Nano-particle formation and coating

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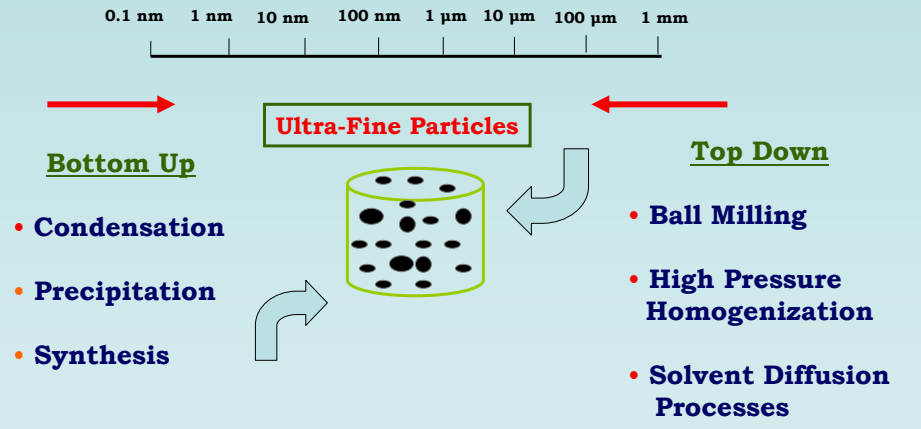
The module

- Nano-particle formation and coating
  - General Introduction to nano-particle formation and coating
  - Supercritical fluid processing- research based material
  - Student presentations – class project on literature review of nano-particle formation or coating

What is Special about Nano?

- Nano-materials exhibit unique properties, in part due to large number of atoms on the surface as compared to bulk materials
  - Mechanical properties
    - **Small enough to be defect-free, thus exhibiting ideal strength**
  - Thermal properties
    - **Can be designed to conduct heat substantially better (or much worse) than nearly every bulk material**
  - Electronic & optical properties
    - **Nanowires and nanotubes are the most confining electrical conductors - puts the squeeze on electrons**
    - **Can be defect free - electrons move "ballistically"**
    - **Quantum confinement - tunable optical properties**
  - Chemical properties
    - **Dominated by large surface-to-volume ratio**

Approaches for Precipitation of Ultra-Fine Particles



Synthesis of Nano and Nano-structured Particles

- Top-down Approach
  - Mechnoalloying and mechnochemical synthesis
  - Nano-milling
  - High-pressure homogenization/cavitation milling (piston-gap-technique)
- Bottom-up Approach
  - Chemical techniques
  - Physico-chemical techniques
  - Vapor phase, liquid phase, bio-inspired, etc

Nanovehicles & Drug Carriers:

(few to 250 nm)

- Numerous engineered constructs, assemblies, architectures, & particulate systems:
  - Polymeric micelles
  - Dendrimers
  - Polymeric and ceramic nanoparticles
  - Protein cage architectures
  - Viral-derived capsid nanoparticles
  - Polyplexes and Liposomes
- Superparamagnetic iron oxide crystals
- Quantum Dots

A slide from Prof. Michniak's class

Nanoparticle Synthesis and Fabrication

- **Chemical techniques –(self assembly)**
  - **Solution methods**
  - **Supercritical processing**
  - **Bio-inspired synthesis**
  - **Sol gel methods**
- **Physico-chemical techniques**
  - **Nucleation of Clusters from an oven source**
  - **Laser vaporization**
  - **Nanoparticles from supersaturated vapors**
  - **Thermal/Plasma Enhanced Chemical vapor deposition**

Nanoparticle Synthesis

- Numerous techniques have been reported is last 20-30 years
  - Majority deal with inorganic materials
    - Vapor phase synthesis, e,g, pyrolysis
    - Laser ablation, plasma synthesis, etc
    - Microemulsion based processing
- Application of *nano in new drug delivery systems* has been an active area in recent years

Final Project/Exam

- Write a report on your choice of nano-particle formation (or nano-particle coating) method
  - The method should be preferably suitable for pharmaceutical/drug delivery; if not, discuss clearly why it is not suitable, at least in its present form
  - Your report must include a list of references and essentially explain in details 2 or more research papers (not from text books)
  - The method cannot be based on supercritical fluid approach
    - Include: Description of the method with schematic sketches, sample results, short list of key references, list advantages and disadvantages and commercializability/status (check on patents if applicable)
  - By March 25, send me by email the title of your talk and list of key references
  - By April 8, send me by email a one page report in form of an abstract of your work and a list of key references.
  - Draft of the final report should be in form of 10-20 PowerPoint slides, use the "notes" area for explaining each slide, send that to me electronically by April 21
  - Your presentations will be on April 22 and 29, and based on the feedback, the final report as a PPT file with note is due May 13

Nanoparticle-based Drug Delivery Systems

- Nanosuspensions and nanocrystals
  - Mostly used for poorly water soluble drug, and consist of the pure drug suspended in an appropriate dispersion media
- Solid lipid nanoparticles
  - an alternative carrier system to emulsions, liposomes and polymeric nanoparticles as a colloidal carrier system for controlled drug delivery
- Polymeric nanoparticles
  - polymeric nanoparticles (PNPs) consists of a biodegradable and biocompatible polymer

O. Kayser, A. Lemke and N. Hernández-Trejo, *Current Pharmaceutical Biotechnology*, vol 6, pp. 3-5, 2005

Nanoparticle-based Drug Delivery Systems (references)

- Nanosuspensions and nanocrystals
  - Rabinow, B.E. (2004) *Nat. Rev. Drug Discov.*, **3,** 785-796.
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  - Sarkari, M; Brown, J.; Chen, X.; Swinnea, S. and Williams, R.O.3rd and Johnston, K.P. (2002) *Int. J. Pharm.,* **243,** 17-31.
- Solid lipid nanoparticles
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  - Fundaro, A.; Cavalli, R.; Bargoni, A.; Vighetto, D.; Zara, G.P. and Gasco, M.R. (2000) *Pharmacol. Res.,* **42,** 337-343.
  - Maia, C.S; Mehnert, W. and Schäfer-Korting, M. (2000) *Int. J.Pharm.,* **196,** 165-167.
  - Dingler, A.; Blum, R.P.; Niehus, H.; Müller, R.H. and Gohla, S. (1999) *J. Microencapsul.,* **16,** 751-767.
- Polymeric nanoparticles
  - Fattal, E.; Vauthier, C.; Aynie, I.; Nakada, Y.; Lambert, G.; Malvy, C. and Couvreur P. (1998) *J. Control. Release,* **53,** 137-143.
  - Fernandez-Urrusuno, R.; Calvo, P.; Remunan-Lopez, C.; Vila-Jato, J.L. and Alonso, M.J. (1999) *Pharm. Res.,* 16, 1576-1581.
  - Farrugia, C.A. and Groves, M.J. (1999) *Anticancer Res.,* **19,** 1027-1031.
  - Farrugia, C.A. and Groves, M.J. (1999) *J. Pharm. Pharmacol.,* **51,** 643-649.
  - Aynie, I.; Vauthier, C.; Chacun, H.; Fattal, E. and Couvreur, P. (1999) *Antisense Nucleic Acid Drug. Dev.,* **9,** 301-312.
  - Soppimath, K.S.; Aminabhavi, T.M.; Kulkarni, A.R. and Rudzinski, W.E. (2001) *J. Control. Release,* **70,** 1-20.

Question: What about microemulsions? What are their advantages and disadvantages? (potential report topic)

Applications of Microemulsion Based Drug Delivery System, Jadhav, K. R. etal, Current Drug Delivery, Volume 3, Number 3, July 2006, pp. 267-273(7)

Nano-crystal/milling process

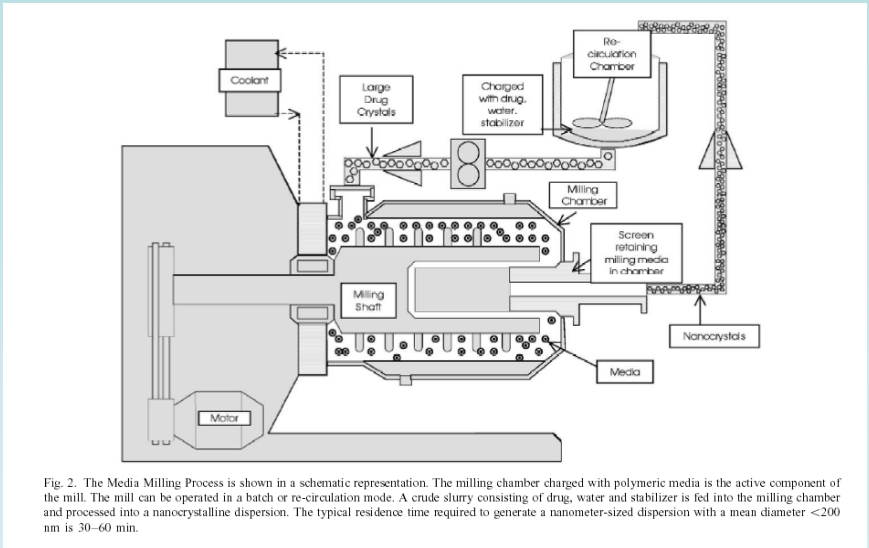


Fig. 2. The Media Milling Process is shown in a schematic representation. The milling chamber charged with polymeric media is the active component of the mill. The mill can be operated in a batch or re-circulation mode. A crude slurry consisting of drug, water and stabilizer is fed into the milling chamber and processed into a nanocrystalline dispersion. The typical residence time required to generate a nanometer-sized dispersion with a mean diameter <200 nm is 30–60 min.

Merisko-Liversidge, E.; Liversidge, G.G. and Cooper, E.R. (2003) *Eur. J. Pharm. Sci.*, **18,** 113-120.

Liversidge, G.G.; Cundy, K.C.; Bishop, J.F.; Czekai, D.A. Surface Modified Drug Nanoparticles. US Patent 5,145,684, 1992

Typical Results

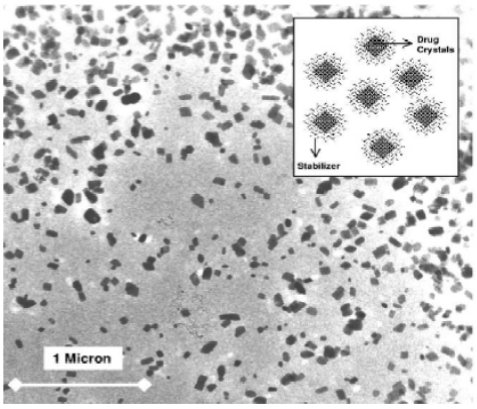


Fig. 1. Nanocrystalline drug particles. The transmission electron micrograph of a NanoCrystal® Colloidal dispersion magnified 35,000×. The insert provides a visual description of the crystalline nanoparticles generated using wet milling technology. The nanoparticles are typically less than 400 nm and are physically stabilized with a polymeric excipient.

- Milling media used for the NanoCrystal Technology could be zirconia spheres or a proprietary highly cross-linked polystyrene resin. The spheres have size less than about 3 mm
- The surface modifiers/stabilizers include various polymers, low molecular weight oligomers, natural products and surfactants, such as polyvinyl pyrrolidone, pluronic F68, pluronic F108, and lecithin
- The weight ratio of drug to stabilizer is 20:1 to 2:1

Particle Size Distribution

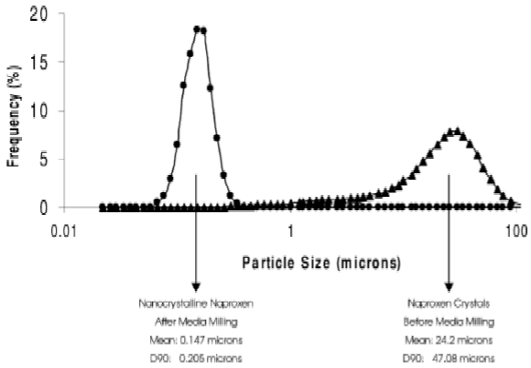
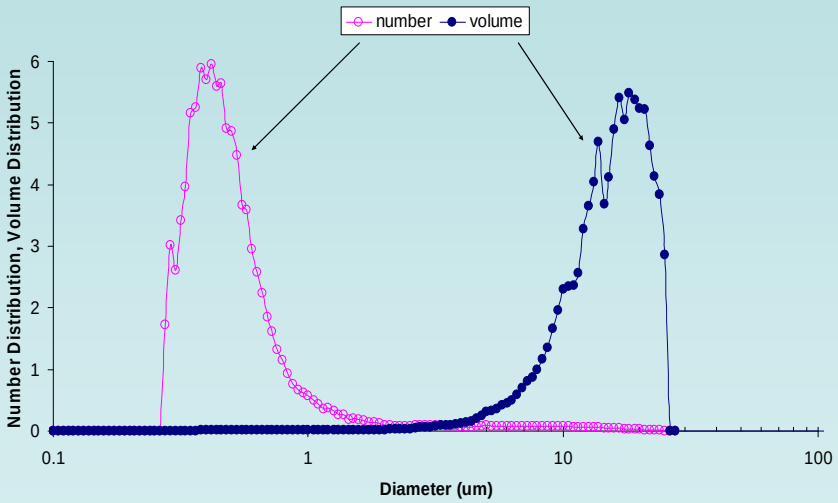


Fig. 3. The particle size distribution profile of naproxen crystals before (▲) and after milling (●). Before milling, the drug crystals had a mean particle size of 24.2 microns. After being processed for 30 min in a media mill, the mean particle size of the nanocrystalline dispersion was 0.147 microns with D_{90} = 0.205 microns. The particle size measurements were generated using laser light diffraction in a Horiba LA-910 using polystyrene nanospheres ranging in size from 0.1 to 10 microns as standards.

Key Features

- Good top-down approach, commercialized, can be scaled-up, but it is a batch process
- Toxicity due to excessive use of modifiers and surfactants
- Contamination from grinding media and system components
- Processing time- excess of 24 hours
  - Liversidge et al. reported that the poorly water soluble drug, naproxen, was reduced in average particle size from 20–30 mm to 270 nm over 5 days of wet milling

A Caution: Number vs. Volume



High-pressure homogenization process

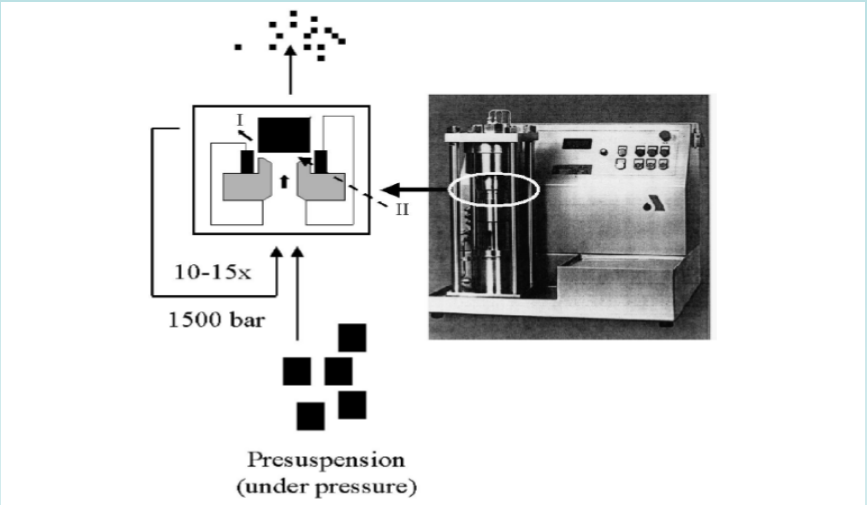


Fig. 2. Production of nanosuspensions by high pressure homogenization (I: implosion area, II: boiling area).

Müller, R.H.; Jacobs, C. and Kayser, O. (2001) *Adv. Drug Deliv.Rev.*, **47,** 3-19.

Muller, R.H.; Becker, R.; Kruss, B.; Peters, K. Pharmaceutical Nanosuspensions for Medicament Administration as Systems with Increased Saturation Solubility and Rate of Solution. US Patent 5,858,410, 1999.

NJ Center for Engineered Particulates

Typical Results

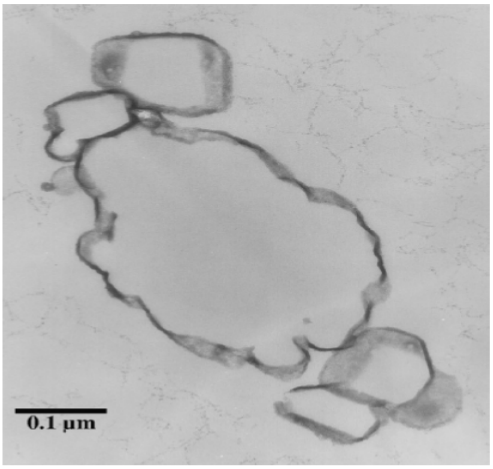


Fig. 4. Transmission electron micrographs of a atovaquone nanosuspension (medium size: 468 nm).

The mean particle size in the nanometer range and depends on the pressure, number of cycles applied, and the hardness of the drug itself.
For example, for drug budesonide a pressure of 1500 bar and ten cycles lead to a mean PCS diameter of 511 nm, 15 cycles to 462 nm, and increasing the pressure to 2500 bar and ten cycles leads to particles with a diameter of 363 nm

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Key Features

- Good top-down approach, commercialized, can be scaled-up, and made continuous
- Stability issues due to change in crystal structure
- Contamination from system components

Examples of Commercial Technologies

Nanoparticulate-based technologies.

Technology	Company	Approach	Focus of applications
Stealth Liposomes	Alza/J&J	Drug-carrying liposomes	Enhanced circulatory persistence
NanoCrystal	Elan	Drugs reduced to nanometre-sized particles by wet milling; formulated with stabilizers to prevent reagglomeration	Improving drug solubility
IDD	SkyePharma	Nanometre-sized drug particles produced by homogenization	Improving drug solubility
Nanoedge	Baxter	Drug particles reduced to nanometre size range by homogenization or microprecipitation	Improving drug solubility
BioAqueous	Dow	Precipitation, cryogenic and emulsion technologies	Improving drug solubility
Bioral Technology	BioDelivery Sciences International	Nanocochleate delivery vehicles comprising stable phospholipid-cation precipitates	Oral delivery of injectable drugs and vaccine delivery
Calcium phosphate nanoparticles (CAP)	BioSante	Nanoparticles based on calcium phosphate	Delivery of proteins, for example, insulin and as vaccine adjuvants

www: ptemagazine.com: nano technology applications for drug delivery

Examples of Commercial Technologies

Nanostructured material-based technologies.

BioSilicon	pSivida/pSiMedica	Drugs and other therapeutics nanostructured within BioSilicon microparticles or other BioSilicon structures, for example, fabrics, fibres, implants	Improves solubility of hydrophobic drugs; controlled release of a wide range of compounds; drug delivery in orthopaedics and other applications; potential for 'smart' drug delivery systems
NanoGate	iMEDD	Silicon membrane with 10–100 nm wide pores as part of an implantable system	Drug delivery and biofiltration
DebioSTAR	DebioTECH	Porous silicon membrane as part of an implantable device	Drug delivery

www. ptemagazine.com: nano technology applications for drug delivery

How do we utilize nano-particles in our (drug delivery) applications?

- Class discussion
  - Making drug particles?
  - Where do we exploit the novelty of nano?
  - Is pharmaceutical company ready for this?

Formation of Drug Nanoparticles using Supercritical CO_2

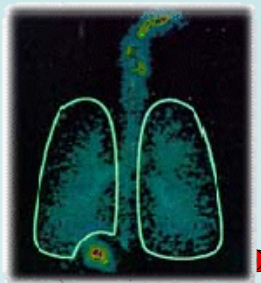
- Particles in drug delivery
  - 2-5 μm for inhalation
  - 100-500 nm for injectable
  - 100-3000 nm for embedding in polymer matrix
- Supercritical CO_2
- CO_2-soluble drugs
  - Rapid Expansion of Supercritical Solution
- CO_2-insoluble drugs
  - Supercritical Antisolvent
- Commercialization
- Examples of controlled release formulations

Notes adapted from Prof. Ram Gupta, Auburn University

Particle Technology in Drug Delivery

Inhalation delivery

- 2-5 micrometer particle size
- Narrow distribution



U.S. Food and Drug Administration

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This is a revised version of this press release, originally issued Jan. 27, 2006.
The release was revised to clarify recommendations for baseline tests.

FDA News

FOR IMMEDIATE RELEASE
P06-13
January 27, 2006

Media Inquiries:
Laura Alvey, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Approves First Ever Inhaled Insulin Combination Product for Treatment of Diabetes

There is a new, potential alternative for many of the more than 5 million Americans who take insulin injections, with the Food and Drug Administration's approval today of the first ever inhaled insulin. Exubera, an inhaled powder form of recombinant human insulin (rDNA) for the treatment of adult patients with type 1 and type 2 diabetes, is the first new insulin delivery option introduced since the discovery of insulin in the 1920s.

"Until today, patients with diabetes who need insulin to manage their disease had only one way to treat their condition," said Dr. Steven Galson, Director, Center for Drug Evaluation and Research, FDA. "It is our hope that the availability of inhaled insulin will offer patients more options to better control their blood sugars."

Diabetes is a disease that affects the amount of insulin and sugar in your body. Exubera is a human form of insulin and as such, lowers blood sugar concentrations by allowing the blood sugar to be taken up by cells as a source of fuel. Exubera is a powdered form of insulin that

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25

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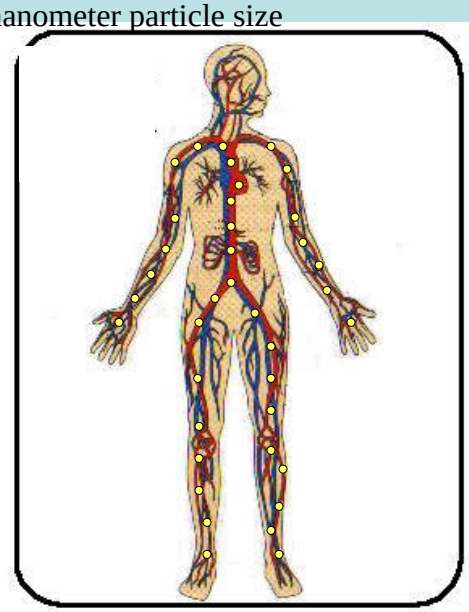
Nanoparticles for systemic injections

- 100-500 nanometer particle size



- Drug Particle

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26

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National Cancer Institute U.S. National Institutes of Health

NCI Alliance for Nanotechnology in Cancer

Transforming the diagnosis, prevention, treatment and clinical outcomes for

About the Alliance | Funding | News Center | Resource Center | Meetings & Events

Nanotech News Back

February 7, 2005

Abraxane™ Approved To Treat Metastatic Breast Cancer

Albumin nanoparticle increases efficacy, reduces toxicity, of Taxol®

On January 7, 2005, Abraxane, a nanoparticulate formulation of the widely used anticancer drug paclitaxel, received final FDA approval for use in patients with metastatic breast cancer who have failed combination chemotherapy. Abraxane, created and developed by American Bioscience (ABI), based in Schaumburg, IL, is the first approved drug to use nanoparticles made of the protein albumin to improve the therapeutic and safety properties of a drug.

One of the major limitations in using paclitaxel is its poor solubility in blood and other biological fluids. As a result, the drug must be mixed with various toxic solvents, which limits the amount of drug that patients receive. In addition, patients receiving solvent-based paclitaxel must also receive corticosteroids to counteract the toxicity of these solvents.

Albumin, the most plentiful protein in human serum, turns out to be a good natural "solvent" for paclitaxel. Scientists at ABI developed methods for making nanoparticles from the material and loading paclitaxel into these nanoparticles, which allows patients to safely receive 50 percent more paclitaxel per dose. In addition, experimental data suggests that the albumin nanoparticles interact with receptors present on tumor blood vessels that transport the nanoparticles into tumors. This interactivity may account for the increased levels of paclitaxel seen in tumors treated with Abraxane compared to solvent-based paclitaxel.

Clinical trials in 454 patients with metastatic breast cancer showed that Abraxane achieved almost a doubling of tumor response rate compared to that obtained by Taxol, the brand name for paclitaxel. In addition, Abraxane appeared to be better tolerated than Taxol, though Abraxane, like Taxol, does produce a variety of side effects, many severe. Additional clinical trials with Abraxane in other cancers are ongoing.

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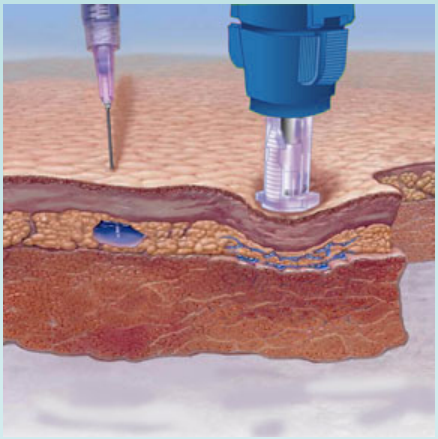
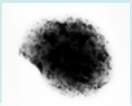
27

rticulates

Particles for sustained/controlled release

- Drug encapsulated in polymer
- 20-100 micrometer overall particle size
- 100-3000 nanometer size embedded drug particles





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28

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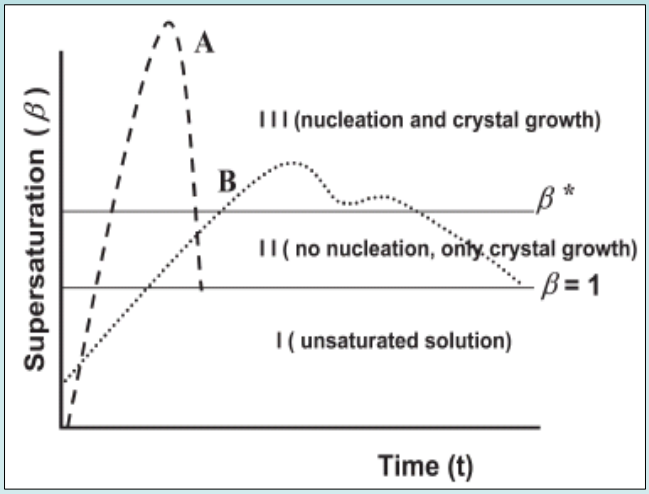
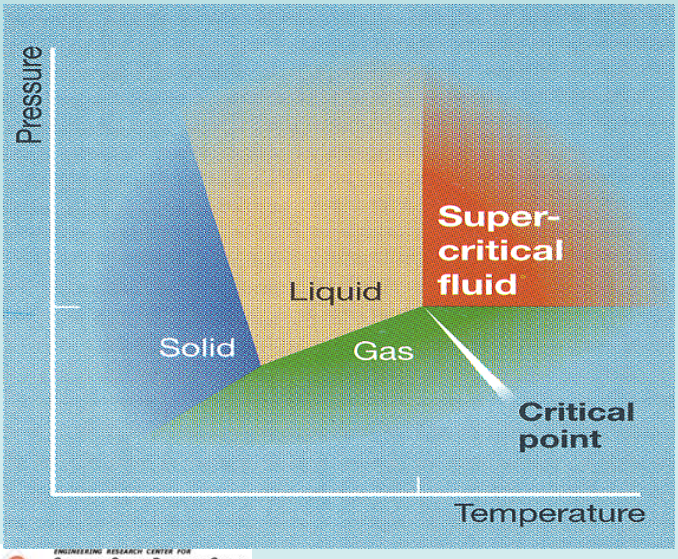
Supersaturation Vs Nucleation and Growth



The schematic P-T phase diagram

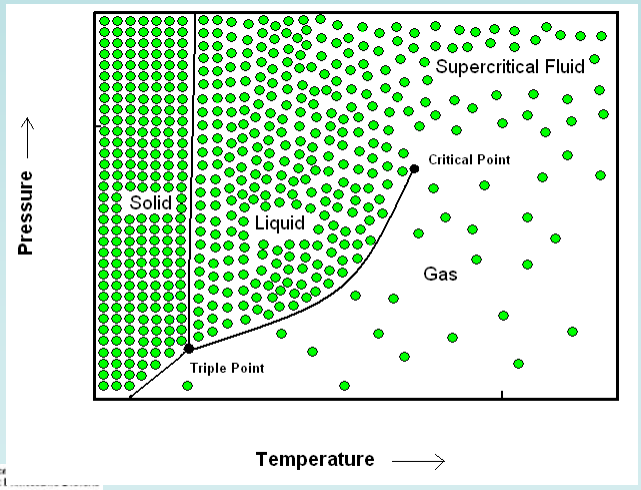


Criterion:

$T > T_c$

$P > P_c$

Supercritical CO_2



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A brief history

- In 1821, French scientist Baron Charles Cagniard de la Tour mixed the first batch of supercritical water.
- In years 1870, Thomas Andrews properly described supercritical state by the name "critical point".
- In 1879, Hannay and Hogarth, reported that supercritical fluids have a pressure-dependent dissolving power.
- During years 1920, application studies were done in petrochemistry fields.
- In years 1960, Kurt Zosel developed natural product extraction with supercritical carbon dioxide.
- During 80s, a first strong development step occurred for supercritical technology, with building of huge industrial units dedicated to solid extraction, in Europe, in the USA and in Australia.
- Late nineties, novel applications for supercritical fluids emerged: precision cleaning, aerogels, impregnation, particle generation and micro-encapsulation, etc.

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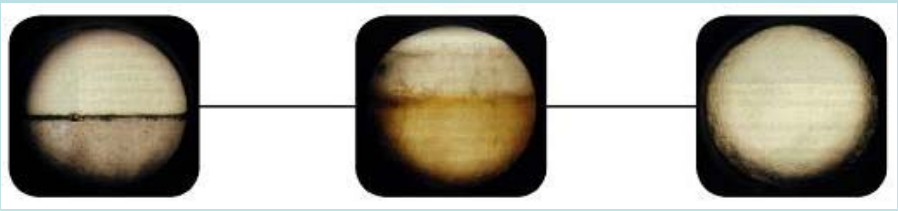
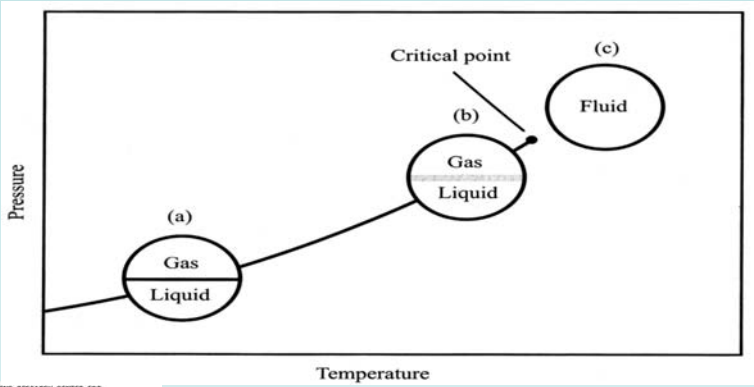
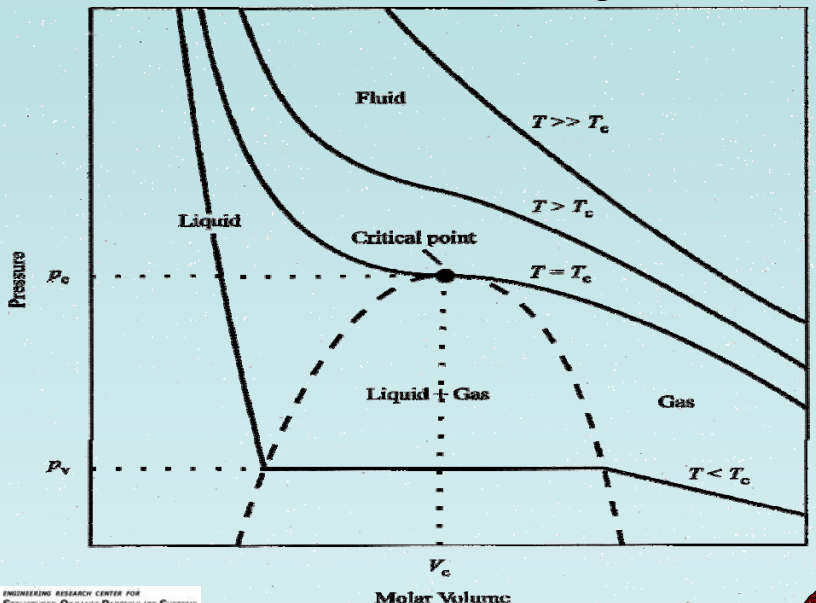
Disappearance of the meniscus at the critical point





From "Fundamentals of Supercritical Fluids" by Tony Clifford, Oxford University Press in 1998

Pressure-volume isotherms for a single substance



- **Properties of Supercritical Fluids**
  - **Liquid-like density and solvent strength**
  - **Gas-like low viscosity and high diffusivity**
  - **Density and solvent strength tunable by T and P**
- **Supercritical CO_2**
  - **Low critical temperature (31.1 ºC) and mild critical pressure (73.8 bars)**
  - **Non-toxic, nonflammable, inexpensive and readily accessible**
  - **Ideal processing medium and an environmental benign substitute for many organic solvents**
  - **Low dielectric constant (relatively non-polar)**
  - **Solubility can be adjusted with pressure**
  - **Pressure can be changed very fast**
  - **~100 fold more diffusive than liquids**

Critical parameter value for some SCFs

Fluid	P_c *(bar)*	ρ_c *(kg m^{-3})*	T_c *(K)*
Carbon Dioxide	73.77	467.6	304.13
Methane	45.92	162.7	190.56
Ethane	48.72	206.6	305.33
Water	220.64	322.0	647.10

Supercritical CO_2

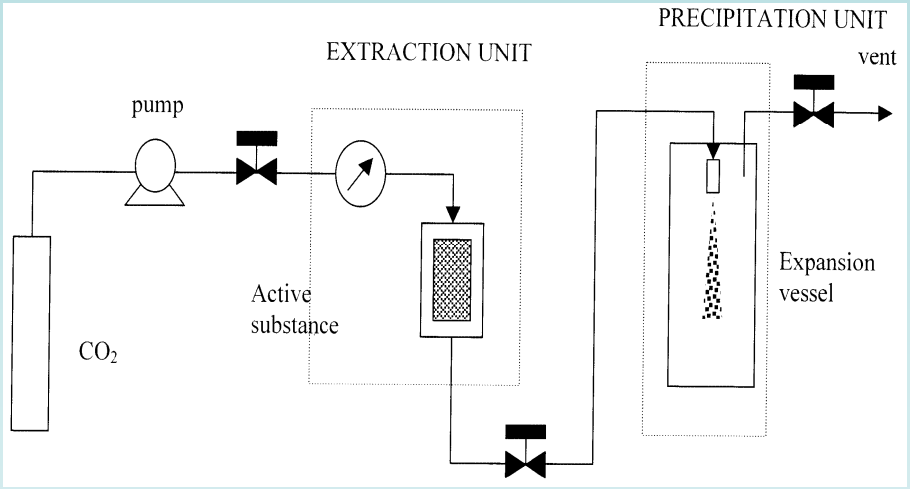
- Critical temperature: 31.1 ^{o}C
- Critical pressure: 73.7 bar
- Non-flammable
- Non-toxic
- Low dielectric constant (relatively non-polar)
- Solubility can be adjusted with pressure
  - Pressure can be changed very fast
- 100 fold more diffusive than liquids

Supercritical fluids applications

- **Supercritical Fluid Chromatography (SFC)**
- **Supercritical Fluid Extraction (SFE)**
- **Supercritical Fluid Reactions**
- **Supercritical fluid Particle Design**
  - **Rapid Expansion of Supercritical Solution (RESS)**
  - **Gas/Supercritical fluids AntiSolvent Process GAS/SAS**

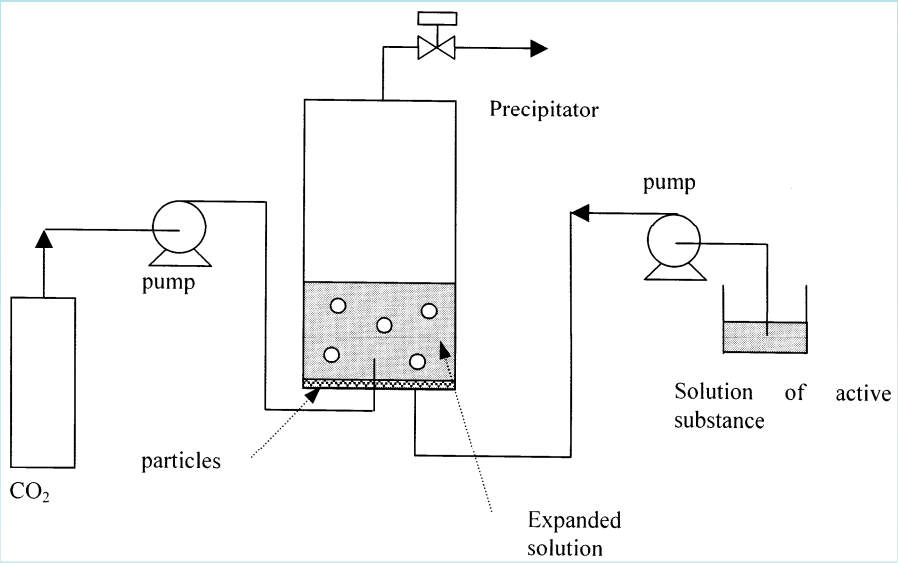
Supercritical Fluid Processes	Role SCF	Specifications
Depressurization Crystallization • RESS • PGSS • DELOS	Solvent Solute Cosolvent	200-400 bar 30-200 °C 50-100 µm nozzle
Antisolvent Crystallization	Antisolvent	70-200 bar 30-100 °C 50-100 µm nozzle
Crystallization by Reactions Using SCF • Thermal decomposition of metal precursors • Hydrolysis of metal precursors • Reverse Micelles	Reaction Media Reactant Bulk Solvent	200-500 bar 150-500 °C

RESS equipment concept



J Jung, M Perrut, J SUPERCRIT FLUID, 20 (2001) 179–219

GAS/SAS equipment concept



J Jung, M Perrut, J SUPERCRIT FLUID, 20 (2001) 179–219

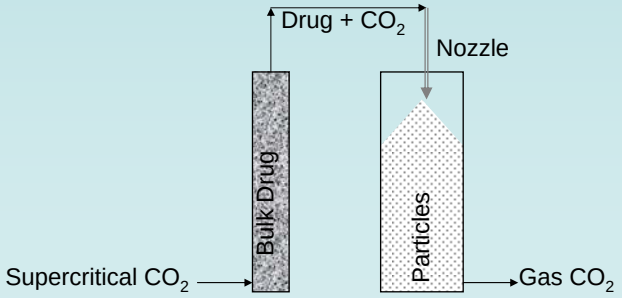
How to choose a formation process

First consider the solubility of the substrate in the SCFs. → RESS

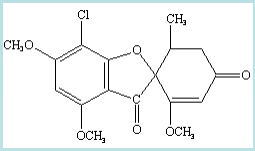
Then consider the desired particle size, shape and structure. → GAS/SAS

CO_2-soluble drugs

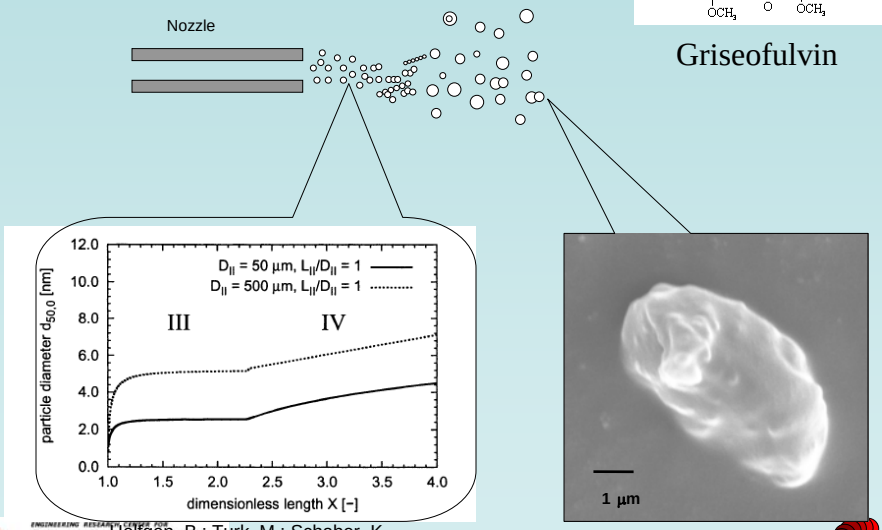
Rapid Expansion of Supercritical Solution (RESS)



RESS



Griseofulvin

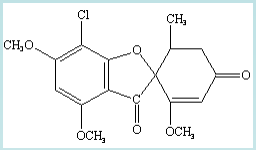


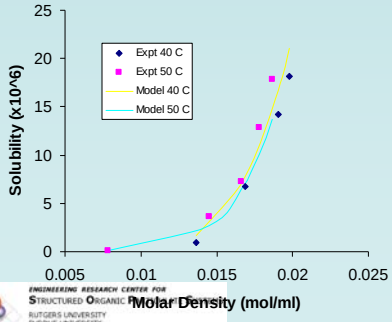
Helgen, B.; Turk, M.; Schaber, K., *J. Supercritical Fluids*, 2003, 26, 225-242

Challenges with RESS

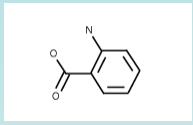
(I) Low drug solubility, (II) Microparticles obtained

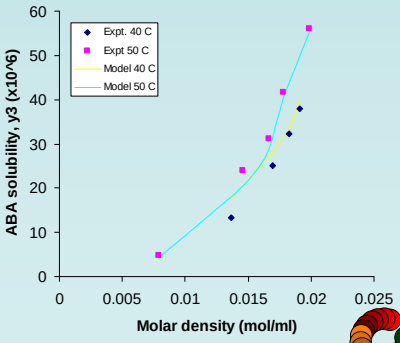
Griseofulvin





2-Aminobenzoic acid





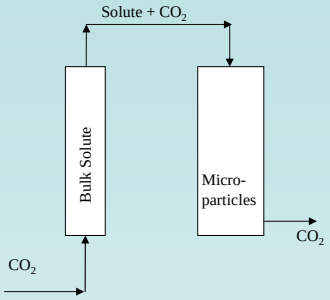
NJ Center for Engineered Particulates

Recent Advancement from Auburn University

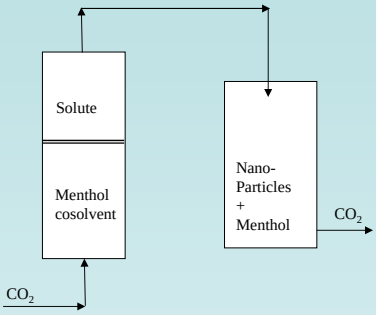
- Rapid Expansion of Supercritical Solution with Solid Co-solvent (RESS-SC)
  - Uses menthol solid cosolvent
  - Increased solubility of drugs in supercritical CO_2
    - Griseofulvin: 30 fold;
    - 2-amino benzoic acid: 100 fold;
    - Phenytoin: 500 fold
  - Reduced particle size from micron to nanometer range, by hindering particle coagulation

NJ Center for Engineered Particulates

Recent Advancement: RESS-SC

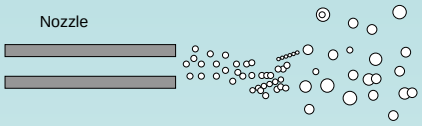


Conventional RESS Process



RESS-SC Process

Expansion Chamber

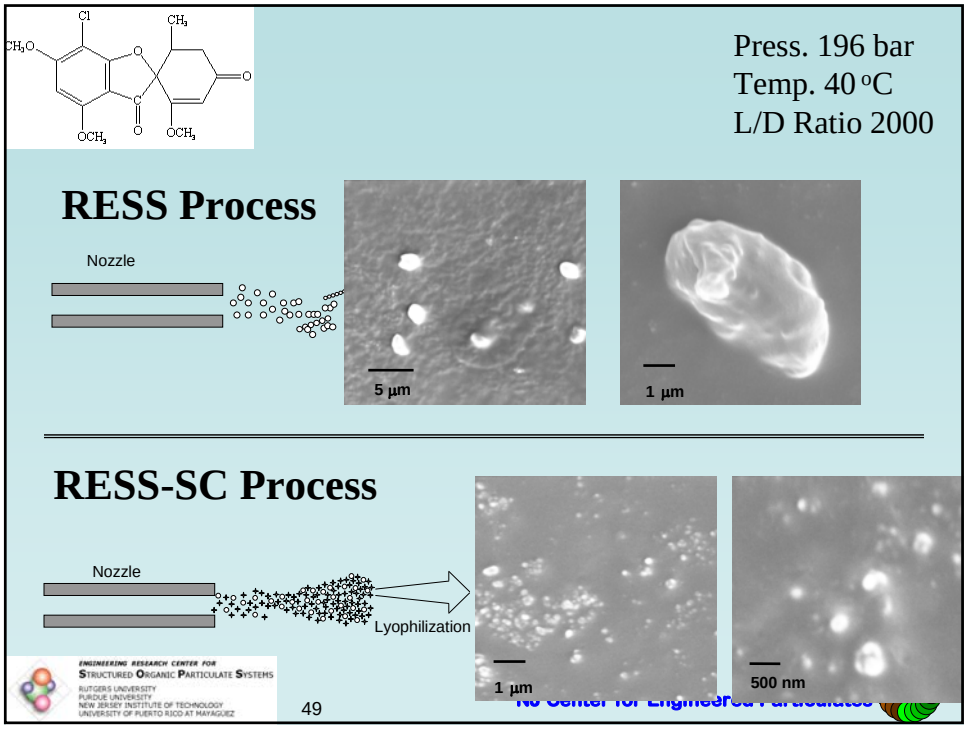


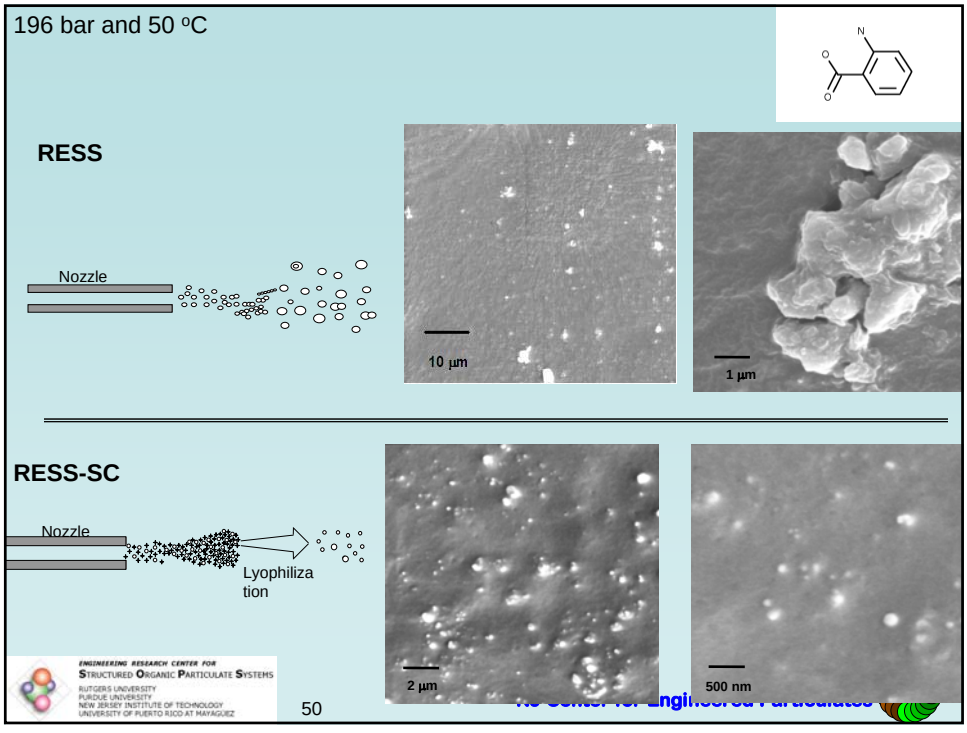
Conventional RESS process

RESS-SC process

[Here are menthol particles and are GF particles]

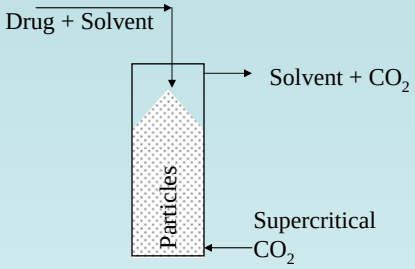
Thakur, Ranjit; Gupta, Ram B. *Industrial & Engineering Chemistry Research* (2005), 44(19), 7380-7387


Press. 196 bar
Temp. 40 °C
L/D Ratio 2000
RESS Process
Nozzle
5 µm
1 µm
RESS-SC Process
Nozzle
Lyophilization
1 µm
500 nm
49


196 bar and 50 °C
RESS
Nozzle
10 µm
1 µm
RESS-SC
Nozzle
Lyophiliza
tion
2 µm
500 nm
50

CO_2-insoluble drugs

Supercritical Anti-Solvent (SAS) process

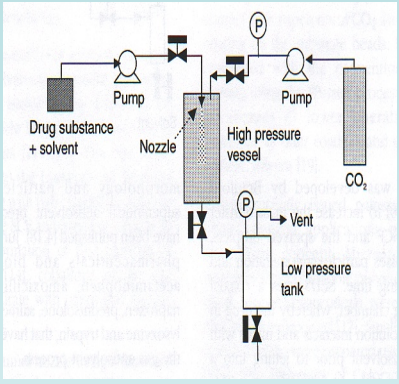


Mostly 1-5 μm particles of drugs or polymers are obtained

Variations:
- PCA (Precipitation with compressed antisolvent)
- SEDS (Solution enhanced dispersion by supercritical fluids)
- SAA (supercritical-assisted atomization)

Challenges with SAS Processes

- For most drugs precipitation of particles in the nanometer range not possible
- Broad size distribution of particles obtained in most cases
- Weak size control
- Harvesting of the particles; having continuous operation versus current batch mode



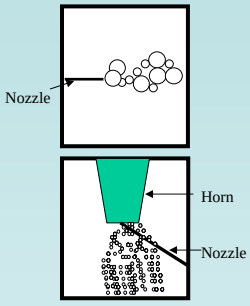
Solving Problems with SAS

- CO_2 is 100 fold more diffusive than liquids, but even greater mixing is needed
  - Most approaches to improve SAS or its versions are based on improved mass transfer
    - SEDS - developed and patented by Hanna and York and owned by University of Bradford; it is based on the use of coaxial nozzle
      - Led to much of the hype and subsequent let down associated with use of SCF based processing
    - Subramaniam et al. developed a process that involved deliberate generation of high energy sonic waves patented by the University of Kansas.
      - Mass-transfer is not as strong as thought to be
    - Other approaches are concerned with variations of the nozzle geometry

Recent Advancement from Auburn University:

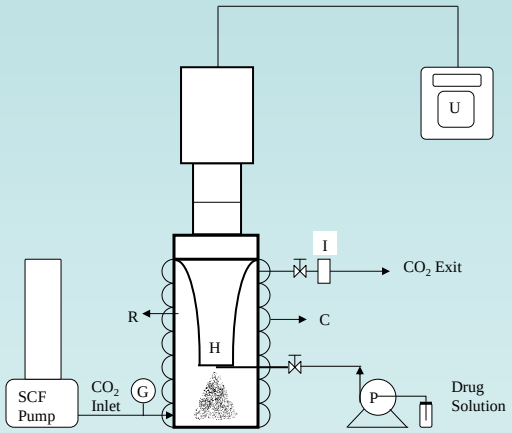
Supercritical Anti-solvent with Enhanced Mass Transfer (SAS-EM)

- A significant improvement in SAS
- Drug solution is atomized by a vibrating surface
- Intensity of vibration controls mass transfer rate
- Particle size is easily controlled



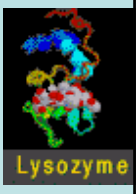
Gupta, R.B.; Chattopadhyay, P. *US Patent 6,620,351*; September 16, 2003.

SAS-EM Process



NJ Center for Engineered Particulates

Lysozyme Particles from SAS-EM



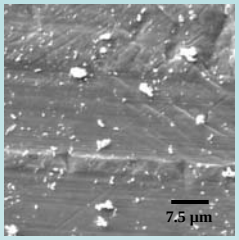
Power supplied (W)	Size Num. avg. (nm)	Size Vol. avg. (nm)	Standard deviation (nm)
0	1200	2000	640
12	730	1040	490
30	650	860	410
60	240	260	75
90	260	370	180
120	230	360	160

Experiments conducted at 96.5 bar and 37°C using 5 mg/ml lysozyme dissolved in DMSO

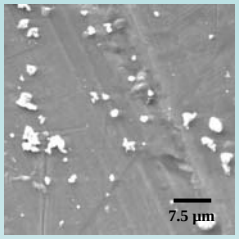
Chattopadhyay, P.; Gupta, Ram B. *AIChE J.* (2002), 48, 235-244

NJ Center for Engineered Particulates

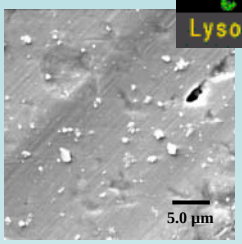
Lysozyme Particles from SAS-EM



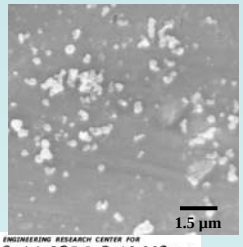
(a) 0 W, x 2,000



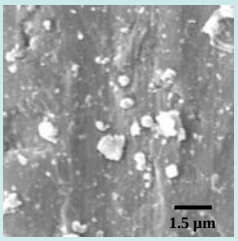
(b) 12 W, x 2,000



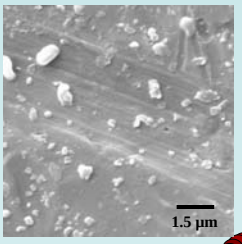
(c) 30 W x 3,000



(a) 60 W, x 10,000

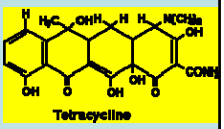


(b) 90 W, x 10,000



(c) 120 W x 10,000

Tetracycline Particles from SAS-EM

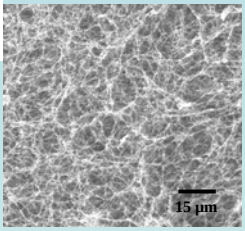


Power supplied (W)	Particle size Num. avg. (nm)	Particle size Vol. avg. (nm)	Standard deviation (nm)
0	800	1100	970
30	270	400	380
60	200	230	172
90	184	200	133
120	110	125	75

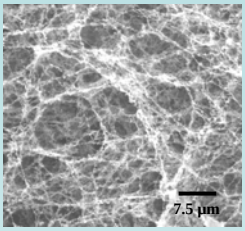
Experiments conducted at 96.5 bar and 37°C using 5 mg/ml tetracycline dissolved in THF

Chattopadhyay, P.; Gupta, Ram B. *Ind. Eng. Chem. Res.* (2001), 40(16), 3530-3539

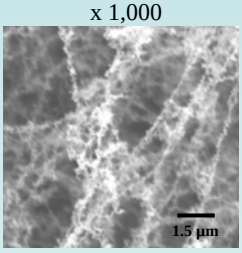
SEM of Tetracycline Fibers from SAS



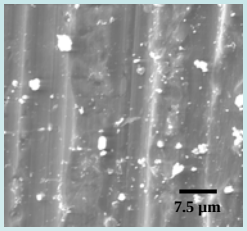
x 1,000



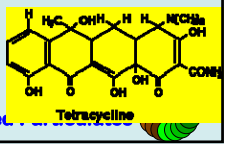
x 2,000



x 10,000



x 2,000



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PURDUE UNIVERSITY
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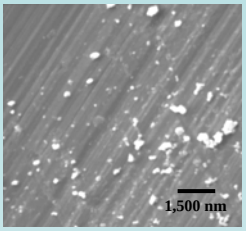
UNIVERSITY OF PUERTO RICO AT MAYAGUEZ

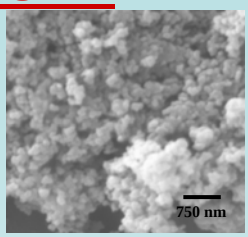
NJ Center for Engineered Particulates

SEM of Tetracycline Particles from SAS-EM

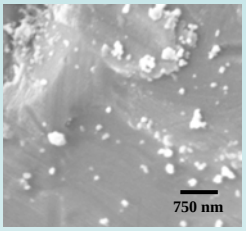


(a1) x 10,000

90 W

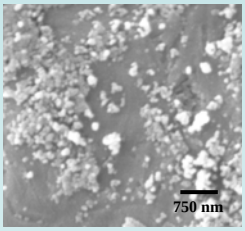


(a2) x 20,000

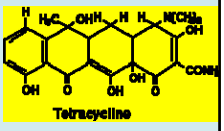


(a1) x 20,000

120 W



(a2) x 20,000



Mean size of the particles obtained in each case is (a1, a2) 400 nm; (b1, b2) 230 nm; (c1, c2) 200 nm; (d1, d2) 125 nm.

NJ Center for Engineered Particulates

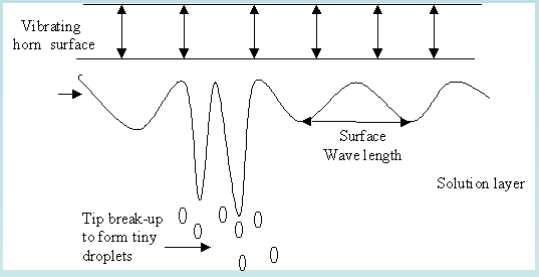
Atomization

SAS Re = 700

SAS Re = 3000

SAS-EM

Control of Atomization in SAS-EM



Scale-up

Increase Vibration Intensity → (Same Flow rate) → Size Reduction

Increase Vibration Intensity → (Increase Flow rate) → Same Size
More capacity!

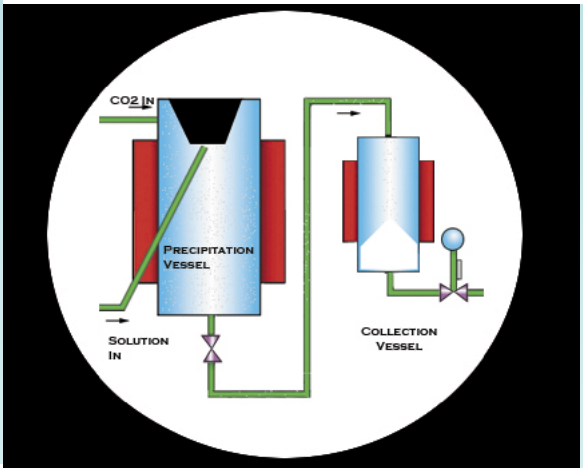
Commercialization

Patent Issued:
Method of forming nanoparticles and microparticles of controllable size using supercritical fluids with enhanced mass transfer, US Patent 6,620,351; September 16, 2003.

Technology Licensed:
Thar Technologies, Pittsburgh, PA
www.thartech.com

Scaled Up:
1 kg/day nanoparticles
Automated, computer controlled
Continuous collection

SAS-EM



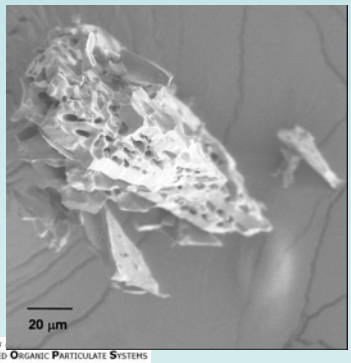
Continuous operation

Separation of precipitation and collection zones

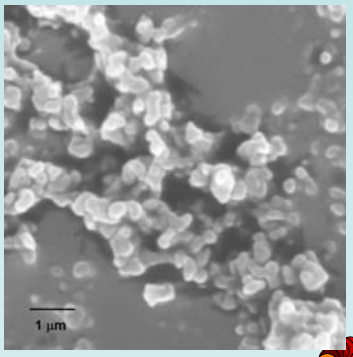
Microencapsulation of Nanoparticles for Sustained Release

- Dexamethasone phosphate

Microparticle from liquid antisolvent



Nanoparticles from SAS-EM



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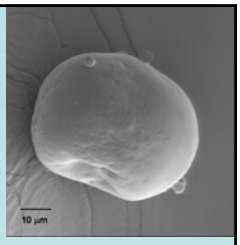
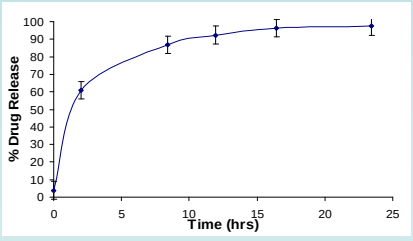
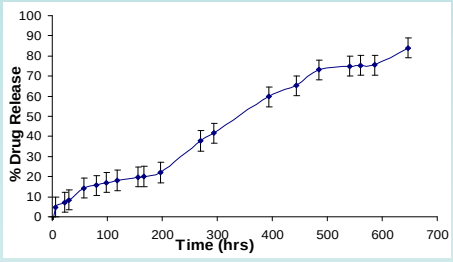
Sustained Release of Dexamethasone Phosphate by PLGA Microencapsulation





Encapsulated microparticles



Encapsulated nanoparticles

Thote, A.; Gupta, Ram B. *Nanomedicine*, 1, 85-90, 2005

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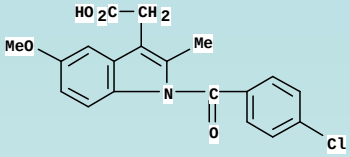
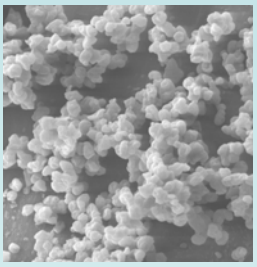
Indomethacin Loaded PLGA/Magnetite Nanoparticles





x 63,000

Chatopadhyay, Prathash; Gupta, Ram B. *Ind. Eng. Chem. Res.* (2002), 41(24), 6049-6058.

NJ Center for Engineered Particulates

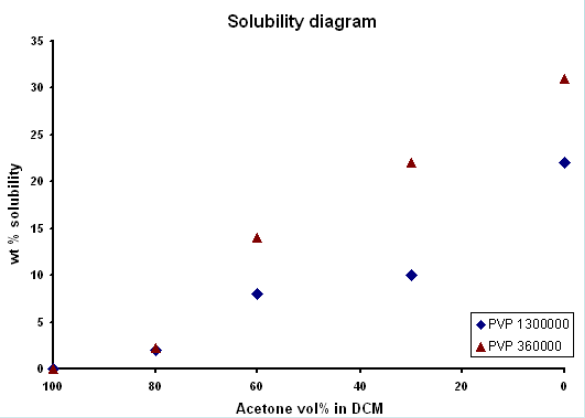
Thermodynamically Good and Poor Solvents

- The chain will expand in a *good solvent*, in order to increase its favorable interaction with the medium

- The chain will contract in a *poor solvent*, in order to reduce the unfavorable interaction

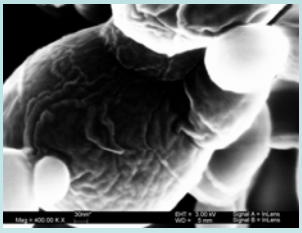
NJ Center for Engineered Particulates

Solubility of PVP into DCM and Acetone

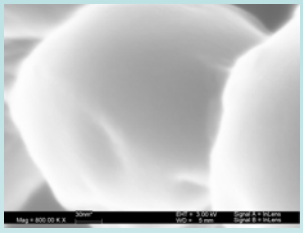


The solubility (in wt%) of PVP MW 1,300,000 and 360,000 in DCM/acetone solvents for room temperature (22 C) and atmospheric pressure.

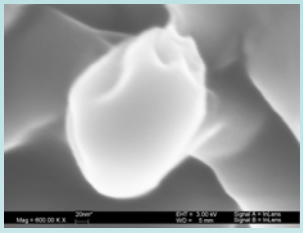
Effects of Poor Solvent on Surface Morphology



No Poor Solvent



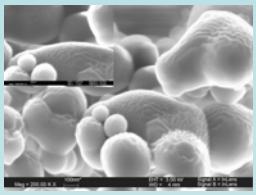
Poor Solvent = 20 %



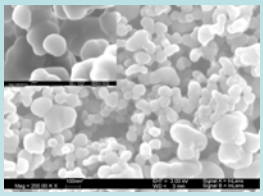
Poor Solvent = 60 %

Good Solvent: dichloromethane, Pressure: 82 Bar, Poor Solvent: acetone Temperature: 35 C, Polyvinylpyrrolidone (Mw: 1,300,000), Nozzle ID: 127 µm, Solute Concentration: 2%, Flow rate: 0.2 ml/min

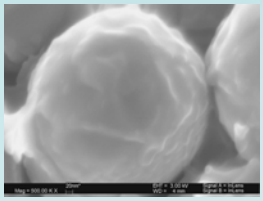
Effects of Poor Solvent on Surface Morphology



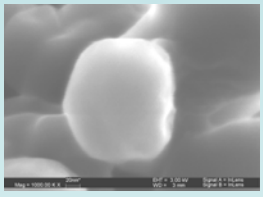
(a)



(b)



(c)



(d)

2-wt % solutions of PVP (MW 360,000) in (a and c) DCM and (b and d) DCM/acetone (40:60 v/v) for the chamber pressure (a and b) 82 bar and (c and d) 79 bar. Temperature 35°C, liquid flow rate 0.2 ml/min, nozzle ID 40 um.

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71

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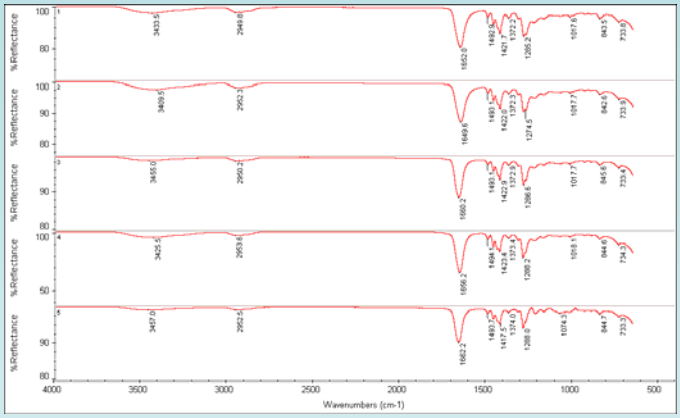
Effects of Poor Solvent on Surface Morphology



FTIR Spectroscopy - (a) Original PVP and PVP particles at 82 bar, 127 um nozzle ID at (b) 0%, (c) 20% and (d) 60% acetone ratios in dichloromethane

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72

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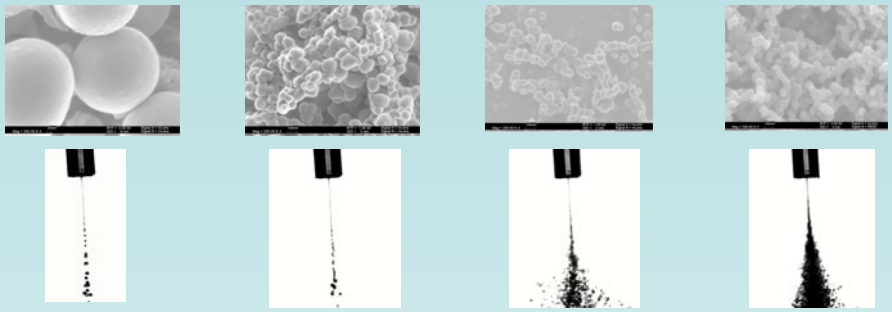
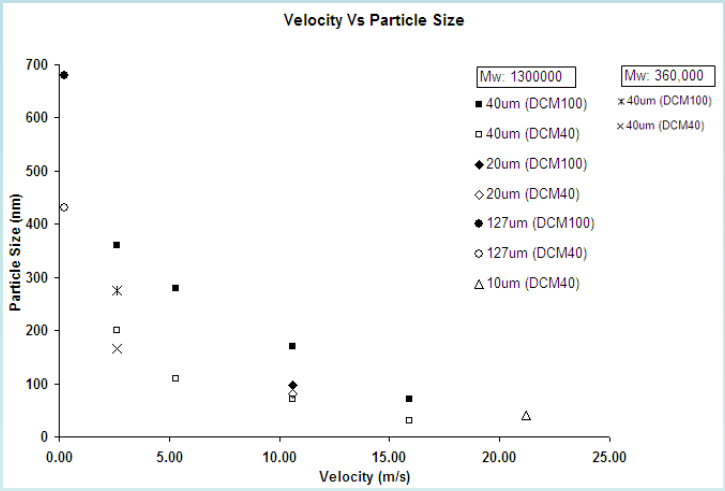
Effects of Jet Velocity on Particle Formation



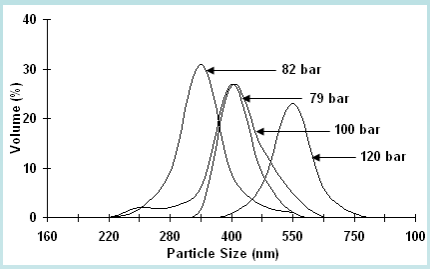
2.65 m/s	5.3 m/s	10.61 m/s	15.91 m/s
Re: 370	Re: 740	Re: 1477	Re: 2215

Nozzle ID: 40 um, Pressure: 82 Bar, Temperature 35 C, Solvent: DCM; Polyvinylpyrrolidone-Mw 1,300,000; Solute Concentration: 2%

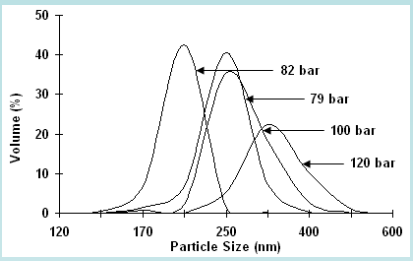
Solution Velocity Vs Particle Size



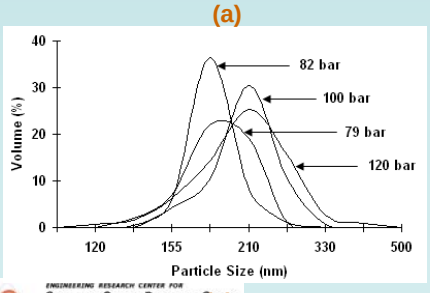
Effects of Pressure on Particles Size



(a)



(b)



(c)

(a) DCM,

(b) DCM/acetone (80:20 v/v),

(c) DCM/acetone (40:60 v/v)

PVP 2 wt%, Temperature 35°C, liquid flow rate 0.2 ml/min, nozzle ID 40 um

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75

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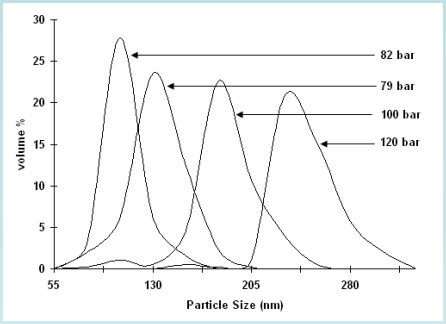
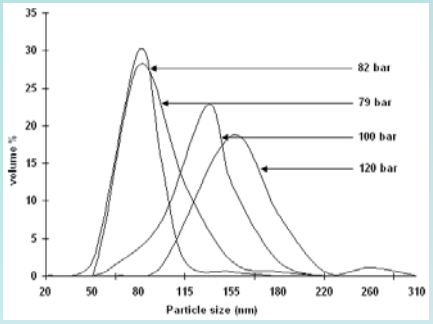
Effects of Pressure on Particles Size



(a)



(b)

(a) DCM, and (b) DCM/acetone (40:60 v/v)

Temperature 35°C, liquid flow rate 0.2 ml/min, nozzle ID 20um.

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76

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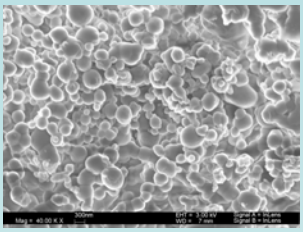
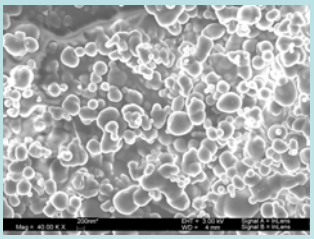
Effects of Mw on Particles



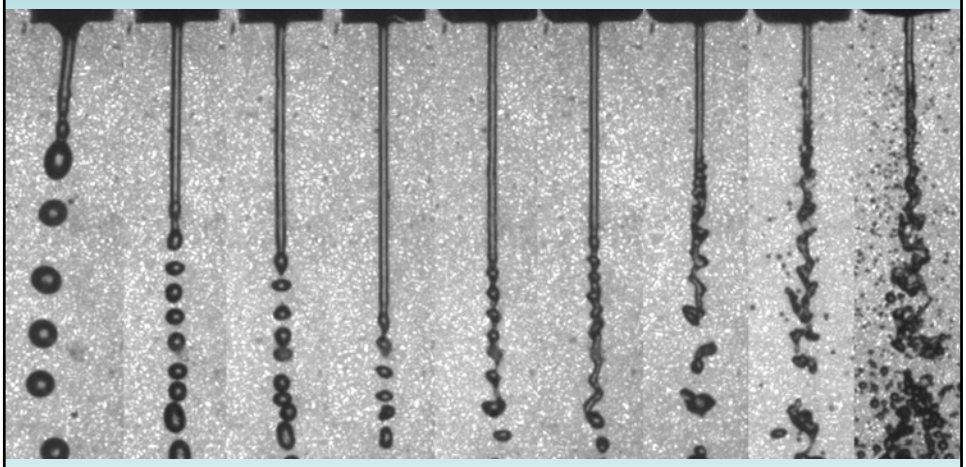
Nozzle ID: 40um
Pressure: 82 Bar
Temp: 35 C **Qsol:** 0.2 ml/min
PVP (Mw: 1,300,000)
Solvent: DCM
Solute Concentration: 2%



Nozzle ID: 40um
Pressure: 82 Bar
Temp: 35 C **Qsol:** 0.2 ml/min
PVP (Mw: 360,000)
Solvent: DCM
Solute Concentration: 2%

	Pressure	DCM(100) /Acetone(0)	DCM(40) /Acetone(60)
Mw: 1,300,000	79 Bar	$340_{\pm 150}$ nm	$200_{\pm 80}$ nm
	82 Bar	$290_{\pm 120}$ nm	$250_{\pm 55}$ nm
Mw: 360,000	79 Bar	$310_{\pm 150}$ nm	$180_{\pm 90}$ nm
	82 Bar	$280_{\pm 100}$ nm	$170_{\pm 50}$ nm

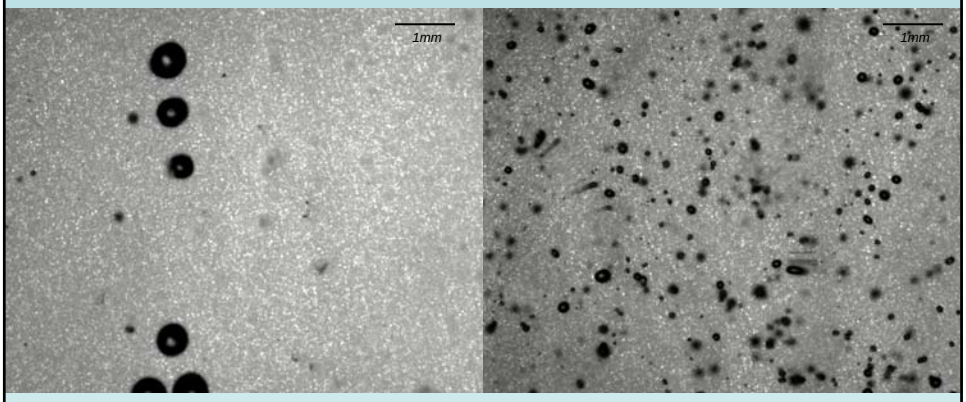
Jet length evolution with increasing injection speeds



v=0.47 v=0.54 v=0.67 v=1.0 v=1.2 v=1.4 v=1.6 v=2.0 v=3.0

Ethanol injected through a 178 micron nozzle at 35^{0}C and 80bar. Unit in m/s.

Droplet Comparison - with and without ultrasound



without ultrasound ***with ultrasound (2watts)***

Both operating at 40bar and 298k. DCM flow rate at 2ml/min.

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79

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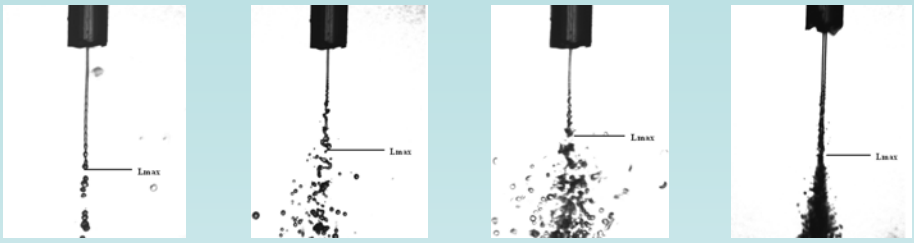
Solution Jet Breakup Into SC CO_2



(a) (b) (c) (d)

The jet breakup length of (a) acetone, nozzle, flow rate 0.08 ml/min; (b) DCM, nozzle, flow rate 0.12 ml/min; (c) DCM/acetone (40:60, v/v), nozzle, flow rate 0.15 ml/min; (d) PVP MW 1,300,000 in DCM/acetone (40:60 v/v) nozzle, flow rate 0.8 ml/min. The chamber pressure 82 bar and temperature 35°C.

Conventional Micro-Nozzles – 40 micron ID

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80

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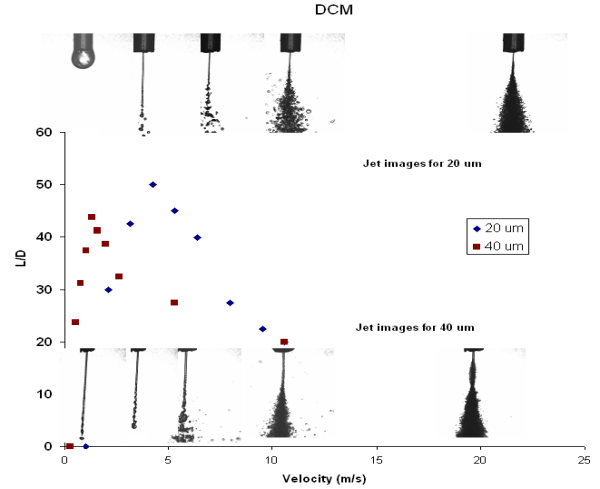
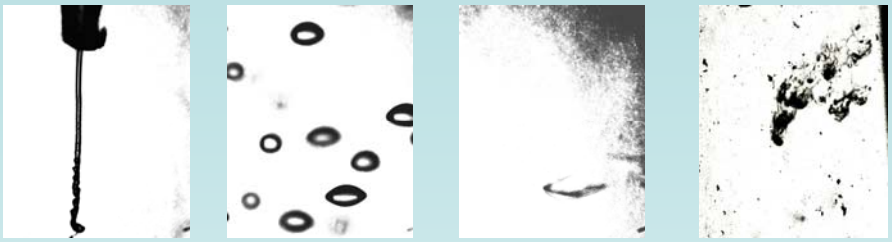
Solution Jet Breakup Into SC CO_2



Jet Breakup of DCM into SC CO_2 at 35 C and 82 bar

Hydrodynamic Mixing of Solution Jets with SC CO_2



(a) (b) (c) (d)

flow rates 0.2 ml/min and 0.4 ml/min for the chamber pressure of 82 bar. Distance below the tip of the pinched jet: (a) 0mm, flow rate 0.2 ml/min; (b) 25 mm, flow rate 0.2 ml/min; (c) 50 mm, flow rate 0.2 ml/min; (d) 50 mm, flow rate 0.4 ml/min.

NanoCoatings Using Supercritical Fluids

Motivation and Objectives

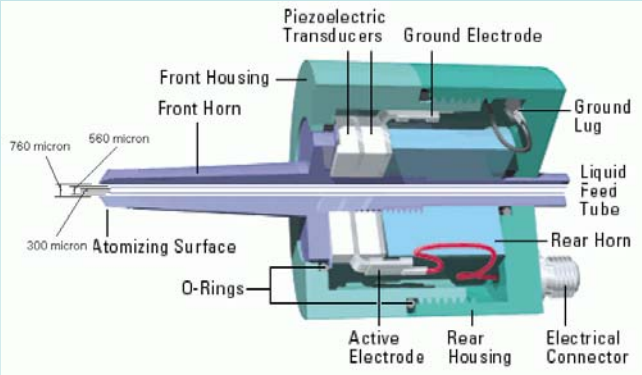
- Develop new techniques to control the coating efficiency and aggregation
- To study the effects of different operational parameters on the particle size and morphology.
- To investigate and compare different methods of particles coating using Supercritical Fluids.

Direction for Particles Coating Work

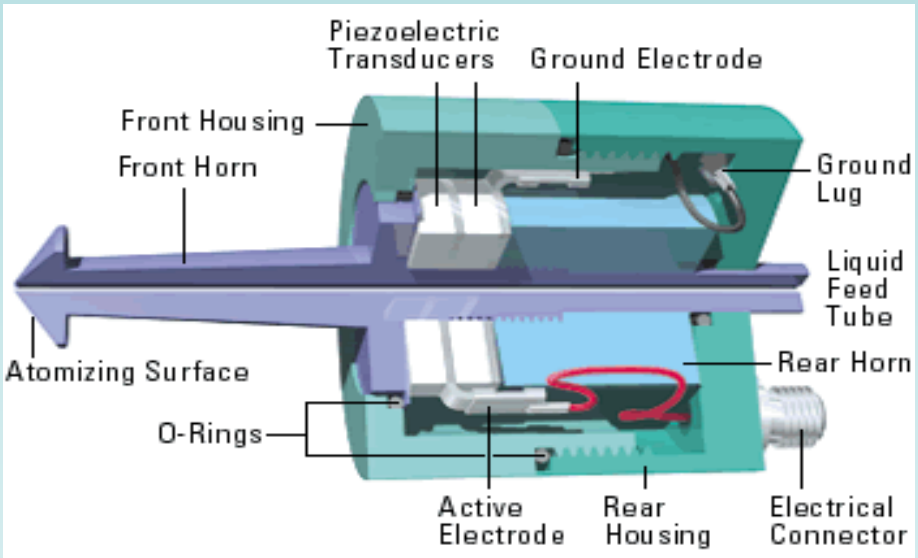
- Particles Coating Using Supercritical As Antisolvent (SAS) technology
  - Investigation of particles coating of different **sizes** of host particles
  - Methods to **suppress the aggregation** using various techniques like ultrasonic nozzle, poor solvent concept
- Particles Coating using Rapid Expansion of Supercritical Fluids Solution (RESS) technology
  - Effects of **pressure** on degree of agglomeration of coated particles
  - Effects of **ratio** of guest to host particles on agglomeration of coated particles
- Particles Coating Using Particles From Gas Saturated Solution PGSS technology
  - Effects of **pressure** on degree of agglomeration of coated particles
  - Effects of **ratio** of guest to host particles on agglomeration of coated particles

Particles Coating using Supercritical As Antisolvent

Configurations of Coaxial Ultrasonic Nozzle



Structure of Ultrasonic Nozzle- NJIT Design



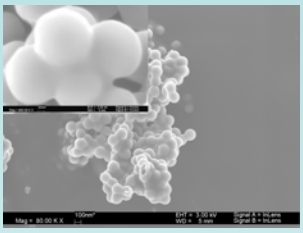
Ultrasonic nozzle and high pressure view cell

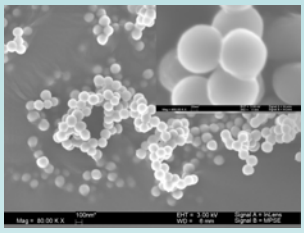
Water bath and solution pump

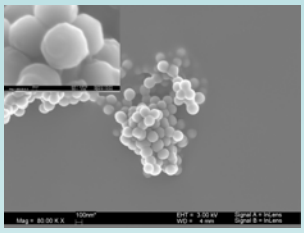
Precipitation vessel

Solvent Effect on Coating

PMMA Coated Silica (180nm) Particles







DCM | **DCM50 : Acetone 50** | **Acetone**

Guest to Host Particles: 1:10 wt/wt%

Solvent to host particles: 100:2 vol/wt%

Host Particles: Silica 180 nm size

Guest Polymer: Polymethyl methacrylate (PMMA)

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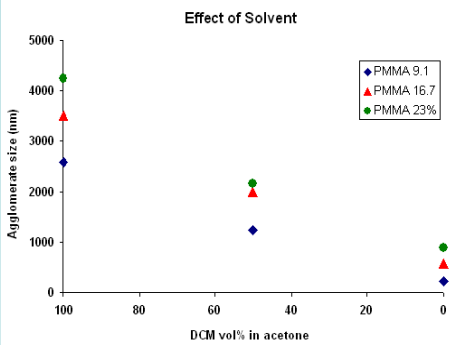
Effect of Parameters on Coating

PMMA Coated Silica (180nm) Particles

Summary



Ultrasonicating for 1 min. (a) DCM; (b) DCM 50 vol% in acetone; (c) Acetone

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91

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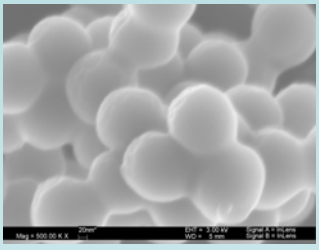
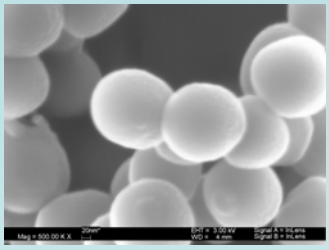
Effect of Poor Solvent on Coating

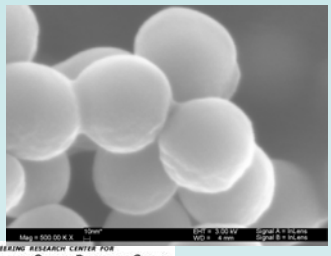
PMMA Coated Silica (180nm) Particles



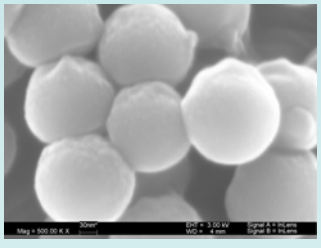
DCM



Acetone



DCM 70 - Hexane 30



Acetone 70 - Hexane 30

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92

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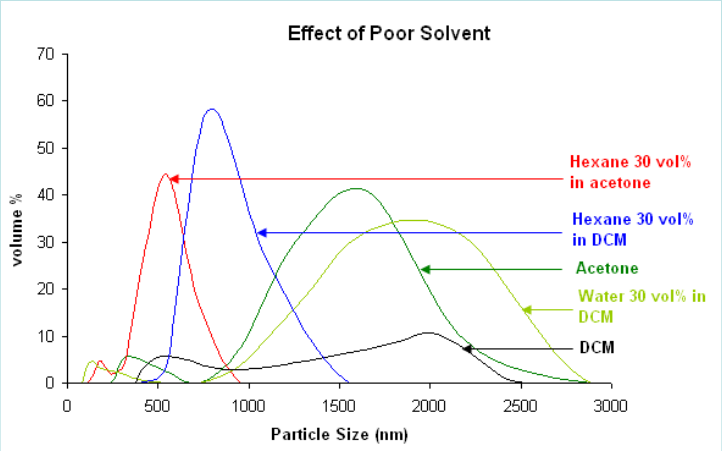
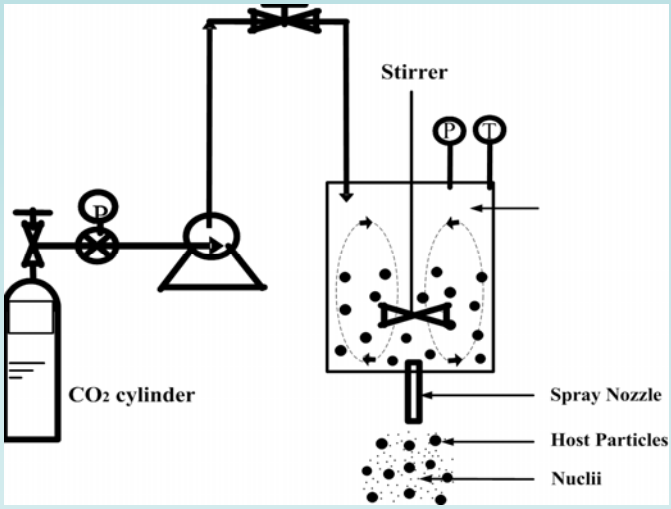
Effect of Poor Solvent on Coating

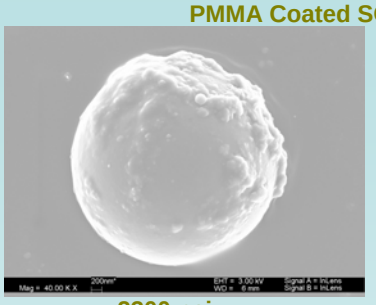


Particles Coating using *RESS*

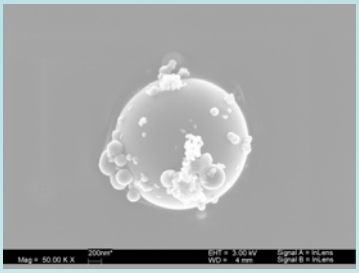


Effect of Pressure on Coating

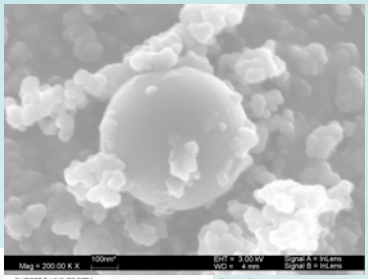
PMMA Coated SO E2 (2 um) Particles



2300 psi



1500 psi



Unexpanded

Polyvinyl difluoride (PVDF) to Silica: 1:10 w/w%

Temp: 65 C,

Capillary Nozzle: 508 um

Stirrer Speed: 90 rpm

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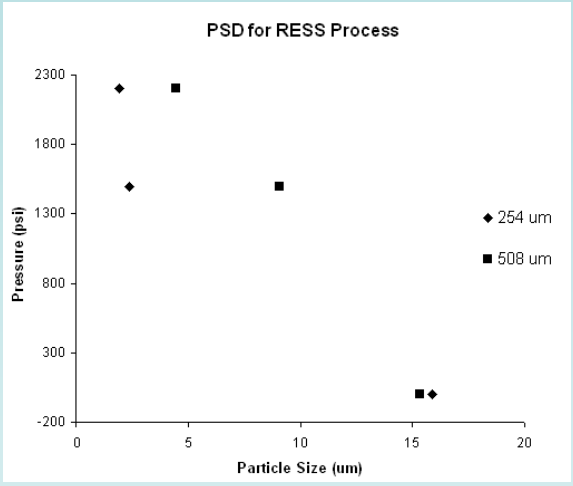
Effect of Pressure on Coating



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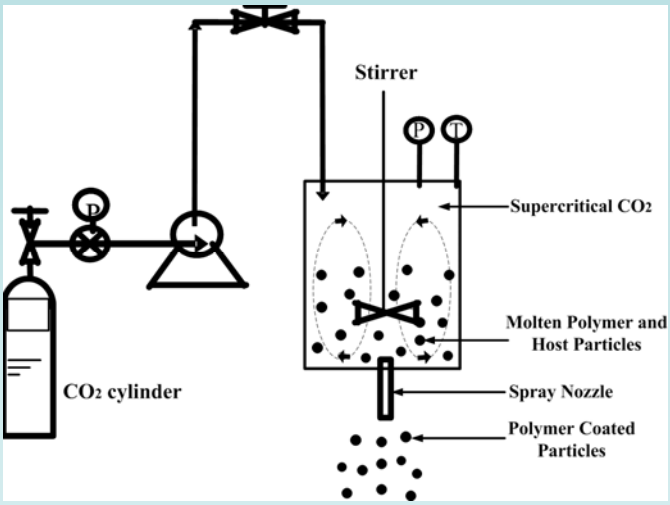
Particles Coating Using *PGSS*



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97

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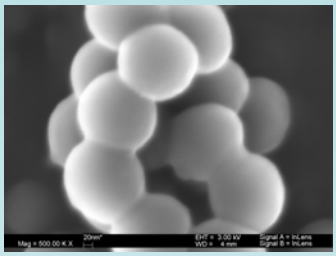
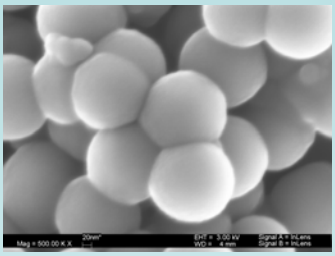
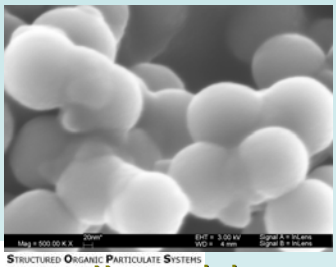
Effect of Pressure on Particles Coating



2300 psi



1500 psi



Unexpanded

65C, 90 RPM, 508um, PEG
9.1wt% of silica 180nm

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98

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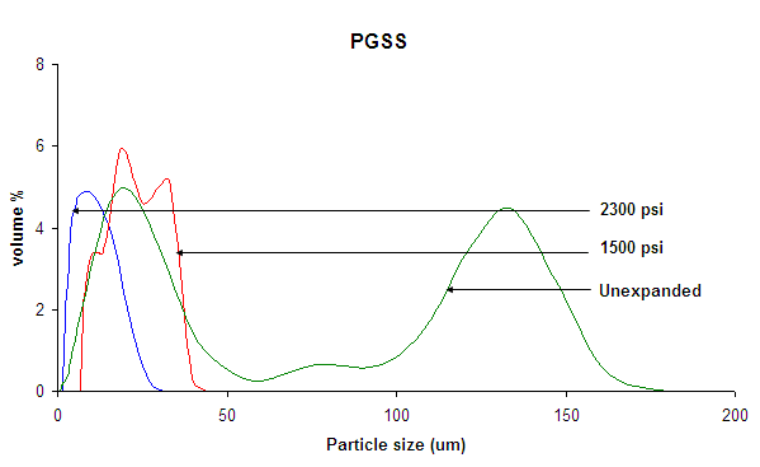
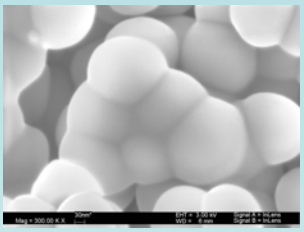
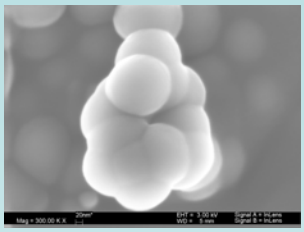
Effect of Pressure on Particles Coating



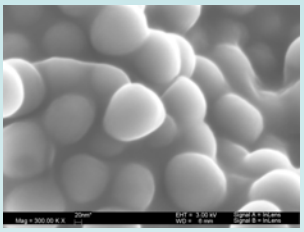
Effect of Pressure on Particles Coating



2300 psi



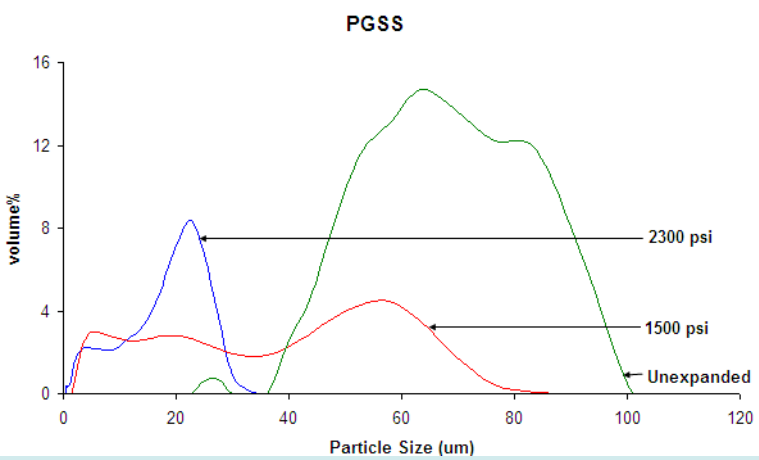
1500 psi



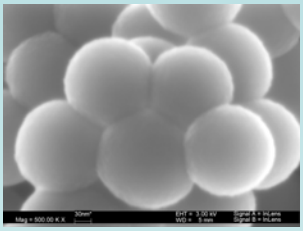
Unexpanded

65C, 90 RPM, 508um, PEG
16.7wt% of silica 180nm

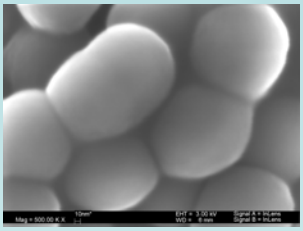
Effect of Pressure on Particles Coating



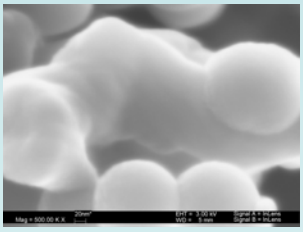
Effect of Pressure on Particles Coating



2300 psi



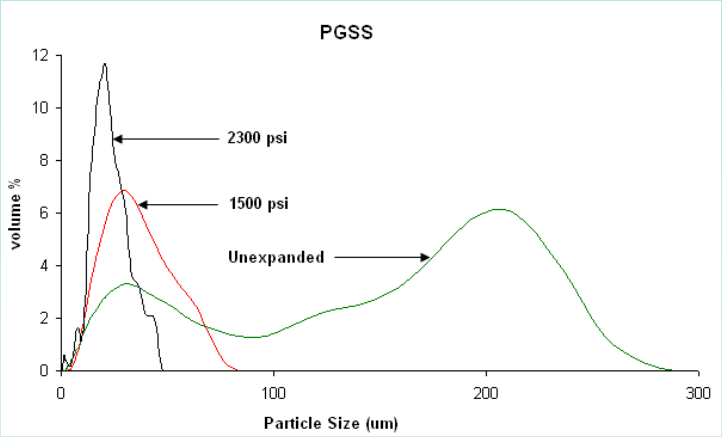
1500 psi

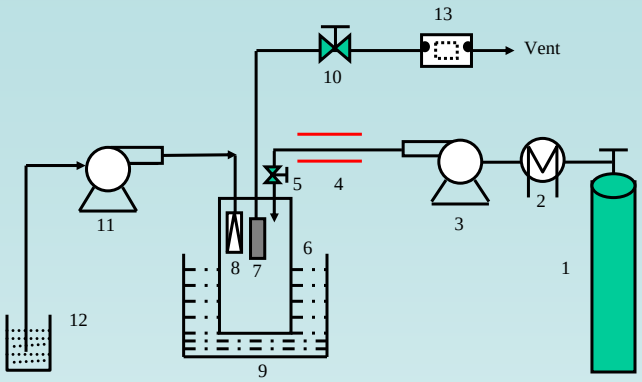


Unexpanded

65C, 90 RPM, 508um, PEG
23wt% of silica 180nm

Effect of Pressure on Particles Coating



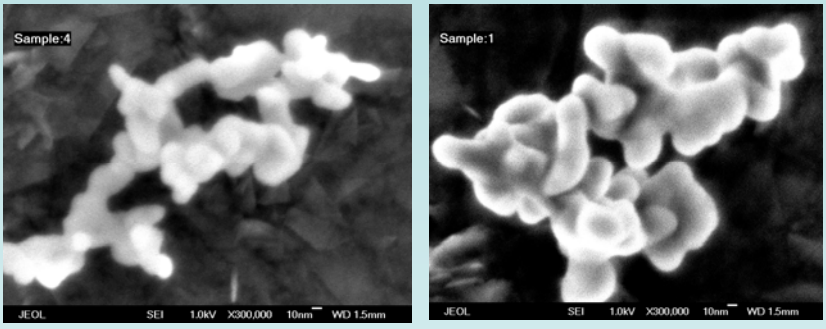


Schematic Diagram of Fine Particle SAS Coating Process

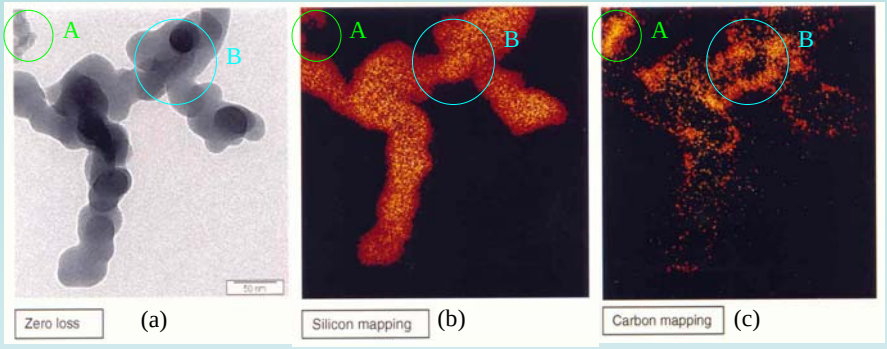
1. CO_2 Cylinder, 2. Cooling, 3. CO_2 pump, 4. Pre-heating, 5. On-off valve,
6. High pressure vessel, 7. Filter, 8. Capillary tube, 9. Water bath, 10. Needle valve,
11. HPLC pump, 12. Suspension, 13. Flow meter

- **Experiment**
  - **Coating Material:**
    Poly lactide-co-glycolide (PLGA, MW, 12,000, 50/50).
    Eudragit RL 100 (copolymer of acrylic and methacrylic acid esters, MW: ~150,000).
  - **Host Particles**:
    Silica particles, 16 nm (hydrophobic), 20 nm (hydrophilic), 500 nm (synthesized).
  - **Operating Parameters**:
    a. Polymer concentration (mg /ml): 4.0-13.0.
    b. Polymer weight fraction (%): 12.5, 16.7, 25, 50.
    c. Pressure (bars): 1300-1600 psi.
    d. Temperature: 32.0-38.0 ^{o}C.
  - **Characterization**: FESEM, TEM-EELS, FT-IR, TGA, PSD.

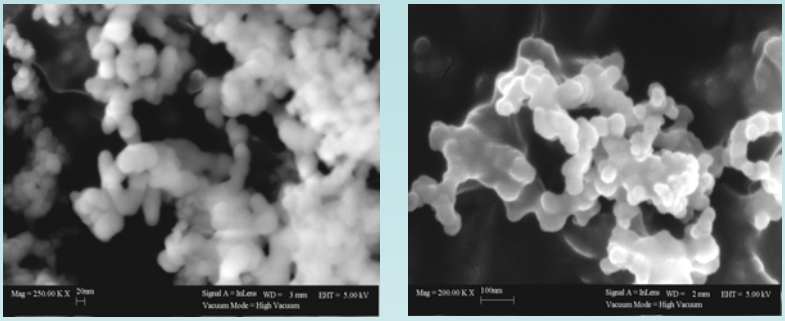
- **Results of nano-size particle coating**



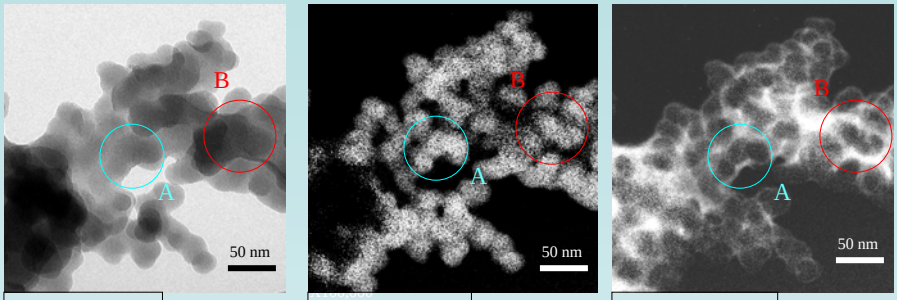
SEM pictures of uncoated and coated hydrophobic silica nanoparticles.



TEM-EELS photographs of coated hydrophobic silica nanoparticles.

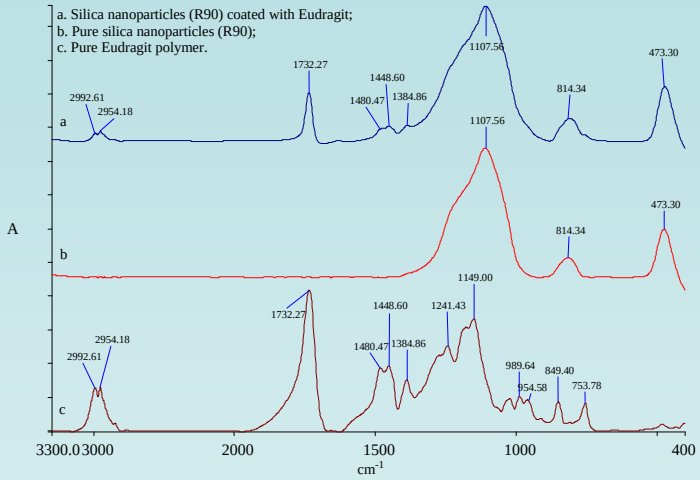


SEM pictures of coated and uncoated hydrophilic silica nanoparticles.



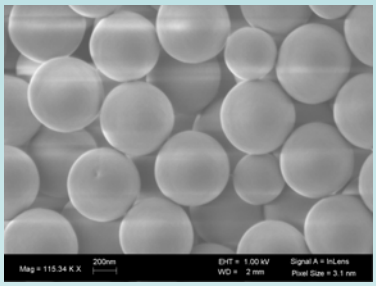
TEM-Zero Loss (a) Silicon Mapping (b) Carbon Mapping (c)

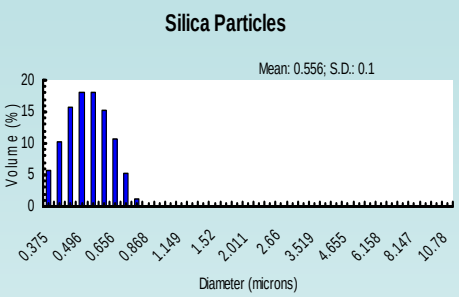
TEM-EELS photographs of coated hydrophilic silica nanoparticles.



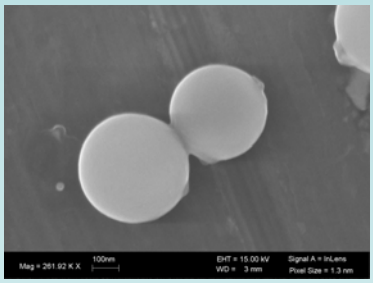
FT-IR patterns of uncoated and coated hydrophilic silica nanoparticles

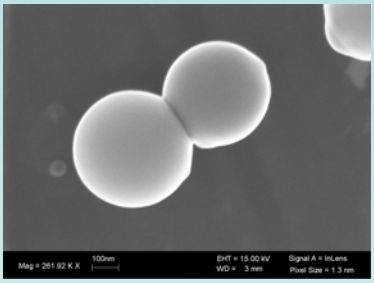
- **Results of sub-micron particle coating**



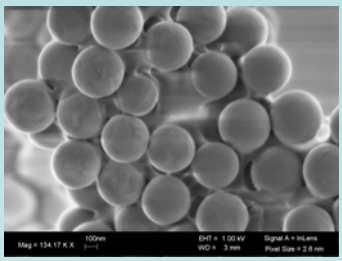


Uncoated silica particles.

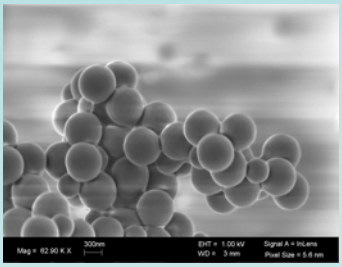




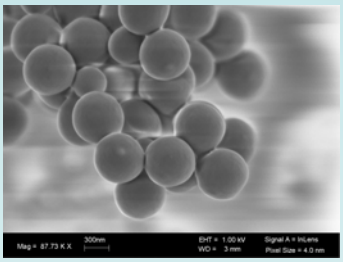
Coated silica particles re-dispersed in EtOH and sonicated for 3 minutes (25%). (a) Coated silica particles. (b) Coated particle after 15 min bombard with electron beam.



a



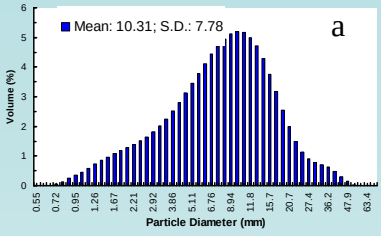
b

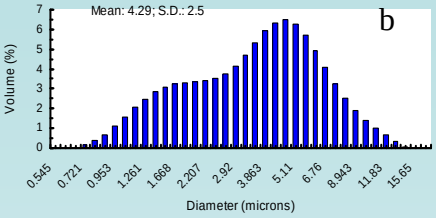


c

SEM pictures of coated silica particles. a). 25.0%; b). 16.7%; c). 12.5%.

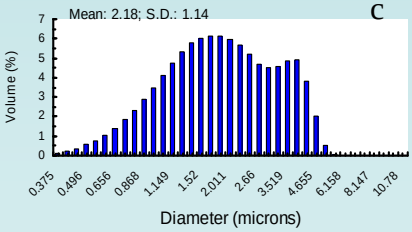
(33 °C, 1300 psi, 10 mg/ml, 0.8 ml/min).

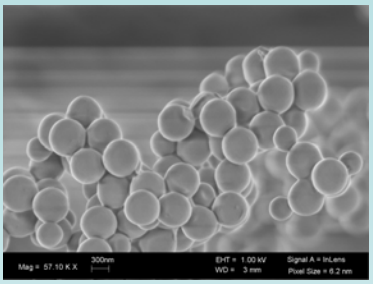




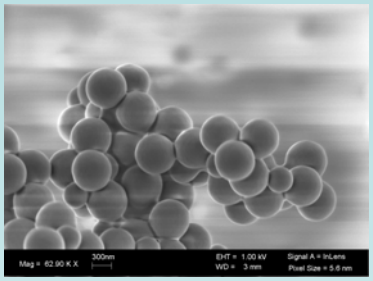
Size of coated silica particles. a). 25.0%; b). 16.7%; c). 12.5%.

(33 °C, 1300 psi, 10 mg/ml, 0.8 ml/min).

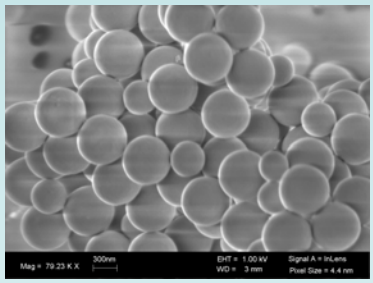




a



b



c

SEM pictures of coated silica particles. a). 13 mg/ml; b). 10 mg/ml; c). 4 mg/ml.

(33 °C, 1300 psi, 16.7%, 0.8 ml/min).

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115

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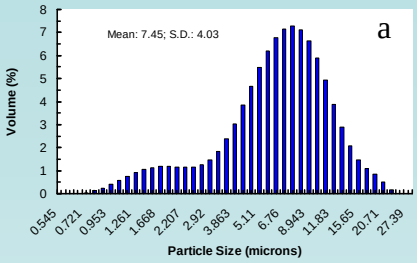

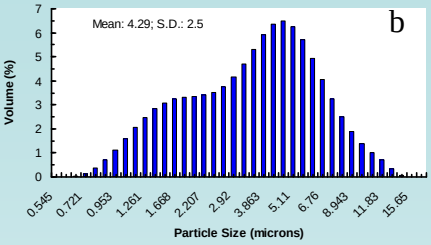

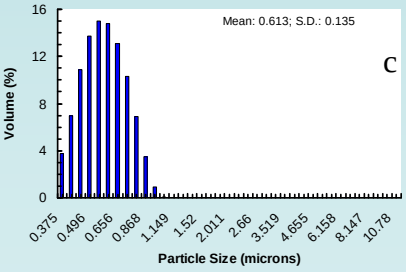

Size of coated silica particles. a). 13 mg/ml; b). 10 mg/ml; c). 4 mg/ml.

(33 °C, 1300 psi, 16.7%, 0.8 ml/min).

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116

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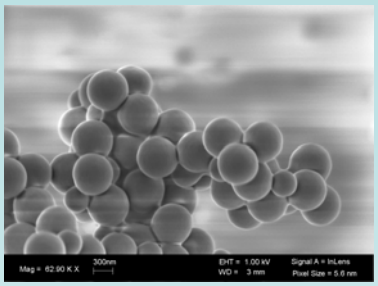
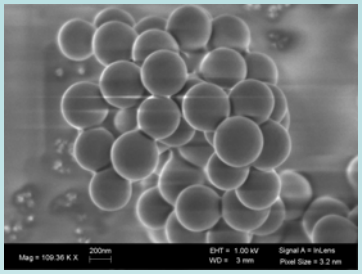
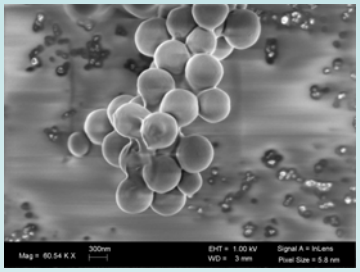


a



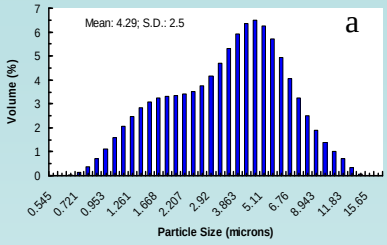
b

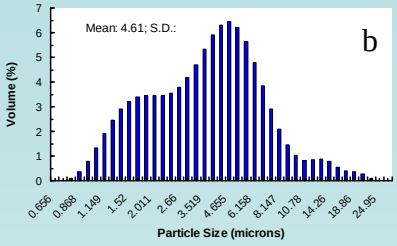


c

SEM pictures of coated silica particles. a). 33 °C; b). 38 °C; c). 42 °C.

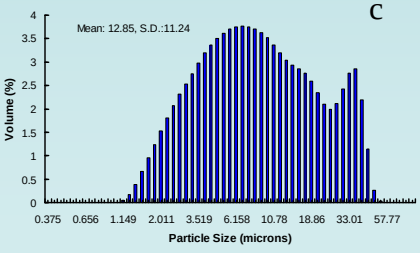
(10 mg/ml, 1300 psi, 16.7%, 0.8 ml/min).

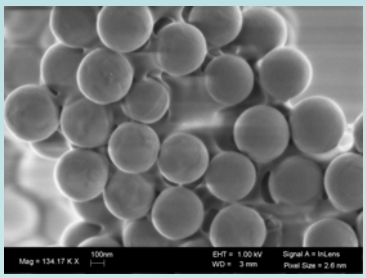




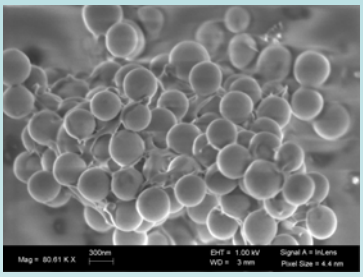
Size of coated silica particles. a). 33 °C; b). 38 °C; c). 42 °C.

(10 mg/ml, 1300 psi, 16.7%, 0.8 ml/min).



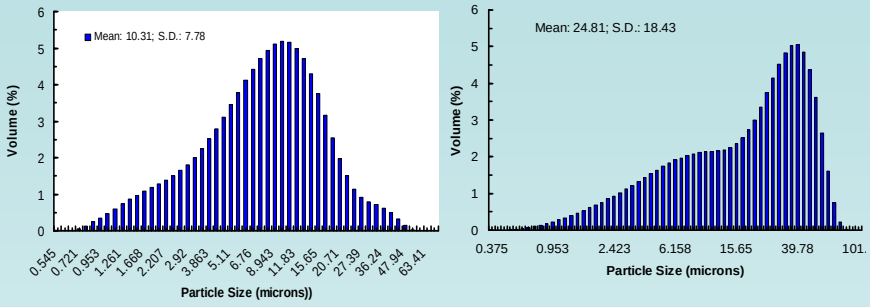


a



b

SEM pictures of coated silica particles. a). 1300 psi; b). 1600 psi. (10 mg/ml, 33 °C, 25%, 0.8 ml/min).



Size of coated silica particles. a). 1300 psi; b). 1600 psi. (10 mg/ml, 33 °C, 25%, 0.8 ml/min).

- **Concluding Remarks – Silica coating**
  - **The silica nanoparticles were successfully coated or encapsulated within polymer by SAS processing using SC CO_2.**
  - **Silica nanoparticles coated with polymer appear to form loose agglomerates.**
  - **Polymer concentration and weight fraction have major effects on the agglomeration of coated particles.**
  - **At higher pressure, sintering of coated particles facilitates agglomeration of coated particles due to the plasticization of coating polymer. At lower pressure, agglomeration of coated particles was attributed to the sticking action between neighboring viscous coated particles when the suspension contacts SC CO_2.**

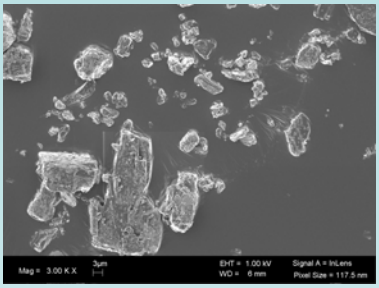
Continued.

- **Operating temperature has little effect on agglomeration of coated particles when the temperature is well below the glass transition temperature, T_g, of the coating polymer. When temperature is close to or above T_g, the polymer coating on the surface of particle sinters resulting in strong agglomeration.**
- **The SAS process is a promising technique for fine particle coating/encapsulation requiring much less organic solvent than conventional wet coating processes and can also treat much finer particles.**

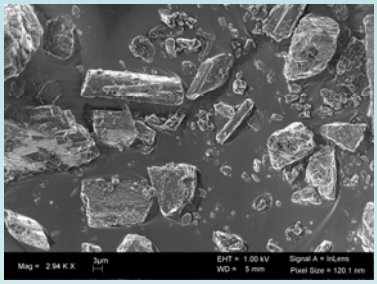
Drug Particle Coating or Encapsulation Using SAS for Drug Delivery

- **Experiment**
  - **Coating Material**: Poly lactide-co-glycolide (PLGA, MW, 12,000, 50/50).
  - **Host Particles**: Hydrocortisone (HC) (20-40 microns).
  - **Operating Parameters**:
    a. Polymer concentration (g /ml): 1.0%;
    b. Ratio of polymer to particles (w/w): 1:4, 1:2,1:1;
    c. Pressure (bars): 1300 psi;
    d. Temperature: 36.0 ^{o}C.
  - **Characterization**: FESEM, HPLC.

- **Results**

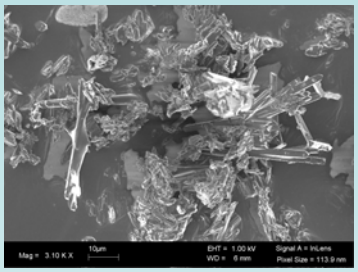


(a)

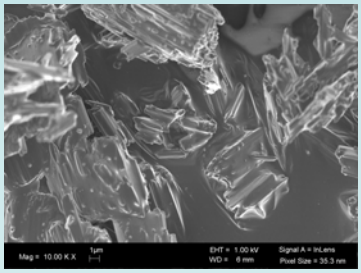


(b)

Uncoated HC particles.



(a)



(b)

Coated HC particles with PLGA at ratio of 1:4.

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125

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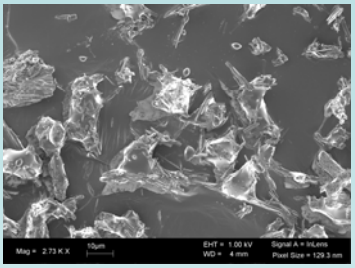
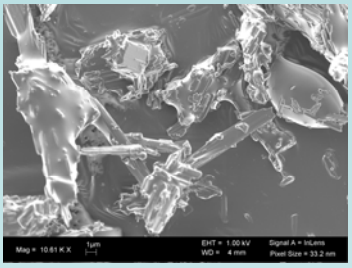
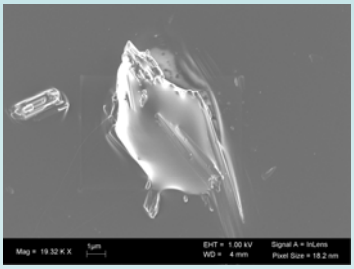


(a)



(b)



(c)

Coated HC particles with PLGA at ratio of 1:2.

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126

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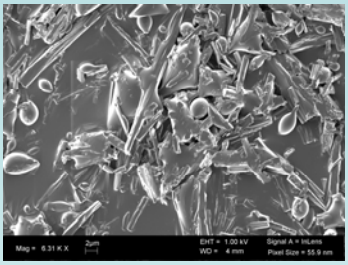
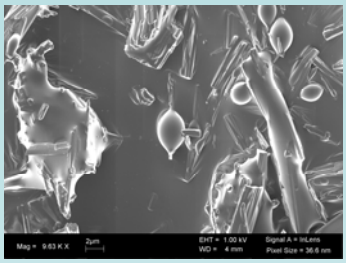
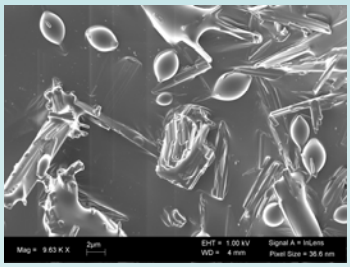


(a)

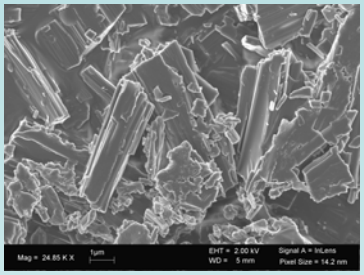


(b)

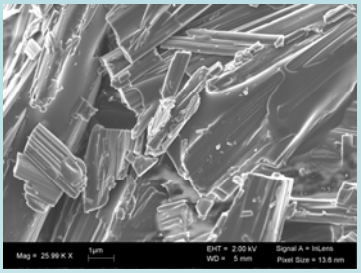


(c)

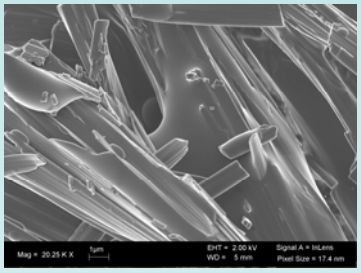
Coated HC particles with PLGA at ratio of 1:1.



(a)



(b)



(c)

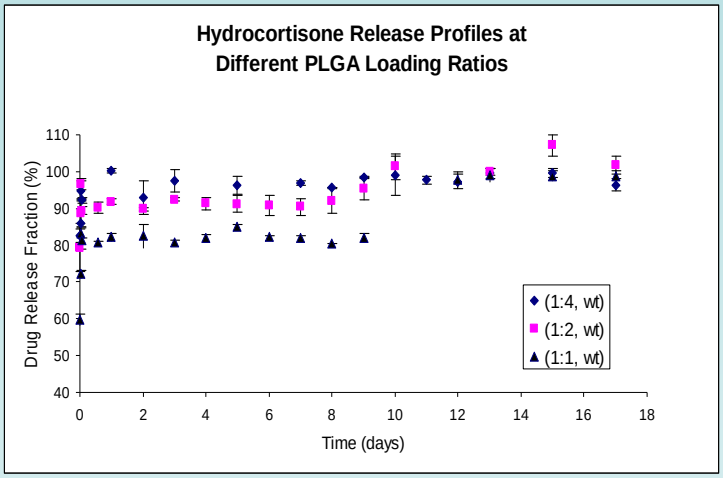
Co-precipitation of PLGA and HC from solution at ratio of 1:1.

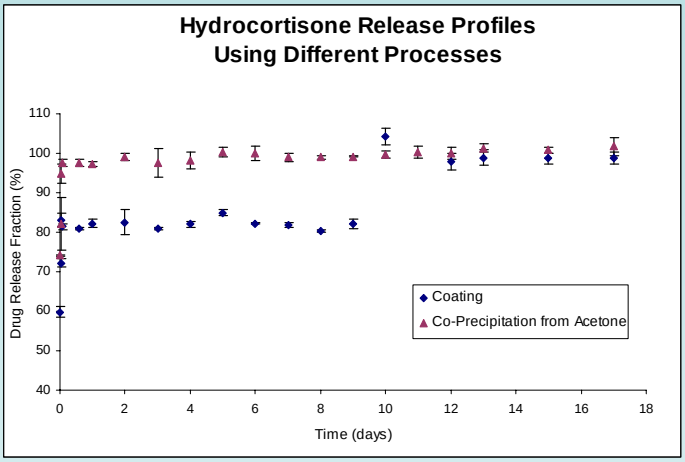
Drug Loading Test

No.	Ratio of HC to PLGA (wt.)	Theoretical HC Loading (wt%)	True Loading (wt.%)	Average (%)	SD
1	1:4	80%	82.2	80.8	±2..9
			82.7		
			77.5		
2	1:2	66.7%	63.6	64.9	±4.1
			69.5		
			61.7		
3	1:1	50%	45.1	46.4	±1.2
			46.6		
			47.5		
4	1:1 Co-presipitation from DCM and EtOH	50%	46.3	48.9	±3.4
			47.7		
			52.7		
5	1:1 Co-precipitation from acetone	50%	52.9	54.0	±1.5
			55.7		
			53.5		

Encapsulation Efficiency

No.	Ratio of HC to PLGA (wt.)	Encapsulation Efficiency (wt.%)	Average (%)	SD
1	1:4	0		0
2	1:2	8.4	6.7	±1.4
		6.3		
		5.4		
3	1:1	21.5	22.6	±2.3
		25.2		
		21.2		
4	1:1 Co-presipitation from DCM and EtOH	0	0	
5	1:1 Co-precipitation from acetone	0	0	


Hydrocortisone Release Profiles at
Different PLGA Loading Ratios
Drug Release Fraction (%)
110
100
90
80
70
60
50
40
0
2
4
6
8
10
12
14
16
18
Time (days)
(1:4, wt)
(1:2, wt)
(1:1, wt)


Hydrocortisone Release Profiles
Using Different Processes
Drug Release Fraction (%)
110
100
90
80
70
60
50
40
0
2
4
6
8
10
12
14
16
18
Time (days)
Coating
Co-Precipitation from Acetone