Particle Size Analysis for Homogenization Process Development

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Horiba Seminar

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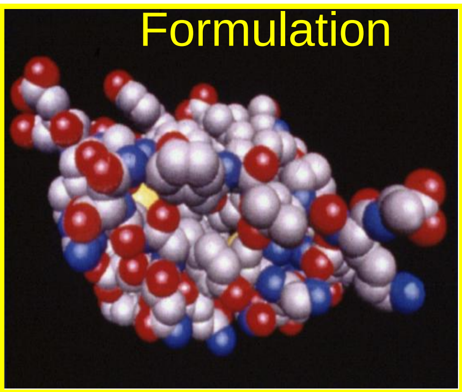
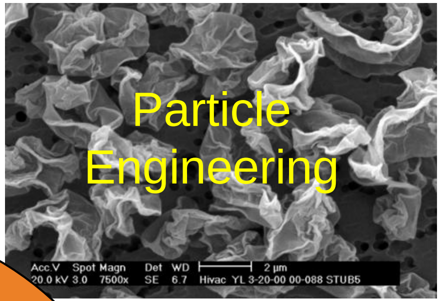
Outline

- Background
- Study Objective
- Equipment Operating Principles
- Emulsion Preparation Process
- Instrument for Evaluation
- Laboratory Study Results
- Summary

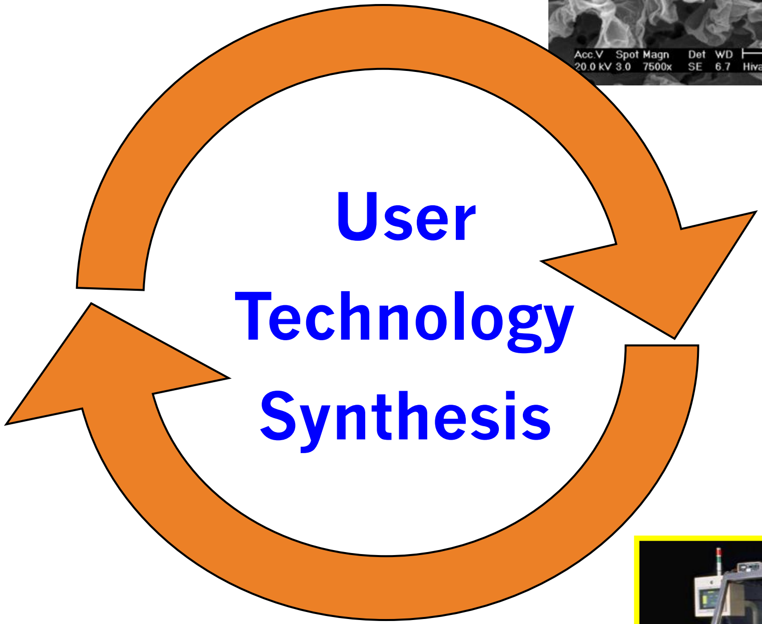
Pulmonary Drug Delivery Product Life Cycle

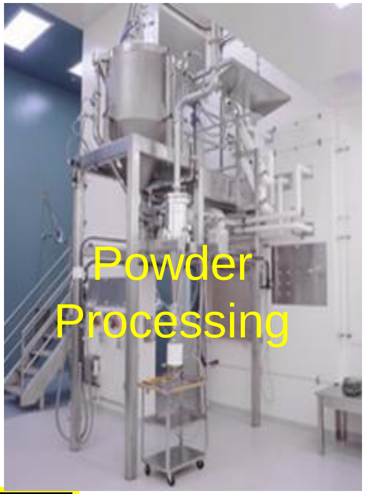


Dose
Chemical/Physical Stability
Solid-state properties
Excipients



Aerodynamics
Dispersability
Process control
Scale up





Patient's needs
Reproducible
Easy to use & reliable

Fine powders
Low mass, tight RSD
Remain dispersable
Billions/year

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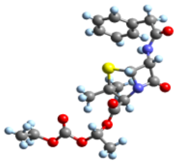
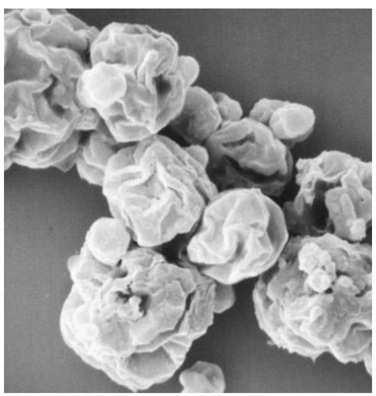
Methods to Produce Fine Particles for Pharmaceutical Applications

Molecule



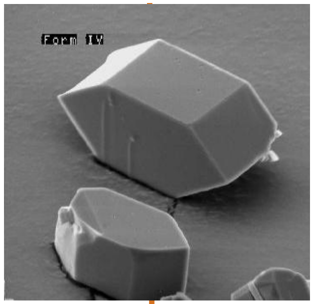
Spray Drying

Emulsion Based



Solution Based

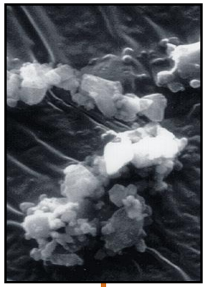
SCF



Lyophilization

Crystallization

Attrition / Jet Milling



Fine Particles (MMAD ~ 1-5 mm)

PulmoSphere® Technology

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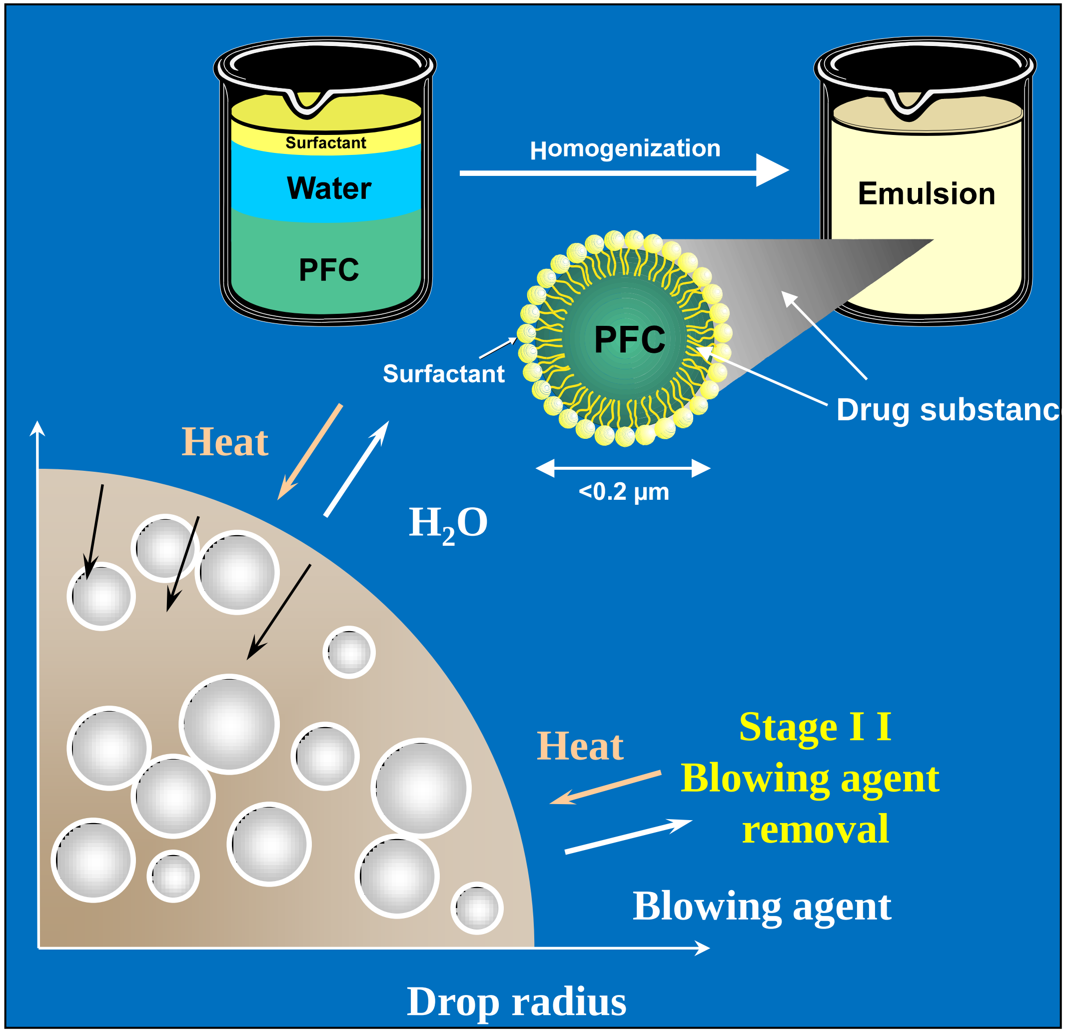
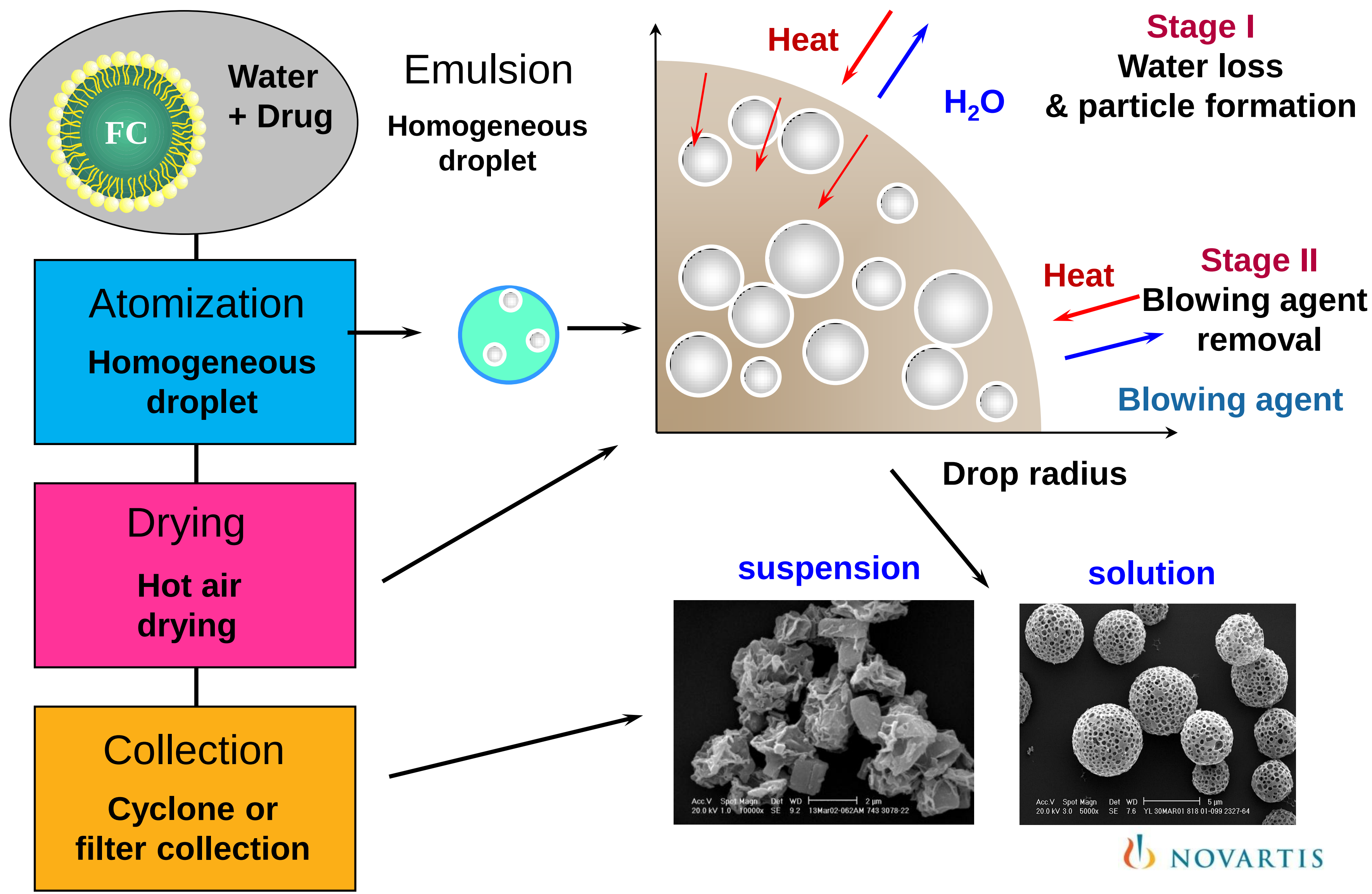
Novartis PulmoSphere Technology



- Manufacture of a Fluorocarbon-in-Water Emulsion
- Excipients primarily composed of phospholipids
  - Perfluorocarbons added as a processing aid
  - Removed in the process

Manufacture of *PulmoSphere* Particles



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PulmoSphere Particle Characteristics

- Particle Physical Properties
  - Hollow and porous
  - Surface roughness
  - Low density

- Particle Performance Attributes
  - Flowability
  - Dispersibility
  - Aerodynamic

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Particle Size Analysis for Homogenization Process

- **The objective of this study is to develop a robust homogenization process for making pharmaceutical emulsions by evaluating droplet size distribution**

Homogenization is a fluid mechanical process that involves the subdivision of droplets or particles into nanometer or micron sizes to create a stable emulsion or dispersion for further processing. This technology is one of most efficient means for size reduction.

Criteria for Evaluating High-Pressure Homogenizers

- Mean Particle Size
- Particle Size Distribution
- Emulsion Stability
- Cycle Time
- CIP/SIP Capability
- Scale Up Capability
- Routine Operation
- Maintenance

High-Pressure Homogenizer Systems

- High-pressure homogenizers generally consist of a high-pressure pump, mostly in the form of a one- to three-piston plunger pump which can be electrically or pneumatically actuated, an interaction assembly, and a cooling unit. High-pressure interaction assembly can be subdivided into three different types:

Types	**Manufacturers**
• **Radial Diffusers/Valves**	**- *Avestin*, APV, Niro…**
• **Nozzle Aggregates**	**- *BEE*, Kombi-Blende…**
• **Counter-jet Dispergators**	**- *Microfluidics*, Bayer, Nanoject…**

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Homogenization Principles

- High-pressure processing equipment for reducing droplet or suspension particle size primarily involves four mechanisms:
  - Shear - is caused by elongation and subsequent breakup of droplets, due to acceleration of a liquid
  - Turbulence - is caused by high velocity fluid resulting in chaotic motion to tear apart the globules
  - Impact - is caused by impinging of pressurized fluid on a hard surface breaking globules into smaller droplets
  - Cavitation - is caused by an intense pressure drop, leading to formation of vapor bubbles in the liquid, which implode causing shock waves in the fluid

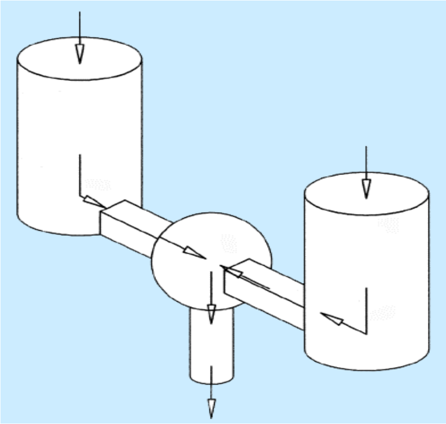
Homogenizers, available from different manufacturers operate based on combination of these mechanical forces

Process and Product Parameters

- Processes
  - Configuration (gap, length, shape, and size)
  - Pressure drop
  - Residence time
  - Cooling efficiency (temperature control)
- Product
  - Concentration
  - Viscosity (ratio and individual)
  - Interfacial tension (surfactant amount and adsorption rate)
  - Coalescence rate (Gibbs elasticity)
  - Temperature sensitivity

Equipment for Evaluation - Microfluidics

- Microfluidics: M-110EH
  - Microfluidics combines high flow with high-pressure, scalable fixed-geometry interaction chambers that impart high shear rates to product formulations
  - The entire product experiences identical processing conditions, producing the desired results, including: uniform particle and efficient droplet size reduction



Emulsion Preparation Process

- Aqueous phase prepared with lipid surfactant
- Addition of modifier
- Pre-mix: Oil phase is slowly added to aqueous phase while mixing with a high-speed rotor/stator mixer
- High pressure homogenization

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Process Parameters Evaluated

- Pressure Drop
- Configuration
- Number of Passes
- Temperature Control

Desirable Quality Attributes

- Mean Particle Size
  - Less than 0.8 micron (fine emulsion)
- Polydispersity
  - RSD Less than 10% (narrow distribution)
- Emulsion Stability
  - Less than 10-20% change in particle size or particle size distribution over extended period of time (long hold time)

Instrumentation Used For Evaluation

- *Instrument for determining emulsion size*
  - Photo sedimentation – CPS
  - Dynamic light scattering – Malvern Zetasizer
  - Static light scattering – Horiba LA-950
- *Criteria for choosing particle size analyzer*
  - Wide dynamic range
  - Broad applications
  - Accuracy and precision
  - Short cycle times (sample prep, measurement, and cleaning)
  - Ease of operation and maintenance
  - Regulatory compliance
  - At-line/on-line application

Instrument for Particle Size Analysis

- Emulsion Sizing
  - Horiba LA-950
  - Laser light scattering technique
  - Mie theory
  - 0.01 – 3000 micron
  - Good reproducibility
  - Fill, auto-alignment, blank, measurement, and rinse in less than 60 seconds

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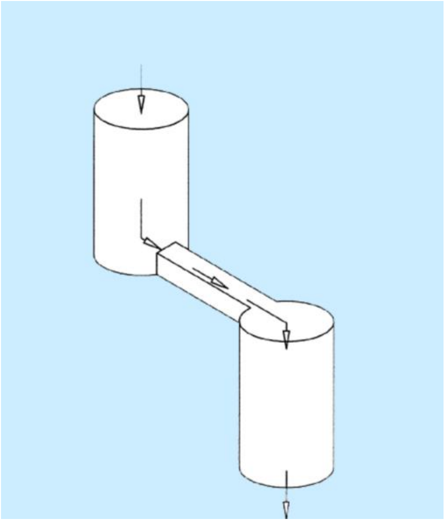
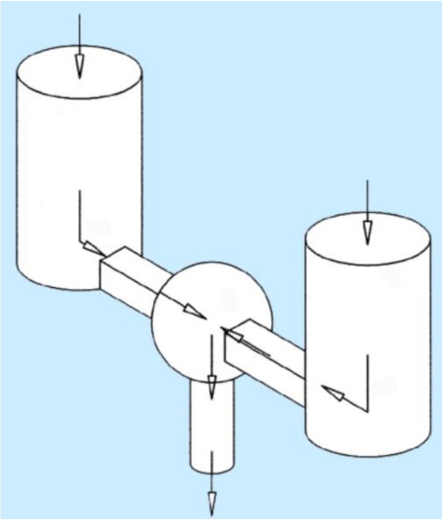
Microfluidics Study

▪ Chambers	G10Z and F20Y
▪ Pressures	15 and 25 kpsig
▪ Passes	1-5

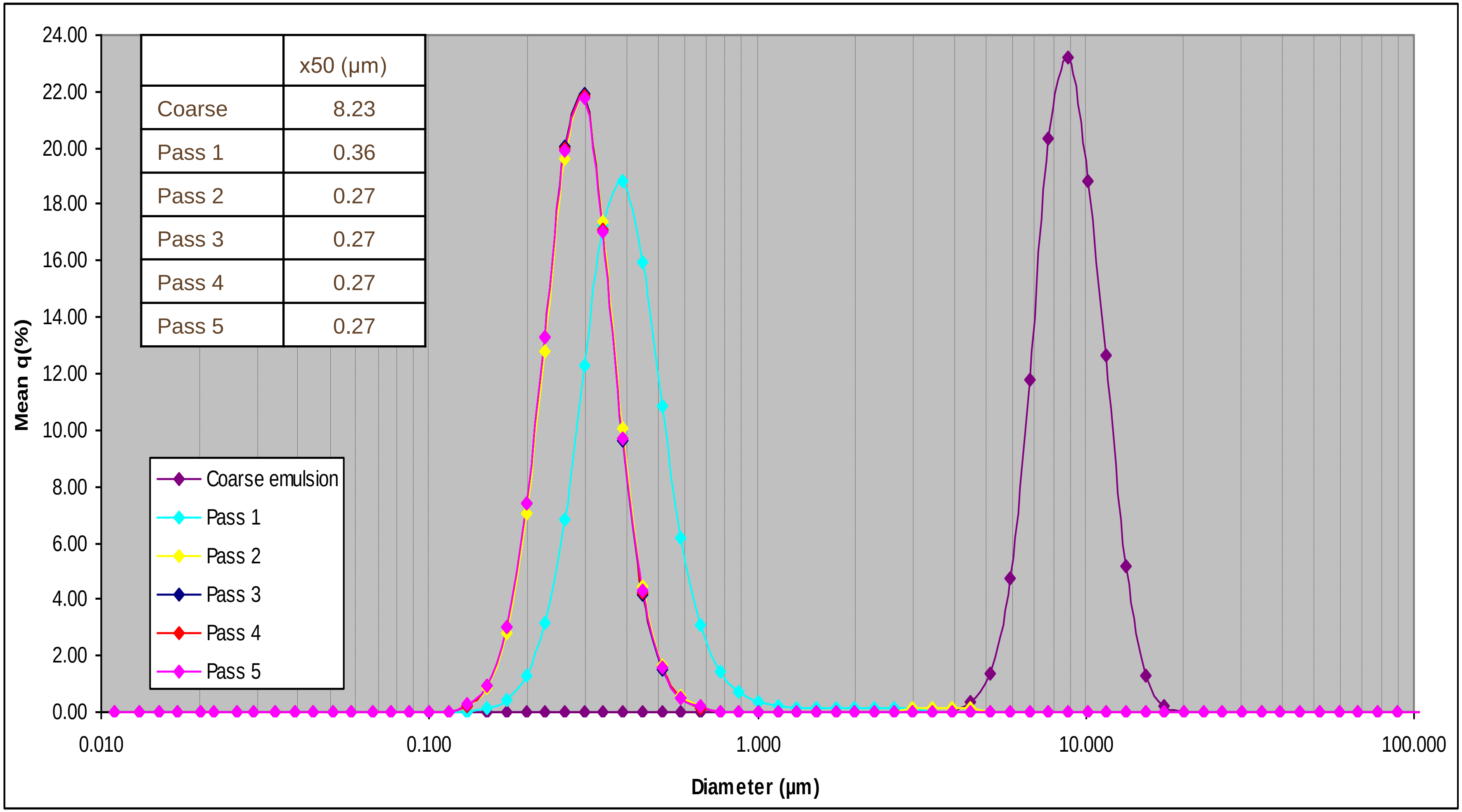
Z - Type



Y - Type



Microfluidics - G10Z at 15 kpsig



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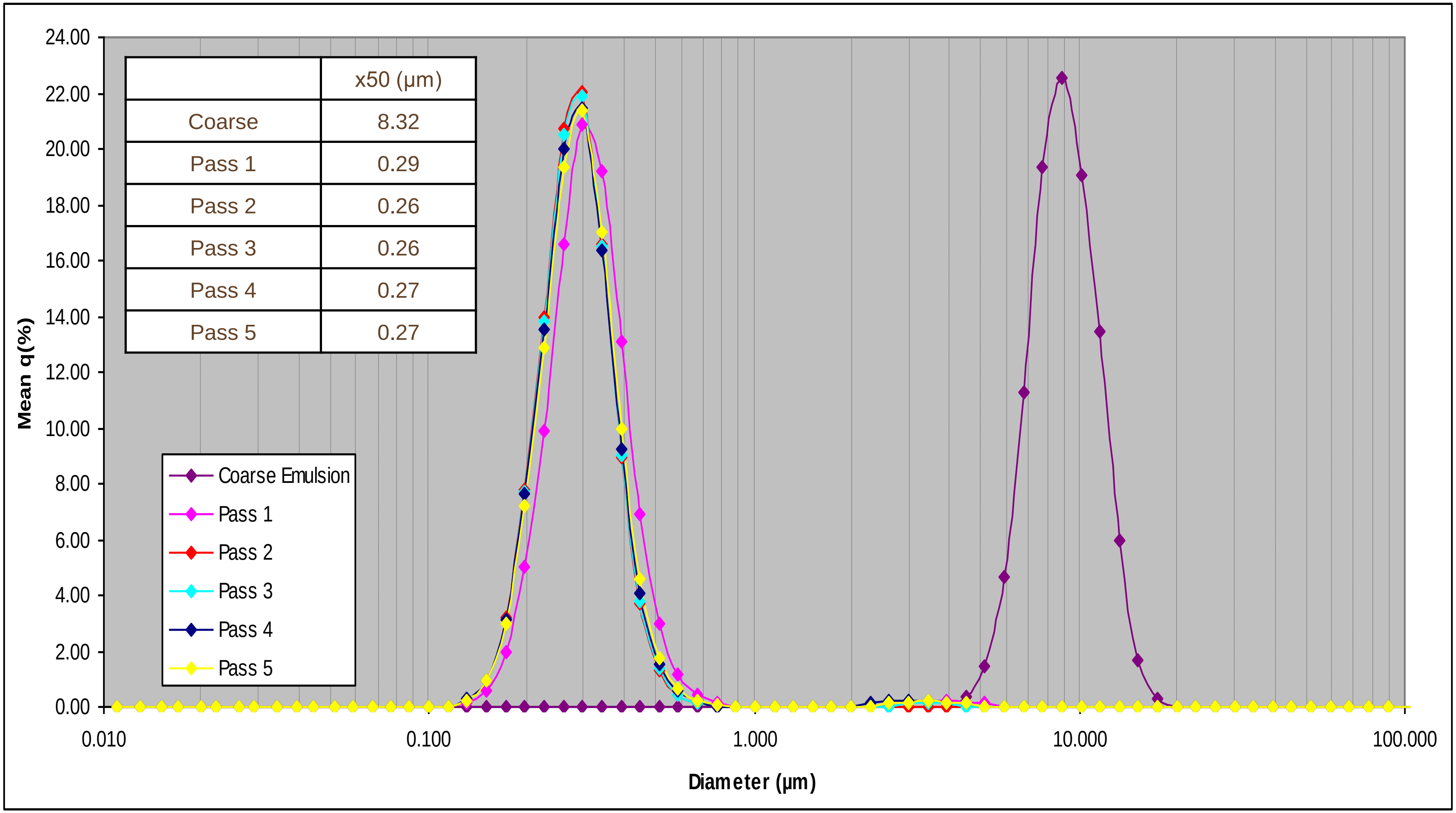
Microfluidics - G10Z at 25 kpsig



	x50 (µm)
Coarse	8.32
Pass 1	0.29
Pass 2	0.26
Pass 3	0.26
Pass 4	0.27
Pass 5	0.27

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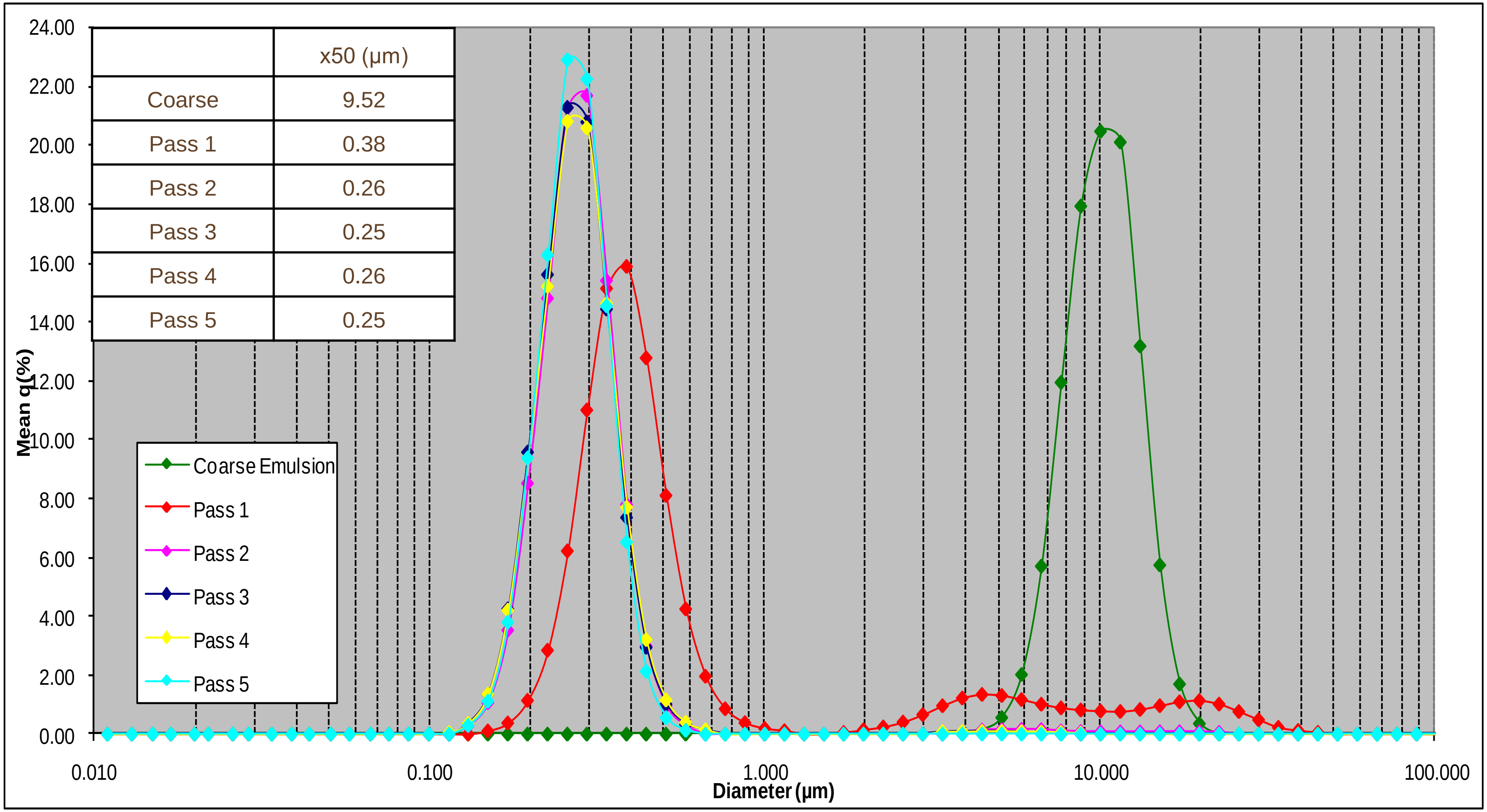
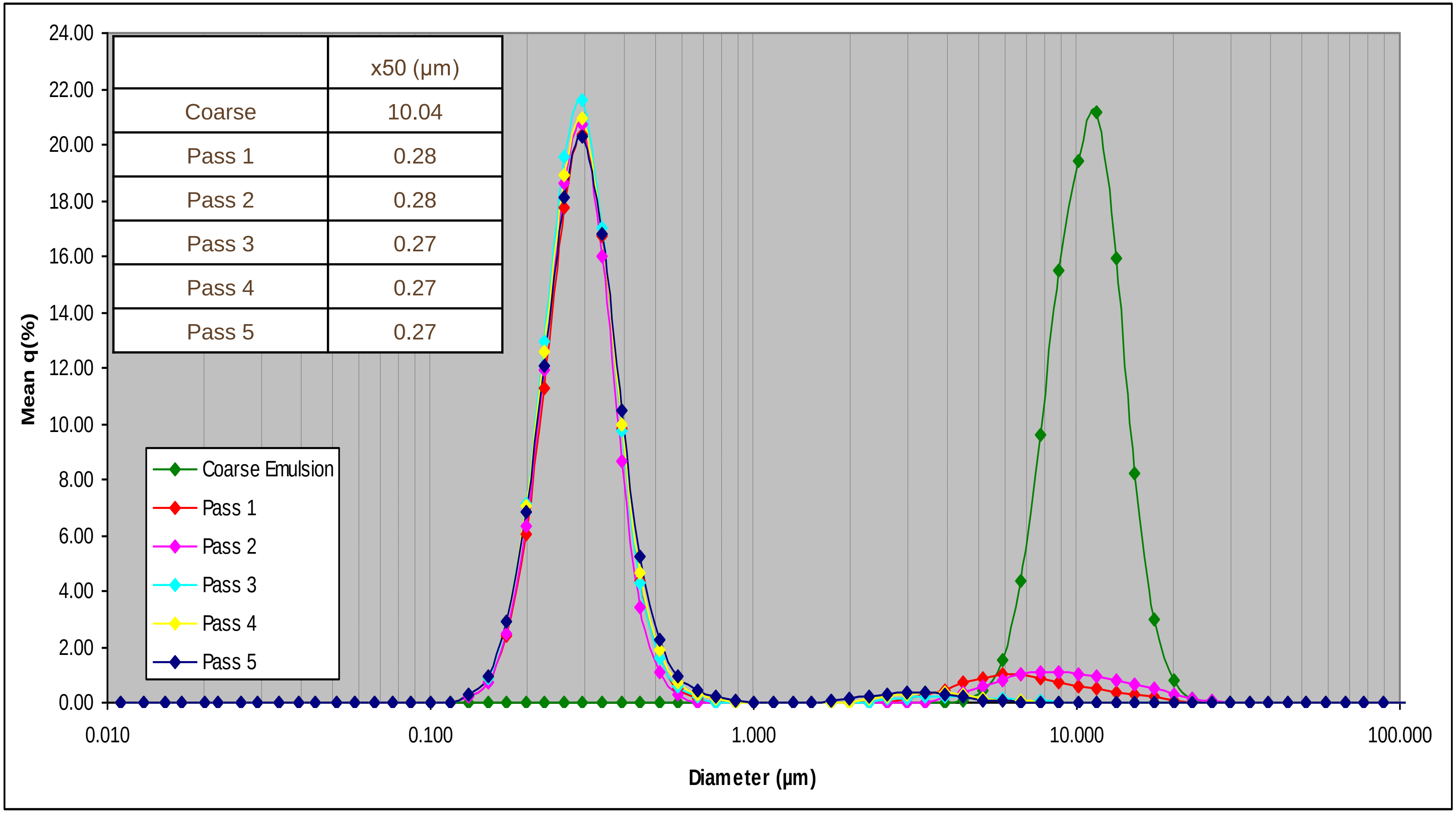
Microfluidics - F20Y at 15 kpsig



	x50 (µm)
Coarse	9.52
Pass 1	0.38
Pass 2	0.26
Pass 3	0.25
Pass 4	0.26
Pass 5	0.25

Microfluidics - F20Y at 25 kpsig



	x50 (µm)
Coarse	10.04
Pass 1	0.28
Pass 2	0.28
Pass 3	0.27
Pass 4	0.27
Pass 5	0.27

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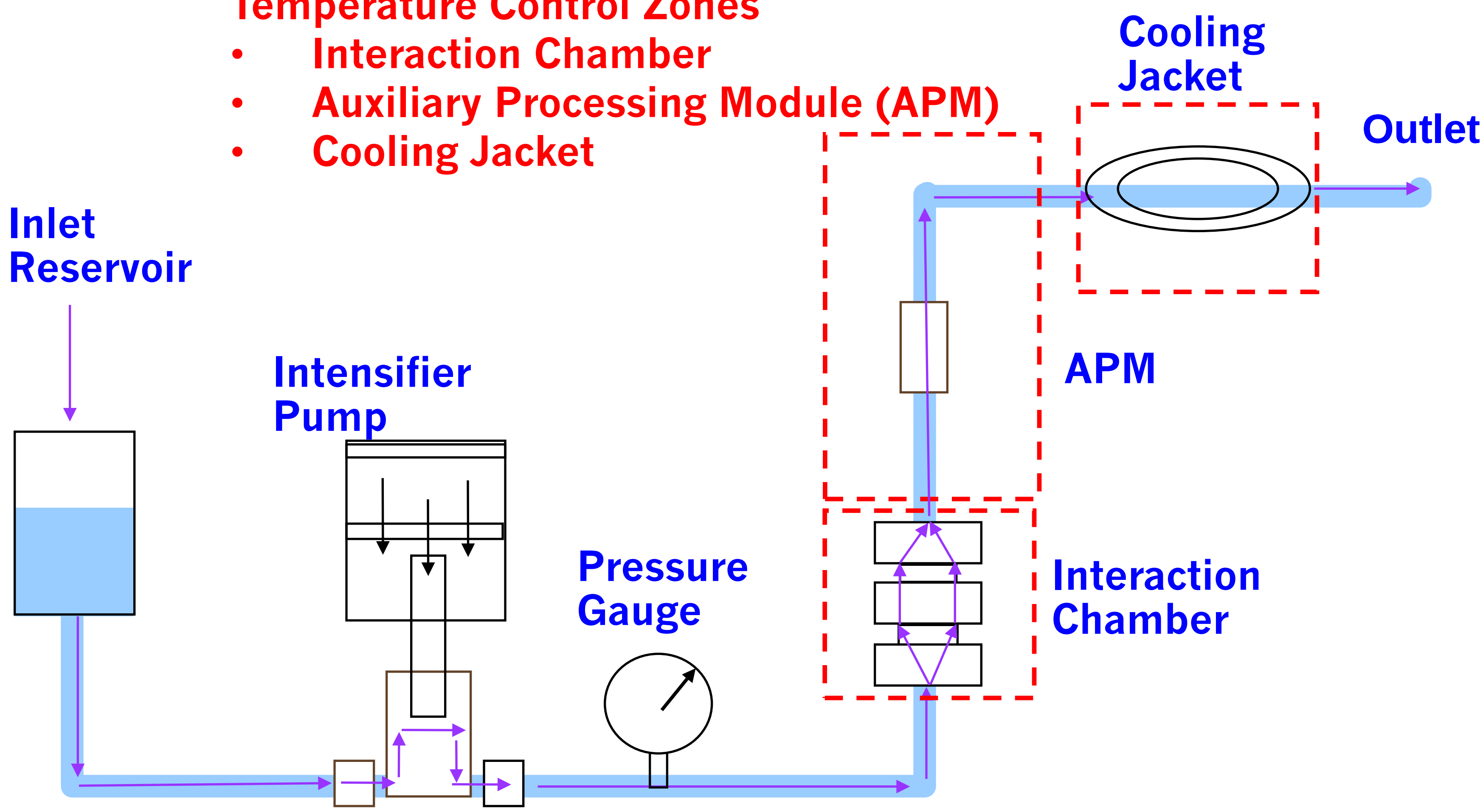
Microfluidics Study – Effects of Temperature Control

Temperature Control Zones
- Interaction Chamber
- Auxiliary Processing Module (APM)
- Cooling Jacket



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Microfluidics Study – Effects of Temperature Control

-	Interaction Chamber	APM	Cooling Jacket
Interaction Chamber	-	+	+
APM		++	+++
Cooling Jacket			+

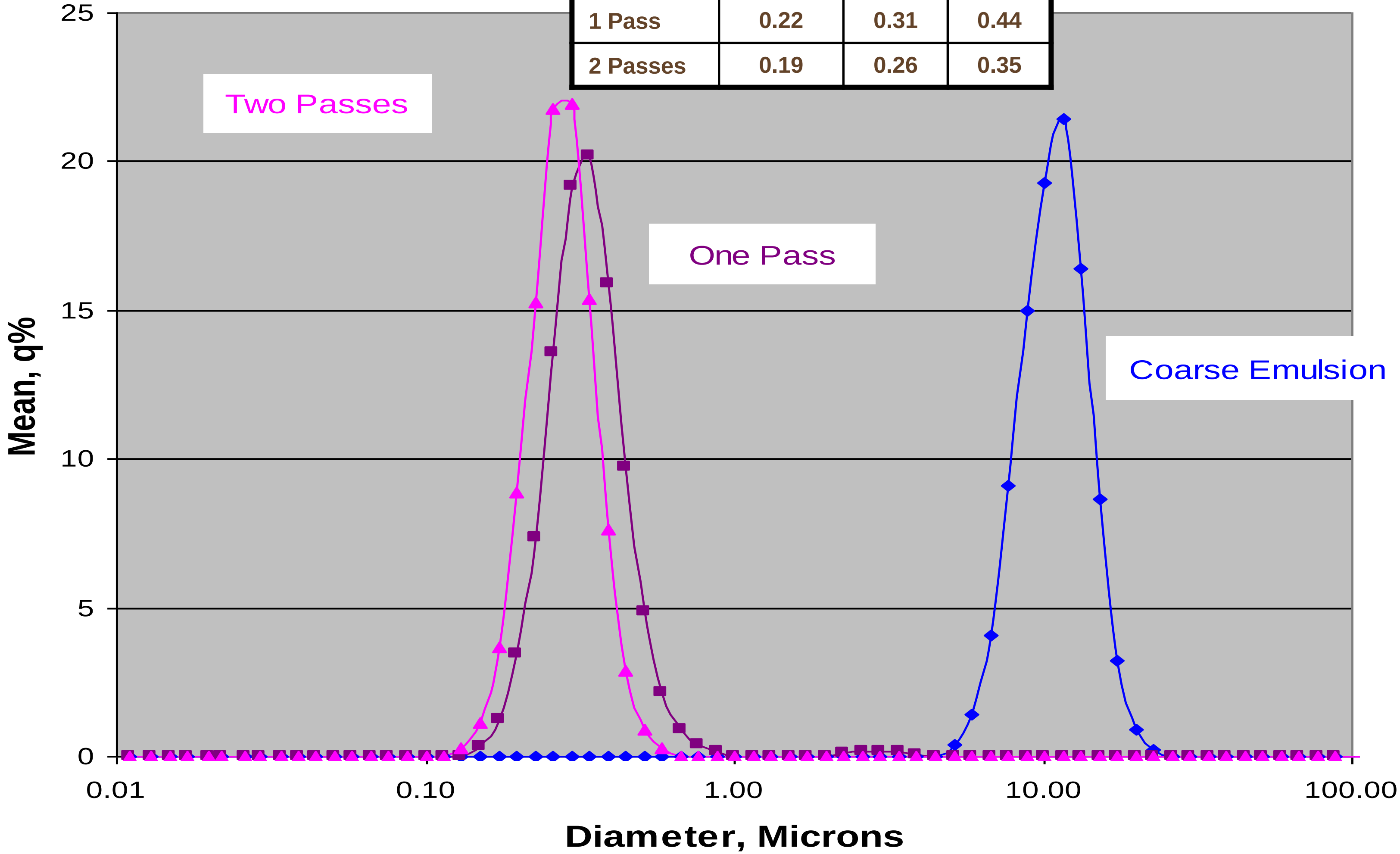
Interaction Chamber + Exit Line + Cooling Jacket = ++

Microfluidics Study – Temperature Control of APM and Cooling Jacket

Condition	Chamber	Pressure kpsig	Particle Size, Micron					
			Pass 1			Pass 2		
			x10	x50	x90	x10	x50	x90
1	G10Z	15	0.26	0.39	0.62	0.19	0.26	0.35
2	G10Z	20	0.21	0.29	0.40	0.19	0.25	0.33
3	G10Z	25	0.20	0.27	0.37	0.19	0.26	0.34
4	F12Y	15	0.22	0.31	0.44	0.19	0.26	0.35
5	F12Y	20	0.19	0.27	0.37	0.19	0.26	0.34
6	F12Y	25	0.19	0.26	0.36	0.19	0.26	0.33

Microfluidics – F12Y at 15 kpsig with Optimized Cooling

	x10	x50	x90
1 Pass	0.22	0.31	0.44
2 Passes	0.19	0.26	0.35



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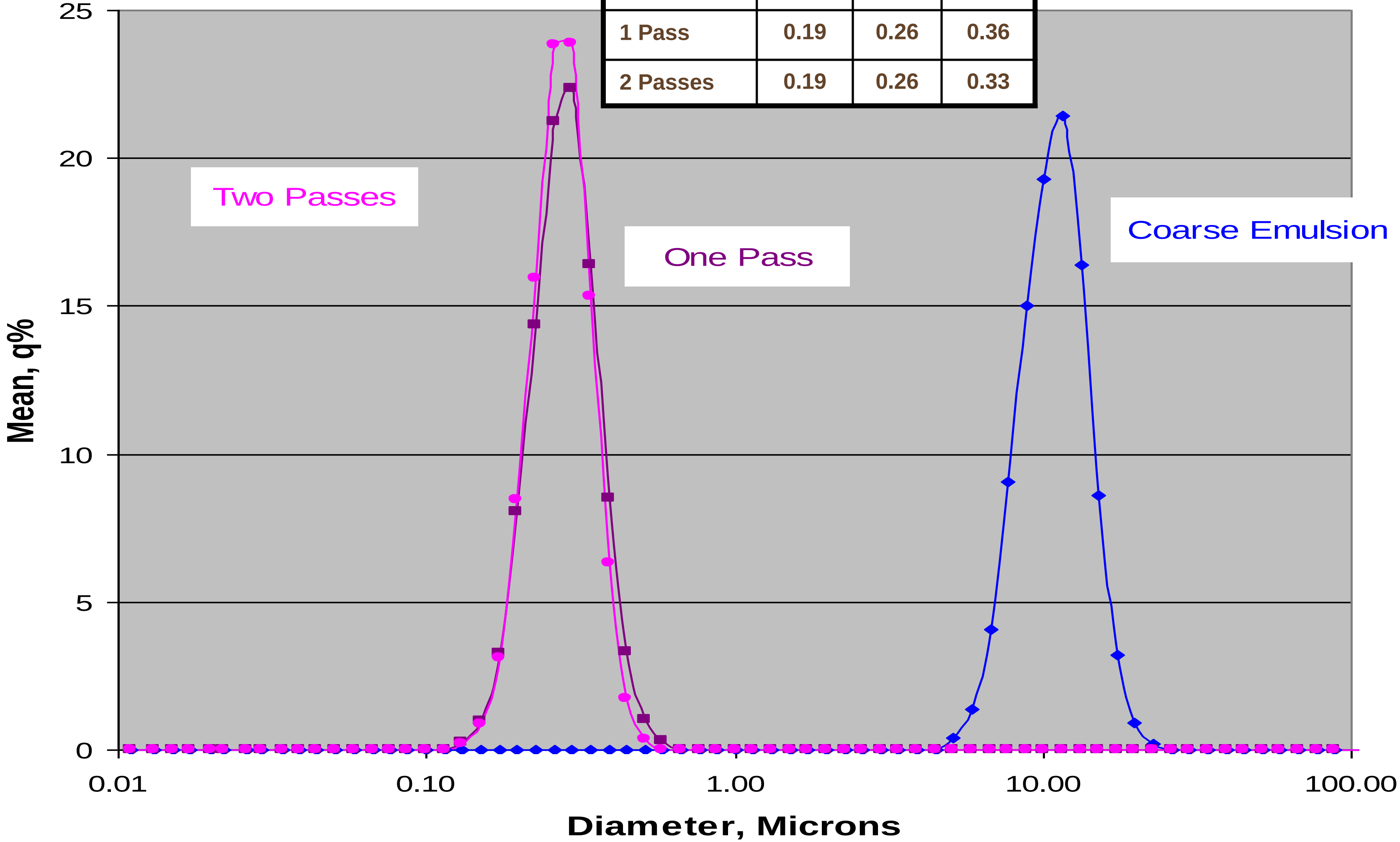
Microfluidics – F12Y at 25 kpsig with Optimized Cooling

	x10	x50	x90
1 Pass	0.19	0.26	0.36
2 Passes	0.19	0.26	0.33



Emulsion Stability Studies

Homogenizer	Sample	Time Point		x10	x50	x90	Mean	Mode
Avestin C-50	Homogenized Emulsion Pass #3	0	Ave	0.18	0.26	0.38	0.35	0.25
Avestin C-50	Homogenized Emulsion Pass #3	24hrs	Ave	0.19	0.28	0.41	0.35	0.28
Avestin C-50	Homogenized Emulsion Pass #3	96hrs	Ave	0.22	0.32	0.59	0.46	0.31
Microfluidics M-110EH	Homogenized Emulsion Pass #1	0	Ave	0.19	0.27	0.39	0.33	0.27
Microfluidics M-110EH	Homogenized Emulsion Pass #1	24hrs	Ave	0.20	0.29	0.42	0.34	0.28
Microfluidics M-110EH	Homogenized Emulsion Pass #1	96hrs	Ave	0.23	0.32	0.49	0.39	0.32
Microfluidics M-110EH	Homogenized Emulsion Pass #2	0	Ave	0.19	0.26	0.35	0.27	0.27
Microfluidics M-110EH	Homogenized Emulsion Pass #2	24hrs	Ave	0.18	0.25	0.35	0.26	0.26
Microfluidics M-110EH	Homogenized Emulsion Pass #2	96hrs	Ave	0.20	0.28	0.38	0.29	0.28

Emulsion Study Summary

- High precision and reproducible data from Horiba LA-950 particle size analyzer provide the critical information for evaluating different equipment and processing conditions.
- Both Y and Z types interaction chambers from Microfluidics produce emulsions with fine size and fairly uniform distribution. Y type is slightly more efficient than Z type.
- Cooling study using Microfluidics demonstrates that immediate quench of the processed emulsions is a critical process parameter to control the emulsions stability.
- When employing new cooling strategy, Microfluidics F12Y interaction chamber is able to produce fine and single-mode emulsions in less than two passes.

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*"Improved Lung Delivery from a Passive Dry Powder Inhaler Using an Engineered PulmuSphere Powder", S. Duddu et al, *Pharmaceutical Research, Vol. 19, No. 5, May 2002*

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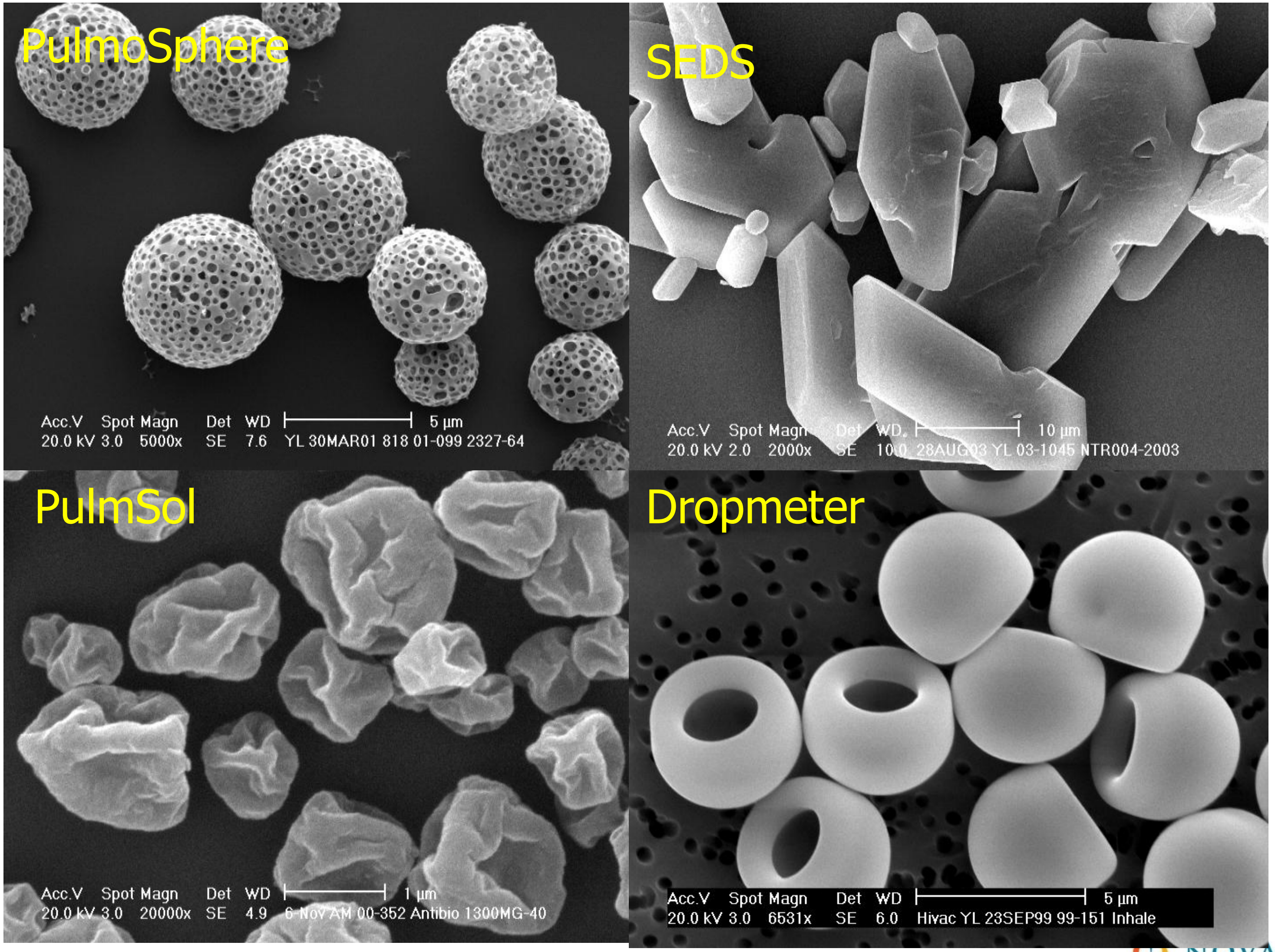
Novartis Particle Engineering Technology



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