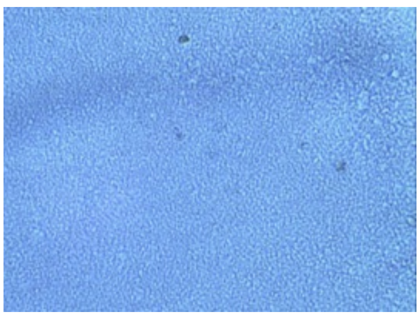
Calcium Stearate Nano-particles *(cont'd)*

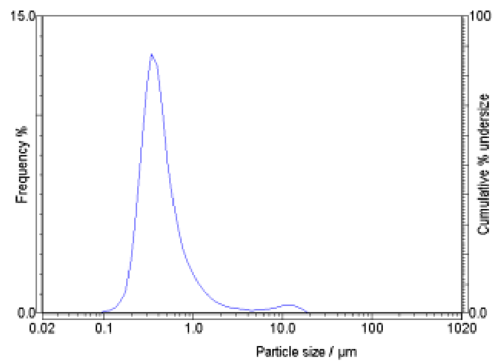
Organic calcium salt sub-micron particles

Process: **Acid-Base reaction**

Reactants: **Calcium hydroxide ($Ca(OH)_2$) water slurry and stearic acid melt at 65-85ºC; reactant streams are immiscible**

Product: **Stable calcium salt nanosuspension with over 38% solids**





• Median particle size (D50): 367 nm

Microfluidics

Fig 4 Photomicrograph of Particles in Resulting Calcium Stearate Nano-particle Suspension (left). Particle Size Distribution Curve Depicting Median Particle Size (D50) of 367nm

Two additional applications are briefly presented below in Figs 5 and 6 that include "Metal Catalyst on a Carbon-based Substrate" and 'Binders for Medical Applications"

Metal catalyst on carbon-based substrate

Process: Chemi-sorption of catalyst onto the substrate
Reactants: Carbon slurry and catalyst solution
Products: Slurry of catalyst coated carbon

- Process was complete in one pass which provides residence time of a fraction of a second
- The conventional method requires contact time for almost 1 hr
- The performance of the catalyst produced with the Microfluidizer technology was as good as that produced with the conventional technology

Microfluidics

Figure 5.

Binder for medical applications
High surface area salt

Process: **Substitution reaction**
Reactants: **Miscible salt solutions**
Products: **Salt suspension**

- **The material produced with Microfluidics reaction technology has three times the surface area of the standard material**
- **Excellent mixing provided by the Microfluidics reaction technology enhances the reaction rate**
- **Reaction time is only a fraction of the time required by the standard method**

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Figure 6.

Additional Benefits of High Pressure Processing

Although the emphasis in this paper is the unique capability of this technology platform in handling high solids loading, it is important to note also that the PureNano Microreactor has other distinct beneficial attributes over competing technologies. For example, the creation of nano-scale emulsions can enhance the observed reaction rates in multi-phase systems where transport limitations exist. The smaller droplet sizes obtained, for the given total volume of species, provides significant improvement in interfacial area and thus mass transfer rates to the reaction zone. This improvement is a direct result of the higher operating pressure and associated greater energy input to the system and efficiency of its dissipation mechanisms.

Looking Forward

The pharmaceutical and fine chemical industries continue to make progress in adopting continuous manufacturing in an effort 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."* [1]

The forthcoming introduction of the PureNano Continuous Flow Microreactor (Fig 7) to

<u>Figure 7.</u> The PureNano Microreactor - Laboratory Model

The marketplace offers a unique capability for chemical reactions to occur in which solids are involved. Large scale continuous flow manufacturing of high purity sub-micron suspensions are now a reality while at the same having the potential of transforming the decades old "tried and true" batch processing to continuous processing. Moreover, the PureNano Microreactor technology offers the capability to reduce the size of overall physical manufacturing plants combined with a significant reduction in capital equipment needs. These benefits are consistent with the concept of Process Intensification* that is now having a major positive impact upon manufacturing productivity and economics.

Notes and References

[1]A chemical reaction may be defined as the interaction of two or more chemicals that produces one or more new chemical compounds, or alters the properties of the mixed chemicals. Most reactions require heat, pressure, radiation, other conditions, and/or the presence of accelerators (catalysts).

[2]*Microreactor Technology: A revolution for the Fine Chemical and Pharmaceutical Industries" D. Roberge et al – Chem. Eng 2005).*

[3] *"An Integrated Approach Combining Reaction Engineering and Design of Experiments for Optimizing Reactions" D Roberge, Org. Proc. Res. Dev.*, 2004, *8* (6), pp 1049–1053)

**Process Intensification – The optimization of capital, energy, environmental and safety benefits by radical reduction in the physical size of the plant. It requires the development of novel apparatuses and techniques, as compared to the present state-of-art, to bring* *dramatic improvements in manufacturing and processing, substantially decreasing equipment size/production-capacity ratio, energy consumption, or waste production.*

Other General References

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"Continuous Processing in Pharmaceutical Manufacturing"; Matthew J Mollam Jr. PhD and Mayur Lodaya, PhD, Pfizer Inc.

Author's Note

Because of confidentiality agreements currently in place with Microfluidics, the name of the subject companies and their product names cannot be used at this time.