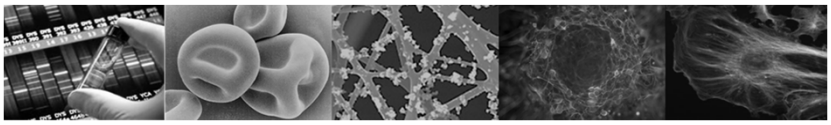

Producing Nanotechnology Based Drugs: From Lab to Production

By:
Thomai "Mimi" Panagiotou, Ph.D.,
Founder - President and CEO
Delphi Scientific, LLC

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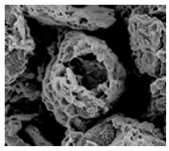
Delphi Scientific at a Glance

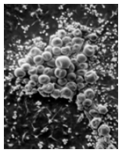
- **Nanotechnology/particle based advanced delivery systems**
- **Holistic approach to development**

  Formulation

  Process **Hardware**



- **<u>Process development</u>, <u>integration</u> and <u>scale up</u>**
  - Homogenization, Aseptic Filtration, Di-filtration, Crystallization, Spray drying
  - cGMP/aseptic



- **<u>Custom hardware configurations</u> to optimize processes**
  - Reaction chambers, aseptic filters, spray nozzles

- **<u>Close collaborations</u>: Dyhydromatics, CMOs, Analytical Labs and Instrumentation manufacturers**
- **<u>Working clients worldwide</u> from Pharma, Food and Chemicals**

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Who we are

Thomai "Mimi" Panagiotou, Ph.D.

Dr. Panagiotou is an expert in nanomaterial processing and associated equipment design. She is currently the President and CEO of Delphi Scientific, LLC. She is also an expert witness in patent challenges in the area of nanomanufacturing that involve Large Pharma companies. Prior to that, she was the CTO of the Materials Processing Group of IDEX Corporation, which includes Microfluidics, Quadro Engineering, Fitzpatrick and Matcon. In that position, Dr. Panagiotou was responsible for the overall direction of the technology, new product development and collaborations with the industry and Academia. Prior to that, Dr. Panagiotou held various management positions (CTO, VP/R&D, etc.) with Microfluidics International, where she lead the development and commercialization effort of award winning microreaction technologies (NANO 50 International award). Dr. Panagiotou holds a MS and Ph.D. in Mechanical Engineering from Northeastern University. She co-authored over 60 papers for journals and conference proceedings, and is a co-inventor of several patents.

Prof. Robert J. Fisher

Dr. Fisher is a station director and senior lecturer in the Chemical Engineering Department at the Massachusetts Institute of Technology (MIT); and actively consulting for a broad range of industries. His B.S. and M.S. degrees are in chemical engineering from The State University of New York at Buffalo, and his PhD, also in chemical engineering, is from the University of Delaware where he worked in the Stability of Reaction and Transport Processes Group under the direction of Professor Morton M. Denn. Through extensive academic and industrial experiences, he has furthered the development of his expertise in Transport Phenomena and Reaction Engineering; now recognized internationally as an expert. Dr. Fisher has helped in the development of innovative Process Intensification systems and novel applications related to microfluidic devices. One such accomplishment, in collaboration with MicroFluidics International Corporation, was recognized with a NANO-50 award. He has co-authored over 150 papers for journals and conference proceedings and is a co-inventor of several patented concepts and devices.

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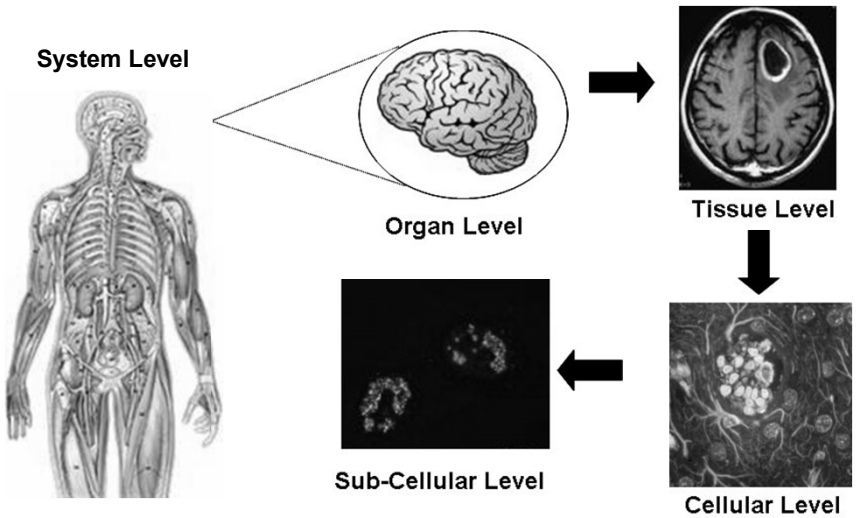
Why Nanomedicine?



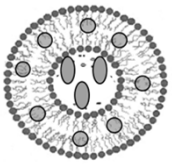
4

Emulsions, Liposomes, Solid Nanoparticles

Emulsion Droplet

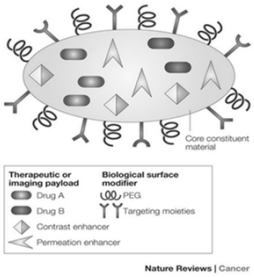
Oil + drug

Liposome Vesicle



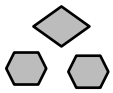
Hydrophobic drug
Hydrophilic drug

Polymer Particle



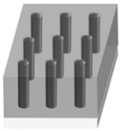
Nature Reviews | Cancer

Drug Nanocrystals



Micelles

Nanorods



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EXAMPLES OF NANOTECHNOLOGY BASED FORMULATIONS

- Vaccines
  - Adjuvants
  - DNA encapsulation
- Cancer drugs
  - Nanoemulsions/Liposomes/Solid lipid nanoparticles
  - Polymeric nanoparticles
  - Abraxane/liposomal doxorubicin
- Gene Therapy
  - Nucleic acid therapeutics
- Ocular drugs
  - Dry eye/ drug delivery
- Inhalable drugs
  - Antibiotics
- Anesthetics
  - Propofol

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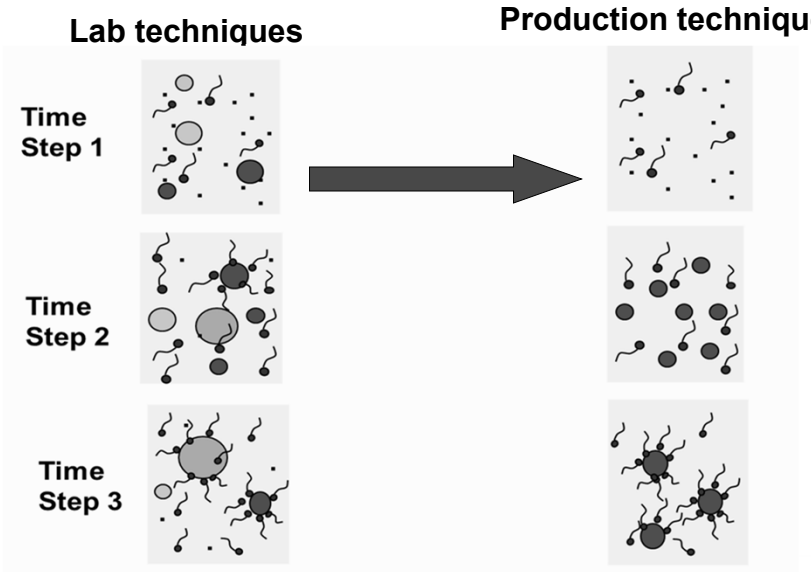
Scalable Production of Nanoformulations



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Our Philosophy:

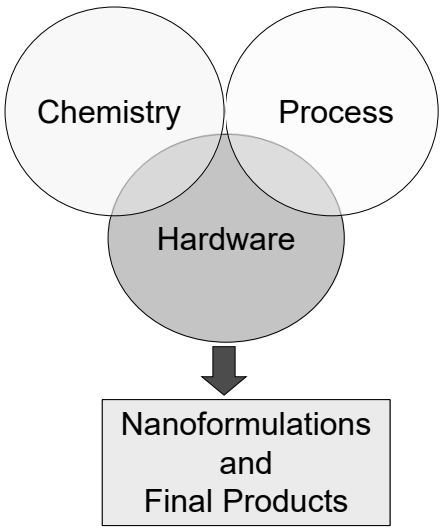
Nano- /Micron- size particle based formulations through integrated multidisciplinary approaches

Chemistry

Actives
Polymers
Polymer chemistry
Surfactants
Kinetics
Stabilization strategies
…

Material characterization

Surface chemistry
Particle size
Crystalline structure
Encapsulation efficiency
…



Hardware and Process

Particle generation
Purification
Scale up
Aseptic processing
Mixing scales
Residence times
…

Final Product Functionality

Enhanced bioavailability
Particle morphology
…

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How do we manufacture nano-formulations?

A. Mechanical methods (Most common)

- High energy density and uniform energy field required
  - Top Down
  - Bottom Up

B. Self-assembly

- Self emulsification
- Phase inversion

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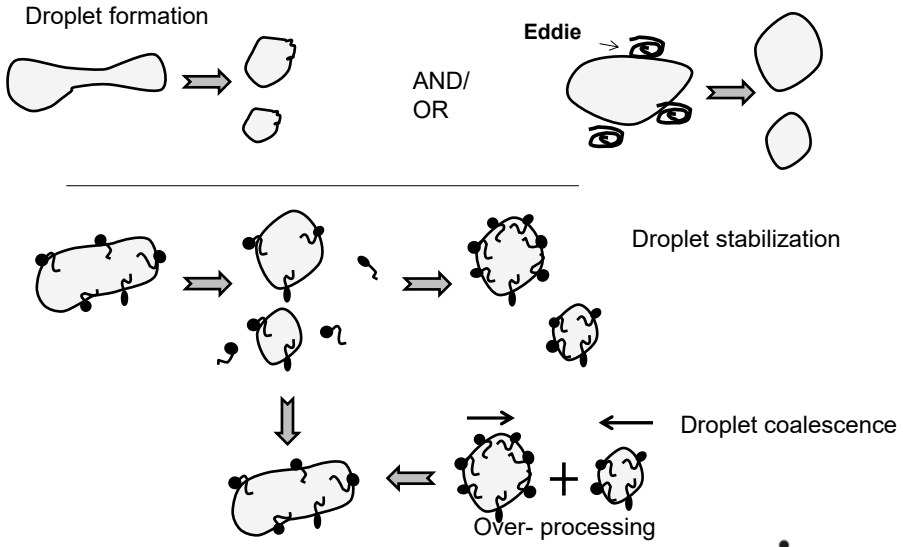
Physical Mechanisms

Droplets Form, Stabilize and Coalescence in Liquids



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Equations-Theory

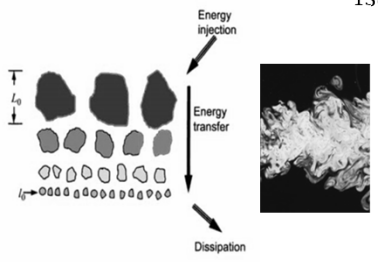
Kolmogorov scale : $\lambda = [\nu^3/\varepsilon]^{1/4}$

Kolmogorov-Hinze:

$$d_{max} = \left(\frac{We_{crit}}{2.0}\right)^{3/5}\left(\frac{\rho_c}{\sigma}\right)^{-3/5}\varepsilon^{-2/5}$$

Adsorption timescale: $\tau_{ads} = \frac{\Gamma}{cE}\left(\frac{\rho_c}{d\varepsilon}\right)^{1/3}$

Collision timescale: $\tau_{col} = \frac{1}{15\varphi}\left(\frac{d^2\rho_c}{\varepsilon}\right)^{1/3}$



λ: Kolmogorov scale

ε: local energy density

We_{crit}: Critical Weber Number - E_{kin}/E_{sur}

d_{max}: Max droplet size

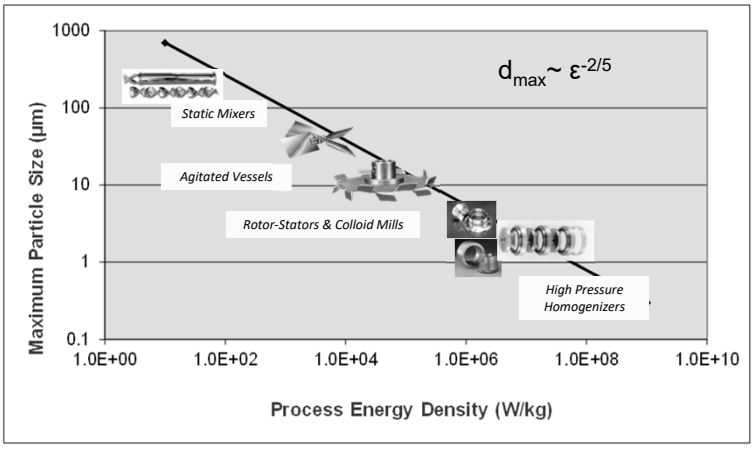
ρ_c/σ : fluid density interphasial tension

c_E: bulk conc.-emulsifier

Γ: surface excess conc. emulsifier

φ : vol. fr. – cont. phase

Mixing scale is a function of the energy density transfer rate in the mixing unit; Particle uniformity is achieved when the energy is delivered uniformly to the liquid.



Adapted from: "Handbook of Industrial Mixing: Science and Practice", ISBN 0-471-26919-0, John Wiley & Sons, Inc, 2004.

Manufacturing Challenges

- **Damaging the actives**
- **Stability**
- **Particle size uniformity**
- **Minimizing amount of surfactants**

  Although this may be viewed as a formulation challenge, we have demonstrated that process substantially affects the amount of emulsifier required.

- **Micro-to-Macro**

  Once are formed, the next challenge is that they are incorporated in macro- products

- **Cost**

  Nano-formulations are costly to manufacture; they usually require high energy, expensive equipment and multi-step processes

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PARTICLE SIZE, ENCAPSULATION EFFICIENCY, SCALE UP AND ECONOMICS

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EXAMPE 1. Anesthetic Formulation

Application/Formulation:

- Reformulation of an existing anesthetic
  - Change the delivery method to intravenous injection
- O/W emulsion - 20% oil content
- Active ingredient is sensitive to heat - filter sterilization is preferable
- Formulation fixed

Key Issues:

- Low yield – less than 20% after aseptic filtration
- Large number of homogenization passes – over 40 passes
- Expensive process

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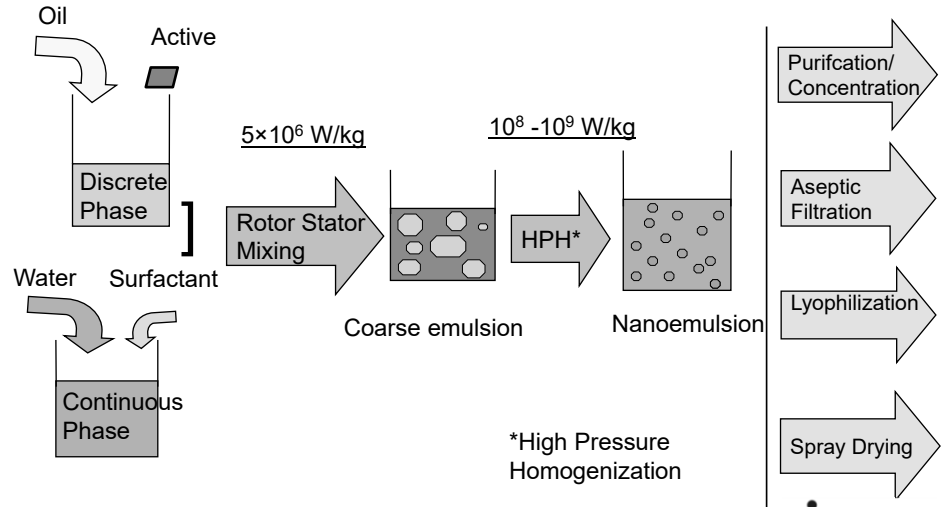
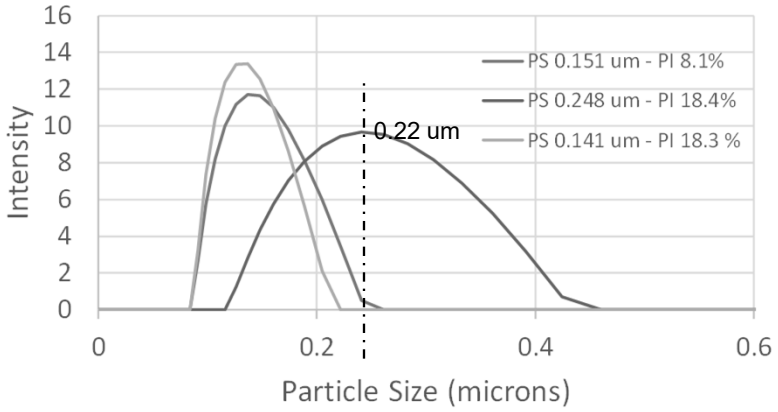
Conventional Production of Nanoemulsions



16

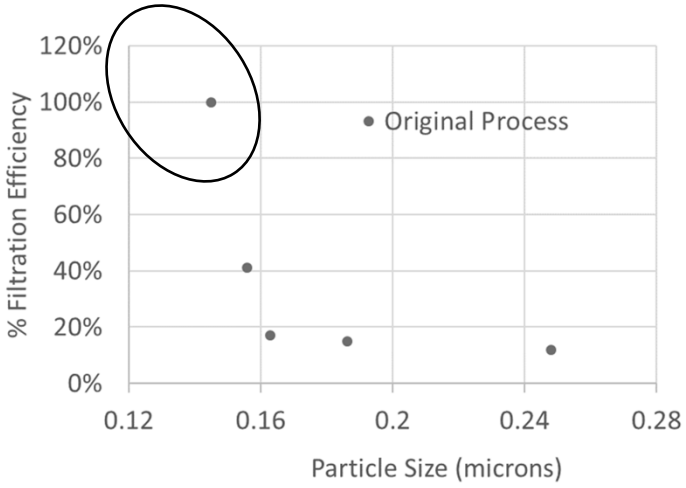
Original process resulted in highly variable average particle size and polydispersity index.



As a result, the volume of the formulation with particles less than 0.22 microns varied dramatically.

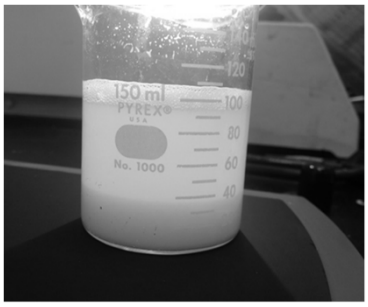
17

Particle size variability resulted in low filtration efficiency and therefore yield; scale 100ml.



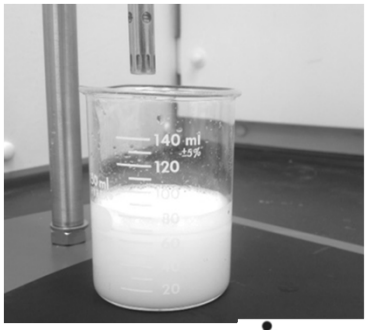
18

Stability of Premix appeared to be the cause of the observed variability.



Unstable premix
Separates prior to homogenization

Stable premix
Does not separate prior to homogenization



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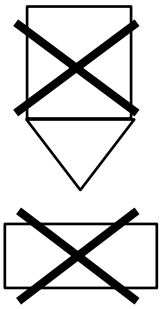
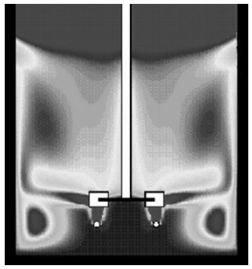
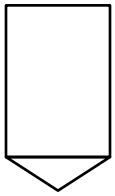
Vessel shape used for the premix affected the product quality in the lab scale and scale up.







- The shape of the mixing vessel may affect the quality of the premix.
- The aspect ratio of the mixing vessel (H/W), as well as shape of the bottom should match with the rotor stator mixer.

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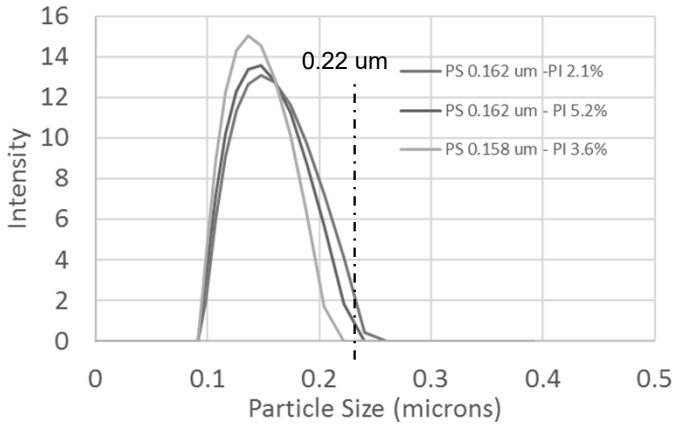
Reproducibility of optimized, large scale process;
Process yield after aseptic filtration was 100%; scale 2 liters.



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Production cost related to homogenization process and yield

	Original Process	Optimized Process
Premix	**Vortex** Non-scalable Not Optimum Vessel	**Rotor-Stator** Scalable Optimized vessel
Homogenization 500 liter batch 8 lpm machine 3 hours processing	40 passes 14 machines required	**5 passes** Scalable 2 machines required
Sterilization Final yield	Filter sterilization Yield (filtration efficiency) **20%** 100 liters	Filter sterilization Yield (filtration efficiency) **100%** 500 liters
Cost $2M / machine	$28 M - 100 liters $140 M -500 liters	$4 M -500 liters

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Example 2. Reducing the particle size with simultaneous increase of manufacturing efficiency

Application:

- Injectable cancer drug nanoemulsion
- O/W emulsion - 28% oil content
- Average particle size requirement is 90 nm

Challenges:

- Scaling up from 100 to 1000 liter batch, required prohibitively costly equipment, including multiple high pressure homogenizers, tanks, rotor-stator equipment, etc.
- Sterile filtration was difficult to achieve due to wide particle size distribution of the formulation

Key Objectives:

- Increase the efficiency of the manufacturing process
- Reduce the particle size and narrow the particle size distribution

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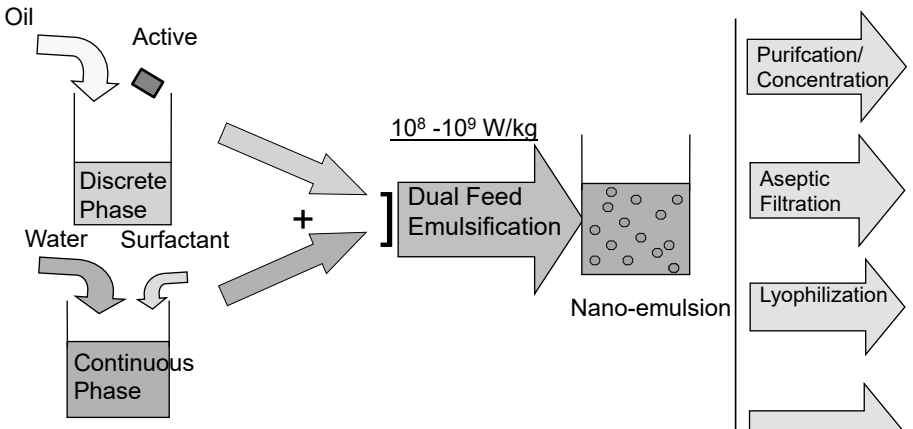
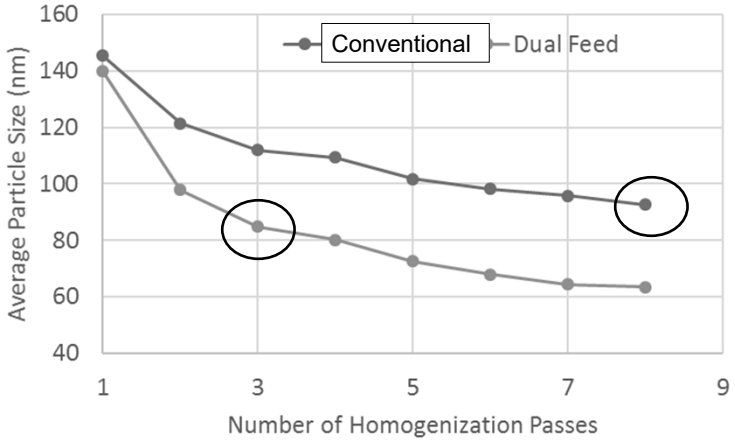
Continuous "Dual-Feed" Nanomulsion Production (No Need for Pre-emulsion)



24

The “Dual Feed” emulsification technology was several times more efficient that the conventional method and resulted in smaller particles.



Tech.Connect Briefs, 2019, TechConnect.org, ISBN 978-0-9988782-8-7.

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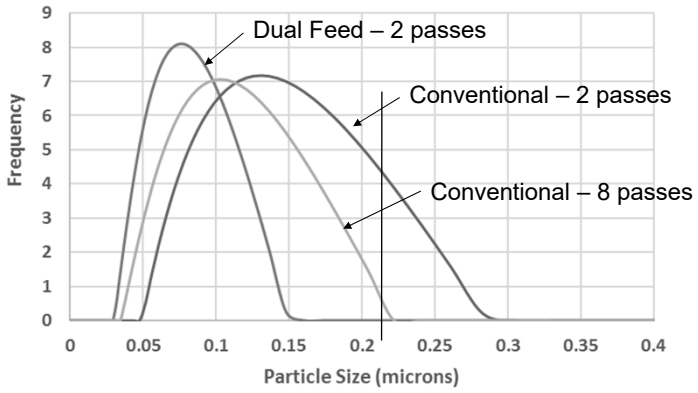
With the “Dual Feed” emulsification technology the material could be easily filtered sterilized, since the particles were substantially lower than 200 nm.



- High Pressure homogenization requires the most expensive equipment and it is the most energy demanding process for emulsification.
- The Dual Feed Technology resulted in smaller particle size and required a fraction of the number of high pressure homogenization passes.

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The “Dual Feed” technology was over 400% more efficient than the conventional methods. This results major savings in the cost of equipment and operational costs.

	Conventional Process	Dual Feed Technology
Premix	**Rotor-Stator Mixer**	**No Premix step required**
Homogenization 1000 liter batch 8 lpm machine 3 hours processing	8 passes 6 high pressure homogenizers required	**2 passes** 2 high pressure homogenizers required
Cost - equipment Homogenizer Rotor-stator mixer Tanks/Pumps	 6 Units 6 Units 6 Sets	 2 Units Not Required 1 Set

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Example 3. Polymer and Solid Lipid Nanoparticles- Maximizing encapsulation efficiency

Application:

- Encapsulation of cancer drug in polymer or solid lipid polymer nanoparticles

Challenges:

- Poor encapsulation efficiency
- Formulation not filter sterilizable

Key Objectives:

- Increase encapsulation efficiency
- Reduce the particle size and narrow the particle size distribution

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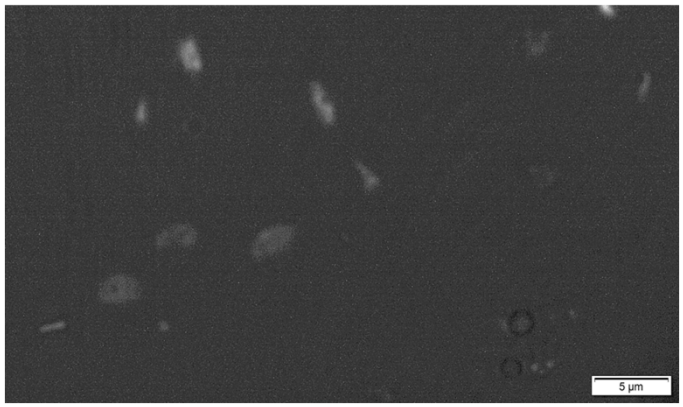
Conventional manufacturing methods result in poor encapsulation efficiency of actives in polymers, lipids or inorganic matrices.



Non-encapsulated crystalline particles are visible using optical microscopy and polarized light.

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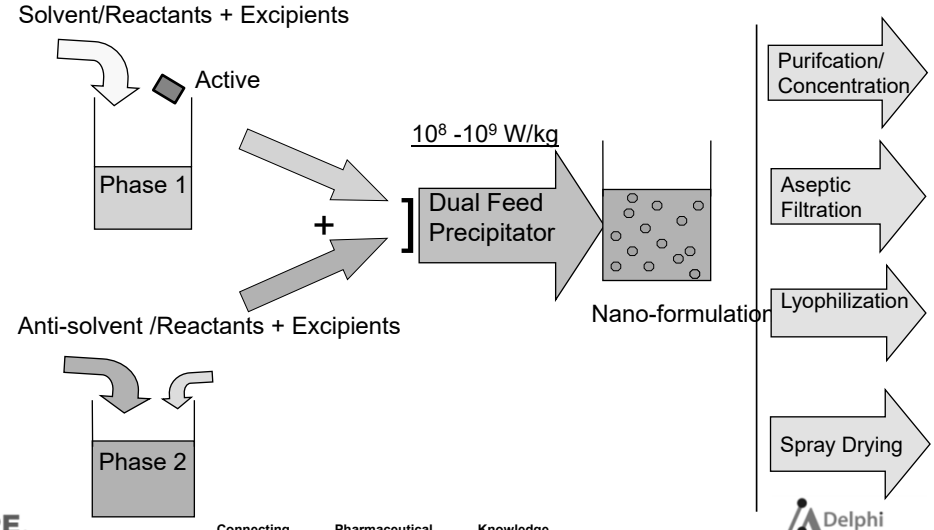
Continuous "Dual-Feed" Nanoparticle Production via solvent/anti-solvent, nanoprecipitation or chemical reactions



30

High encapsulation efficiencies were recorded and small particle size were achieved.

- Polymer nanoparticles
90-110 nm PLGA nanoparticles were produced;
over 65% encapsulation efficiency

- Solid lipid nanoparticles
60-80 nm particles;
over 95% encapsulation efficiency

- Inorganic nanoparticles
siRNA was encapsulated in inorganic nanoparticles.

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Summary

- A variety of nanomaterials is required to address the different applications, and each of those materials requires a specific manufacturing process.
- There is a demand to replace the costly conventional, high energy manufacturing processes with simpler and more efficient processes, capable of accommodating the variety of nanomaterials .
- Continuous and bottom up processes were found to increase manufacturing efficiency by over 400% when compared to conventional methods.
- Such processes were demonstrated in the production of emulsions and solid nanoparticles including polymer, solid lipid and inorganic particles.

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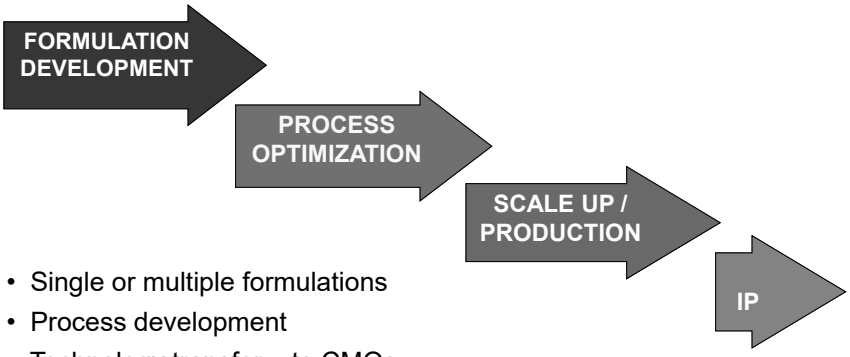
Working With Us



- Single or multiple formulations
- Process development
- Technology transfer – to CMOs
- IP development
- Patent prosecution/litigation
- Various business models

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Selected Publications/Patents

Selected Publications

T. Panagiotou and R.J. Fisher, Tech.Connect Briefs, 2019, TechConnect.org, ISBN 978-0-9988782-8-7.
• Y. Su, T. Panagiotou, and R.J. Fisher, 2014 ***AIChE*** Annual Meeting, Atlanta, Georgia, 2014.
• T. Panagiotou and R. J. Fisher, *Functional Foods in Health and Disease 2013;* 3(7):274-289, http://functionalfoodscenter.net/the-journal-of-ffhd.html.
• T. Panagiotou, K. Chomistek, and R. J. Fisher, NanoFormulation, pp. 135-149, Edited by Gordon Libby and Reginald Tan, Royal Society of Chemistry Publishing, London 2012.
• T.Panagiotou and R. J. Fisher, *Challenges 2012, 3*, 84-113; doi:10.3390/challe3020084, www.mdpi.com/journal/challenges, 2012.
•T. Panagiotou, S. V. Mesite, and R. J. Fisher, *Industrial and Engineering Chemistry Research, American Chemical Society*, 48, pp. 1,761-1,771, 2009.

Patents

- PCT patent application "Interaction Chambers with Reduced Cavitation".
- U.S. Patent # 8,187,554 *"Apparatus and Process for Production of Nanoparticles and/or Process Intensification of Transport and Reacting Systems."*
- World Patent Application PCT/US2009/041511: *"Apparatus and Process for Production of Nanoparticles and/or Process Intensification of Transport and Reacting Systems."*
- U.S. Patent #6,143,370 *"Process for Producing Polymer Coatings with Various Porosities and surface Areas."*
- U.S. Patent: #5,269,980 *"Production of Polymer Particles in Powder Form, Using an Atomization Technique."*

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