Innovative Particle Engineering Techniques for Property Enhancements

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THE STATE UNIVERSITY OF NEW JERSEY RUTGERS

PURDUE UNIVERSITY

NJIT New Jersey's Science & Technology University

uprm.edu universidad de puerto rico Recinto Universitario de Mayagüez

ENGINEERING RESEARCH CENTER FOR

STRUCTURED **O**RGANIC **P**ARTICULATE **S**YSTEMS

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NSF

NJCEP (New Jersey Center for Engineered Particulates) Impact

- E*ngineered particulates* (exploiting unique properties of nanostructured materials) may be used to make advanced materials to meet several grand Challenges as identified by the NAE
  - *Pure Water, Better medicines, Clean Energy, etc.*
  - *Existing consumer products (e.g. sun-screens) to new or emerging materials (e.g., new cancer drugs)*
    - *Tough coatings, structural materials, energetic materials, catalysts, novel pharmaceutical, carbon nano-tubes based composites and films; polymeric composites, organometallics, materials for hydrogen storage, etc*
- For example, in pharmaceuticals:
  - *manipulating the size, structure and surfaces of drug particles for improved bioavailability, resulting in reduced dosage and lower toxicity,*
  - *develop a better understanding of processes to help reduce the time to bring a new drug to market.*

Research Infrastructure

- Particle Characterization
  - *FESEM, TEM-EELS, AFM, SNOM, Fluorescent Microscope, Dielectric Spectrometer*
  - *DelsaNano, Aerosizer, SMPS, SprayTec, Coulter LS230, Sympatec Helos-Rodos*
    - *Surface Energy via IGC (on order)*
  - *N-IR scope, Raman, Tribocharge Measurement, IGC, DSC, TGA*
- Powder Testing
  - *Jenike Shear Tester, Sevilla Powder Tester, Vibrated Packed Density Tester, Hosokawa PT, Flodex, FT4*
    - *Schulz Ring Shear Tester (access)*
- Particle/Powder Processing
  - *Nara RFBC, MAIC, Hybridizer, Mechanofusion, Micros, Mini-Glatt, Supercritical Fluid Systems, V-Blender, Fluid Energy Mill (on order)*
    - *Netzch Nano-mill, Procept Spray Drier (Prof. Bilgili)*

Current Group

- Research Associates

  Dr. Yueyang Shen *Dr. Chinmay Goroi*

- Doctoral Students

  Lauren Beach
  Christian Beck
  Anagha Bhakay
  Maxx Capece
  Xi Han
  Laila Jallo
  Azad Mohammad
  James Scicolone
  Daniel To

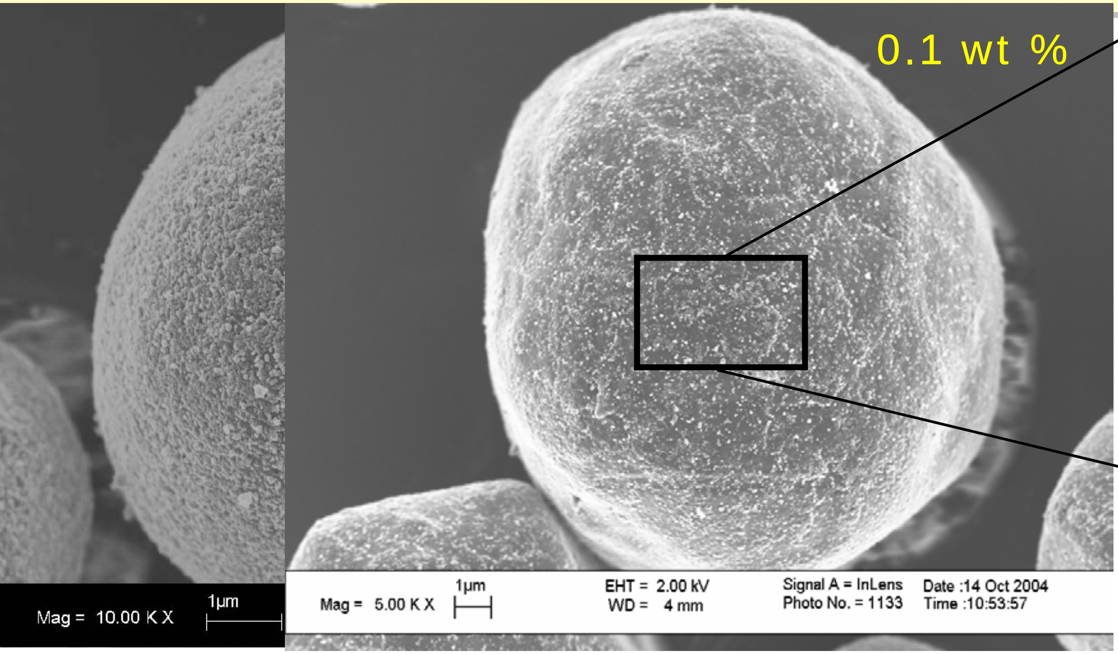
- Masters Students

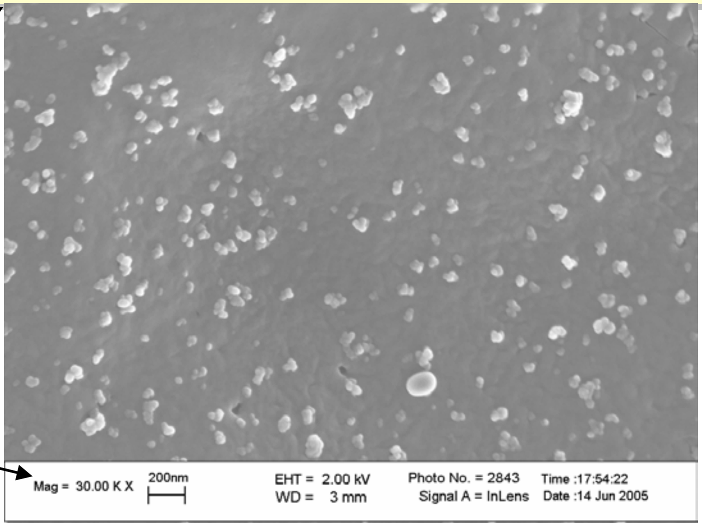
  Lakxmi Gurumurthy

- Undergraduate Students

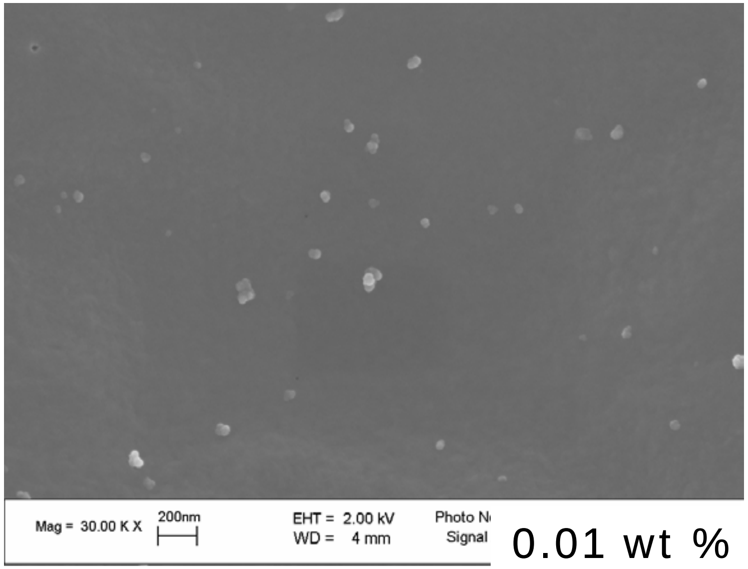
  Sonali Bhatnagar
  Alex Rassekh
  Fernando Rivas

Structured/functionalized Particles





0.1 wt %



0.01 wt %

Physical functionalization

Dry coated particle:
20 nm particle coated onto
< 10 micron carrier

Nano-scale surface roughness can reduce cohesion

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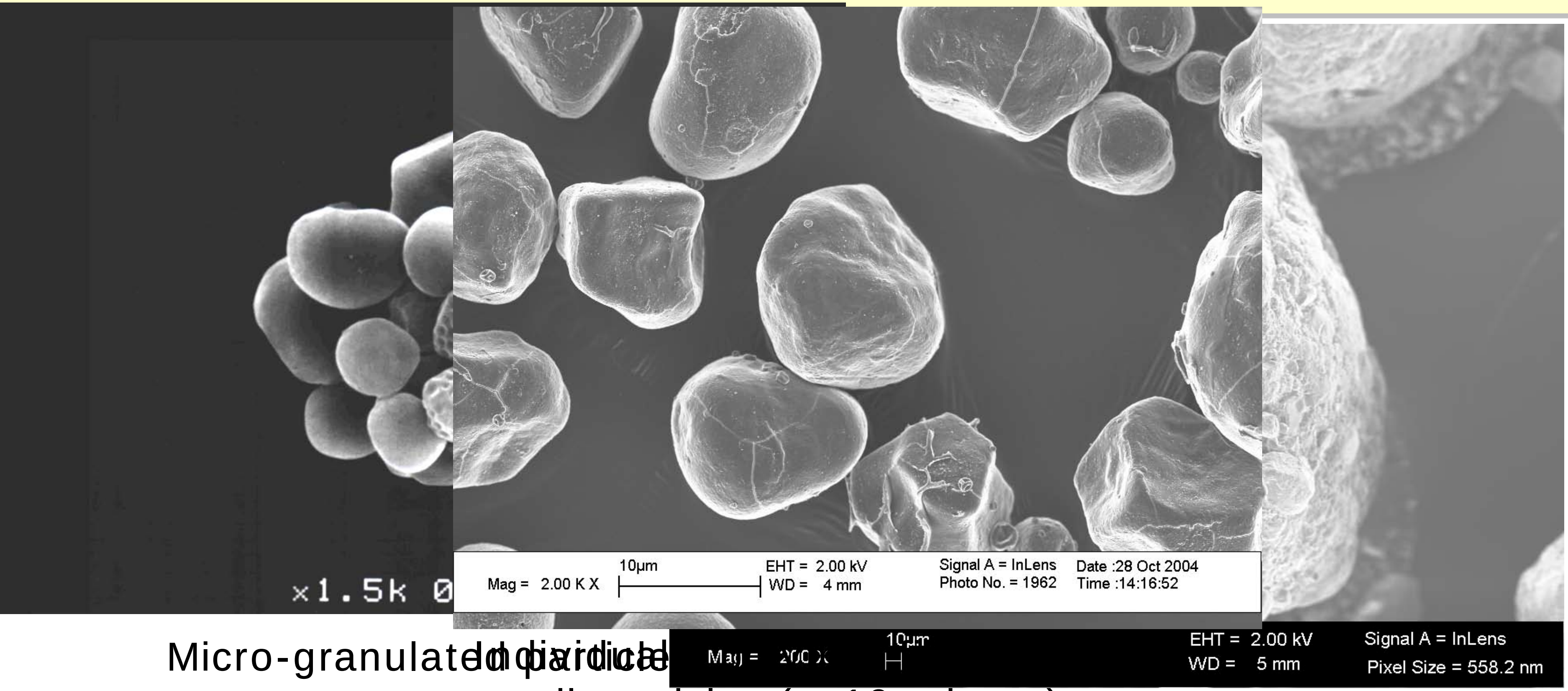
Structured/functionalized Particles



Micro-granulated particles

Individual small particles (< 10 micron)

Hierarchically clustered particles

Each case involves functionalization of ultrafine particles, e.g., by coating nano-particles on their surface

Vision: NSF-Engineering Research Center for Structured Organic Particulate Systems

To be the national focal point
for science-based development
of structured organic particle-based products
and their manufacturing processes.

Multi-Institutional Leadership Team (Rutgers, NJIT, Purdue, UPRM)

- Director: Fernando Muzzio, ChE Rutgers

- Deputy Director/TB2 coordinator: Rex Reklaitis, ChE Purdue

- Manufacturing Science Thrust Leader: Venkat Venkatasubramanian, ChE Purdue.

- Composite Synthesis & Characterization Thrust Leader: Alberto Cuitino (Rutgers site leader), ME Rutgers

- Material Synthesis & Functionalization Thrust Leader/TB3 coordinator: Raj Dave, ME NJIT (NJIT site leader)

- TB1 Coordinator: Marianthi Ierapetritou, ChE, Rutgers

- UPR site Leader: Carlos **Velazquez**, ChE

- Purdue Site Leader: Lynne Taylor, Pharm

- Education Director: Henrik **Pedersen** ChE Rutgers

- Education Associate Director: Aisha Lawrey

- FDA Liaison: Bozena **Michniak**, Pharm, Rutgers

- Industrial Liaison Officer: Eric **Erenrich, Rutgers**

- Administrative Director: Charanjeet Kaur, Rutgers

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ERC re-organization; led by Cuitino and Dave: January 2009

***Goal 1**: To understand impact of material properties and processing inputs on product structure and performance*

***Goal 2**: To use this understanding to design, control and optimize products and their associated manufacturing processes*

Test Beds / Thrusts	**Test Bed 1:** Continuous Manufacture of Tablets	**Test Bed: 2** Strip Films	**Test Bed 3:** Multilayer Architectures Via Drop-on-demand
Thrust D: Integrated Systems Science			
Thrust C: Structural Characterization and Modeling			
Thrust B: Design and Scale up of Material Structuring Operations			
Thrust A: Materials Formation and Characterization			

21 Projects

2 Working Groups: cross fertilization of methodology across thrusts & test beds

NJIT Role: Lead of Thrust A, TB2, and four projects (Dave, Iqbal, Khusid, Mitra)

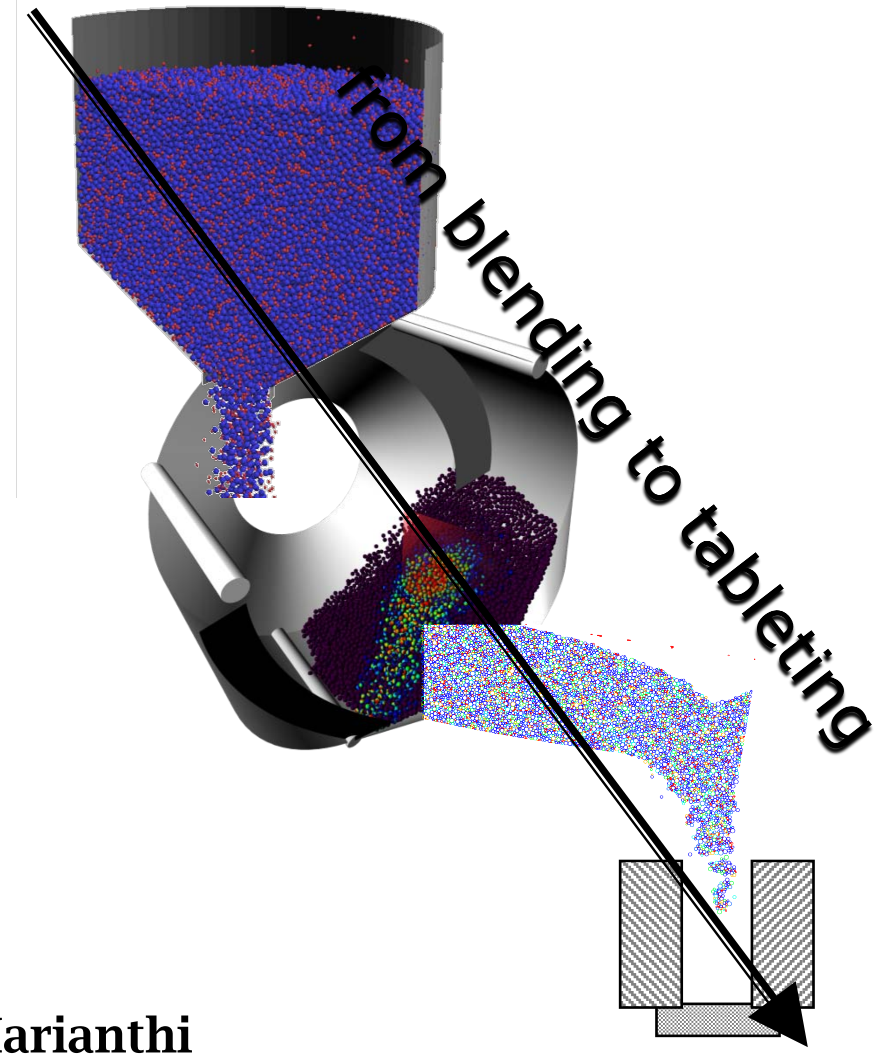
Share of TB3, WGs, several projects

Test bed 1: Continuous Dry Manufacturing of Tablets

Goal: Continuous dry processing of particles to form tablets using conventional unit operations

Impact

- Improved product quality
- Cost Reduction
- Simplified scale up



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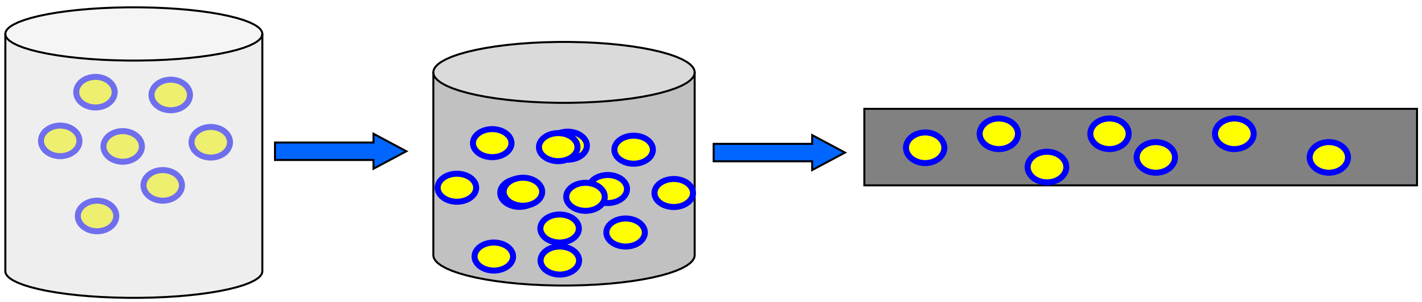
Leader: Marianthi Ierapetritou, Rutgers

Test Bed 2: Manufacture of Strip Film Unit dosage

Goal: *Develop the scalable methods, experimental setups and material knowledge base for forming films loaded with engineered particles of sub-micron and low micron size to achieve desired delivery properties*

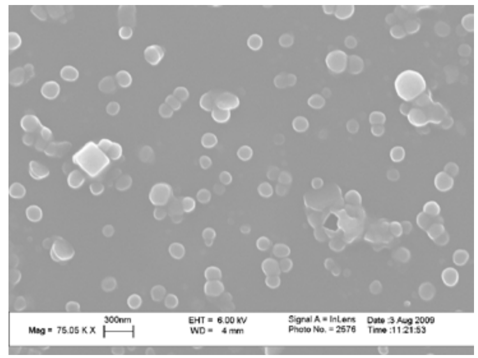
Benefits/Impact

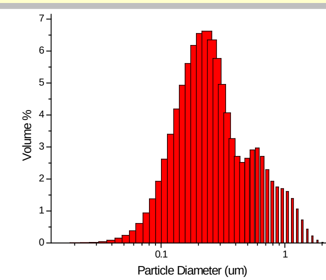
- Allows for incorporating particling
- Manufacturing is inherently continuous
- No dry powder processing – so safe
- Full (100%) automated inspection possible

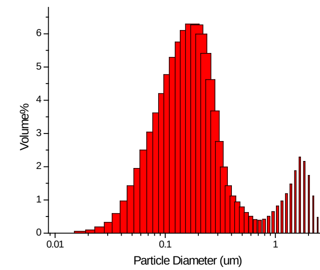


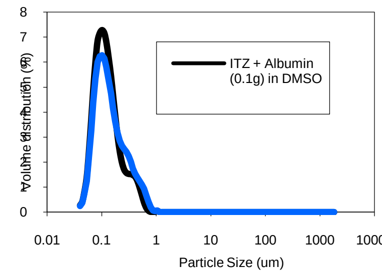
Leader: Raj Dave, NJIT

Test-bed 2 Strip Film Unit dosage: Tasks and Products









Product X (e.g., injectable, capsule filling)

Product Y (e.g., ointments, pastes)

Product Z (e.g., oral strip-films, patch)

Project A.1

Project A.2

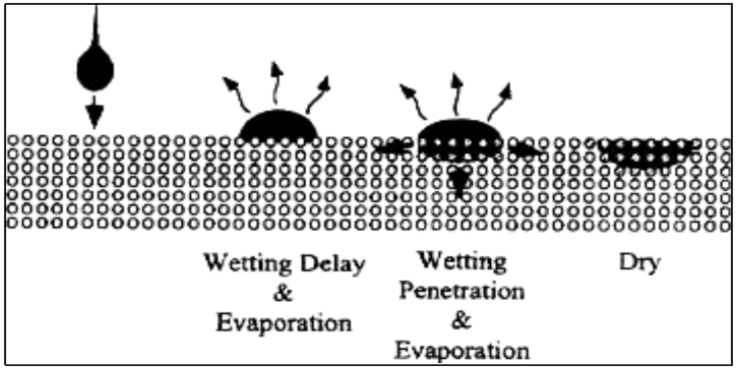
Projects A.4 and B.3

Projects C.3 and C.5

Fine Particle Suspension → Stable Concentrated Particle Suspension → Film Precursor Gel with Stabilized Particles → Formulation and Manufacture of Films Uniformly Loaded with Particles → Film Testing

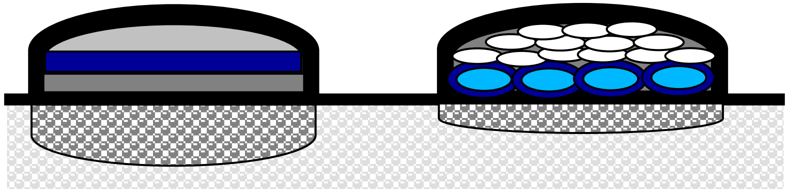
Test Bed 3: Mini-Manufacturing using Drop-on-Demand

Goal: *Integrated application of drop-on-demand for bottom-up formation of 3-D structured dosage on edible substrate*



Impact

- Compact small scale manufacture for clinical trial quantities, military, 3rd world & domestic rural use
- Customized, patient specific dosage formulations



Leader: Rex Reklaitis/Mike Harris, Purdue

Broader Outcomes for Success

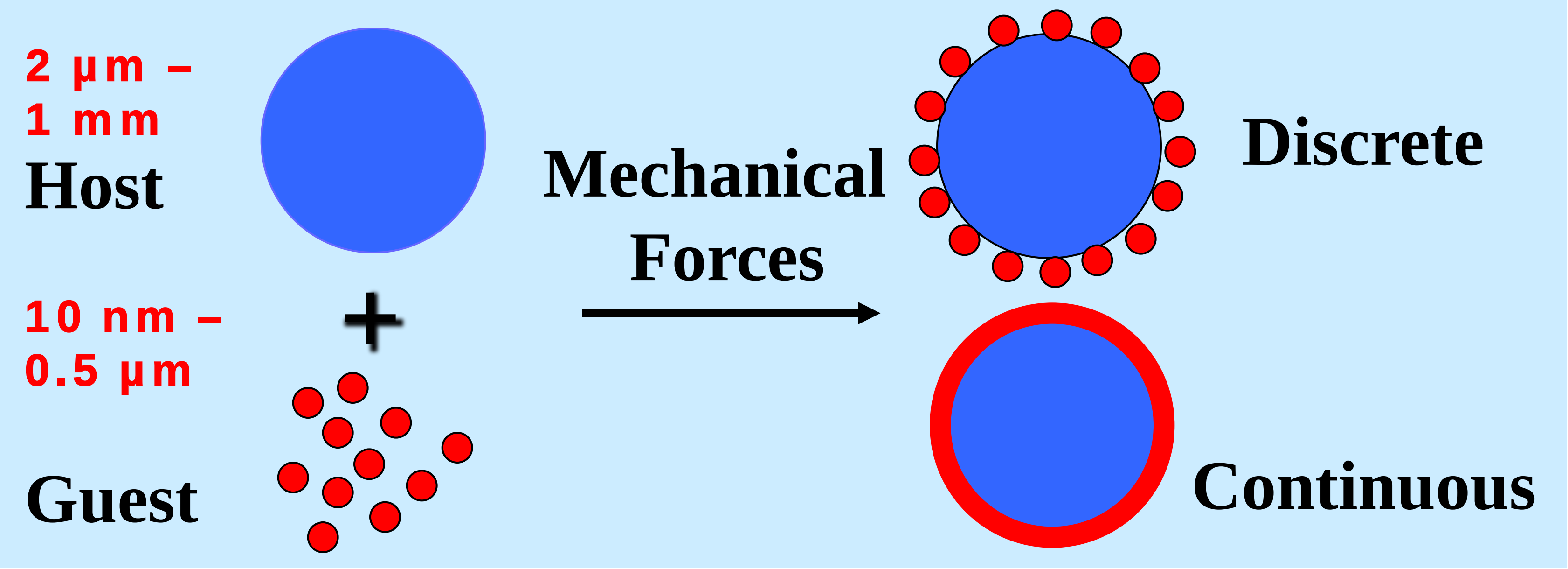
- Faster drug product development
- Savings in manufacturing
- Fewer product batch failures
- Increased product quality – safer to patients
- New multidisciplinary educational programs, enhanced manpower supply
- New technologies benefiting all industries that focus on delivery of bioactive substances

Particle Engineering Strategy

- Novel particle engineering concepts
  - *Property enhancement via surface modification*
  - *Fluid-bed engineering for quick-to-market dosages*
  - *Nanotechnology via stable nano-suspensions (scalable, fast continuous methods)*
- Develop continuously operating, scalable, dry-coating methods (Flow and Fluidization strongly related)
  - *Surface modification without size reduction*
  - *Simultaneous surface modification and micronization*
    - *improved bioavailability (oral dose) and inhalation products*
- Multiple powder testers and particle scale models
  - *Tests at all possible states of consolidation (Jenike, H-PT-N, SPT, VPD, Flowdex, access to Ring Shear tester, FT4)*
  - *Correlating bulk-scale from particle scale characterization*
    - *AFM, IGC & mechanical properties*

Project 7: Dry Particle Coating (*our group is an international leader in this field*)

Process of ***mechanically*** fixing fine particles (***guests, particles or liquids/lipids/waxes***) onto the surface of relatively larger particles



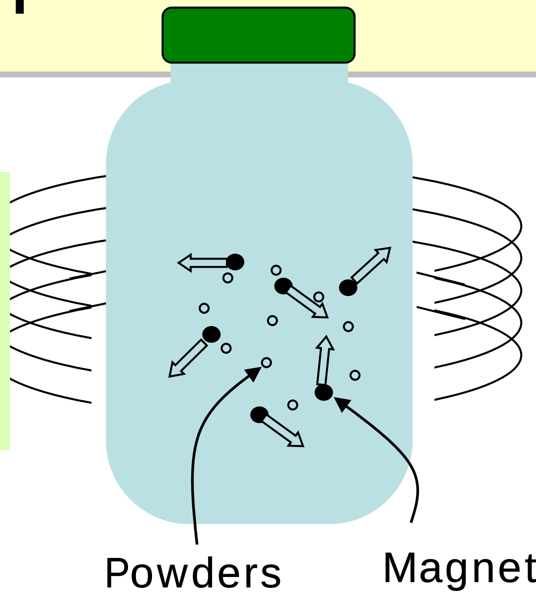
- **The advantages of dry particle coating**
  - ➲ new particles may have completely different functionality and/or much improved properties
  - ➲ the process is environmentally benign, no drying needed and cost effective

Conventional approach

Batch process: blending & coating devices

Magnetically Assisted Impaction Coating (MAIC)

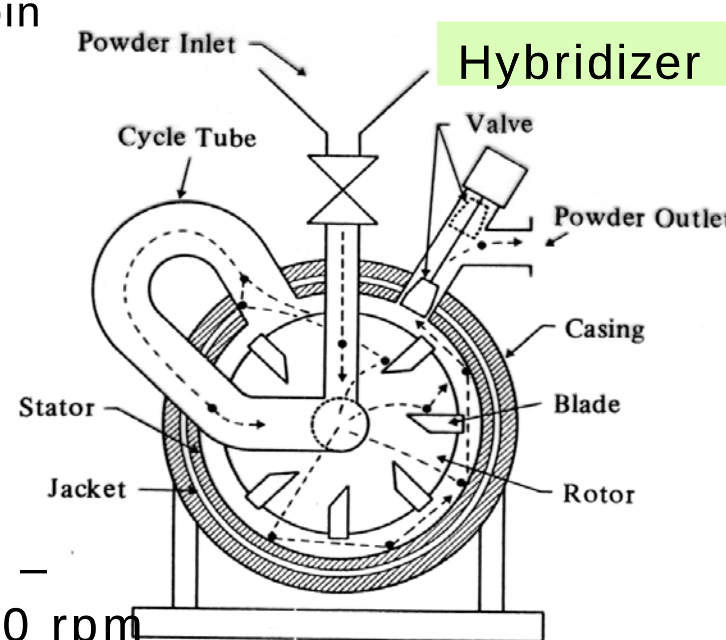
10 min



Oscillating Electromagnetic Field, causes magnets to spin at up to 1000 Hz

2-5 min

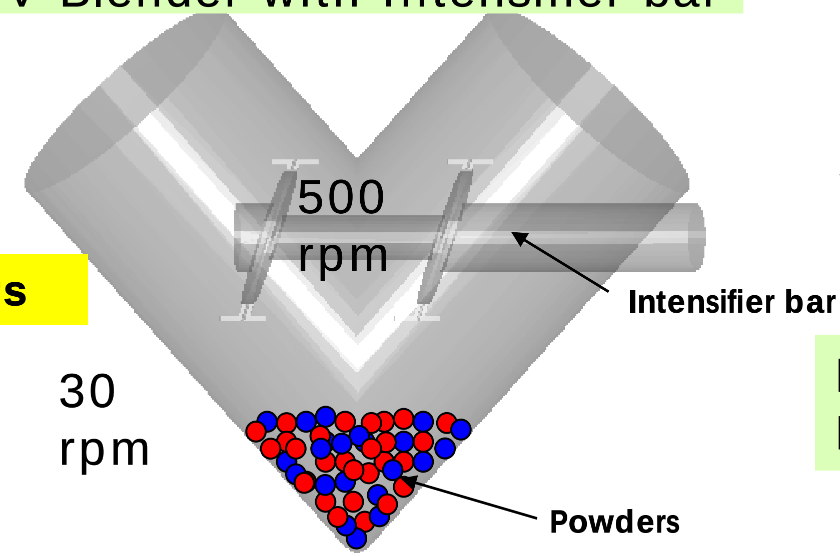
Hybridizer



5000 – 15000 rpm

V-Blender with Intensifier bar

1 to 3 hrs



30 rpm

Not Shown, Mechanofusion by Hosokawa Micron

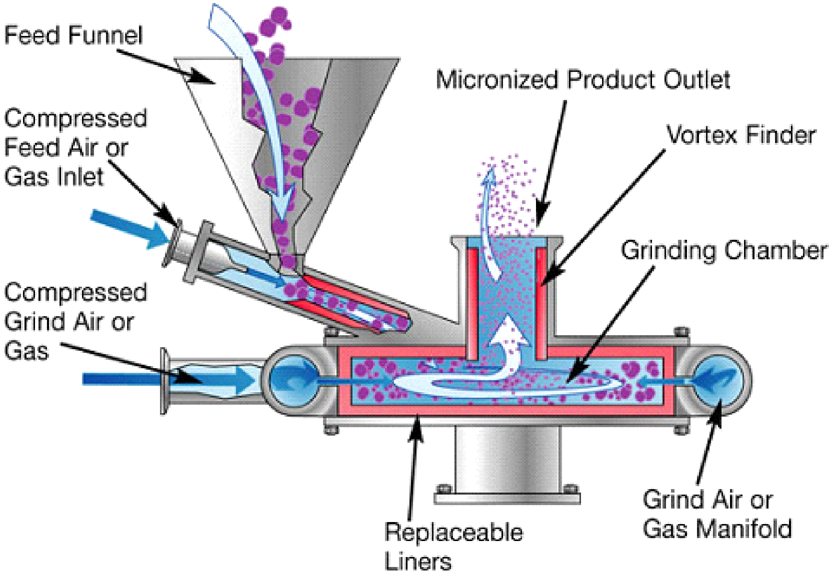
~10 min

Novel Proprietary Approach
Continuous Dry-coating Processes

Retrofitted Co-Mill

Continuous surface modification; capable of adding/coating nano-particles, amino acids, MgSt, and surfactants

Tested at lab and pilot scale at Pfizer



Fluid Energy Mill

Size reduction, micronization, co-grinding with surface modification; capable of adding/coating nano-particles, amino acids, MgSt, surfactants, waxes, lipids, super-disintegrators, and liquids

Tested at pilot and production scale at Army/Holston Plant for RDX

Flow out of a funnel:

Cornstarch before and after dry coating (0.1 % nano-silica)

Before coating: funnel had to be tapped for the powder flow to occur

After coating: the funnel outlet had to be covered to prevent the flow!

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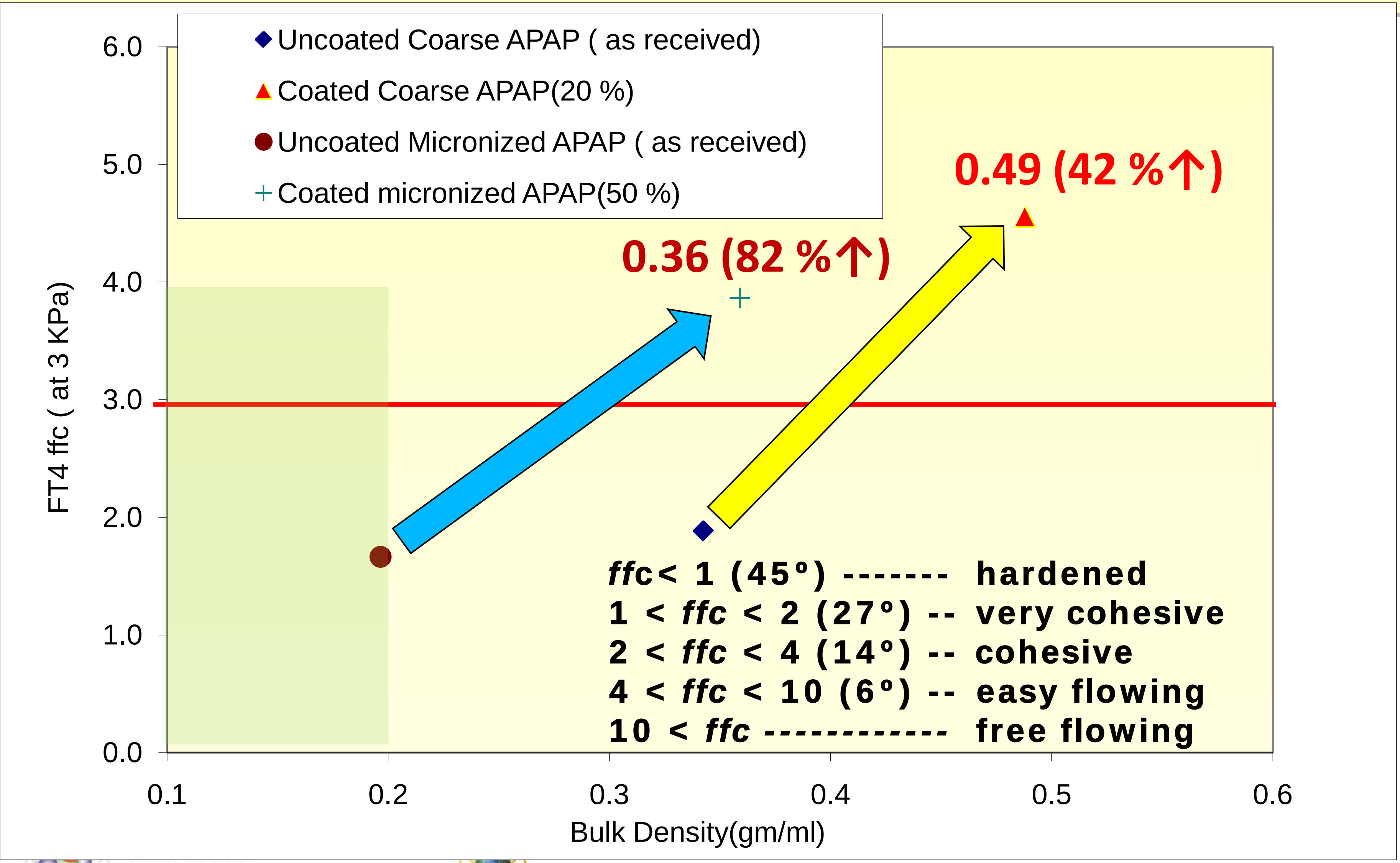
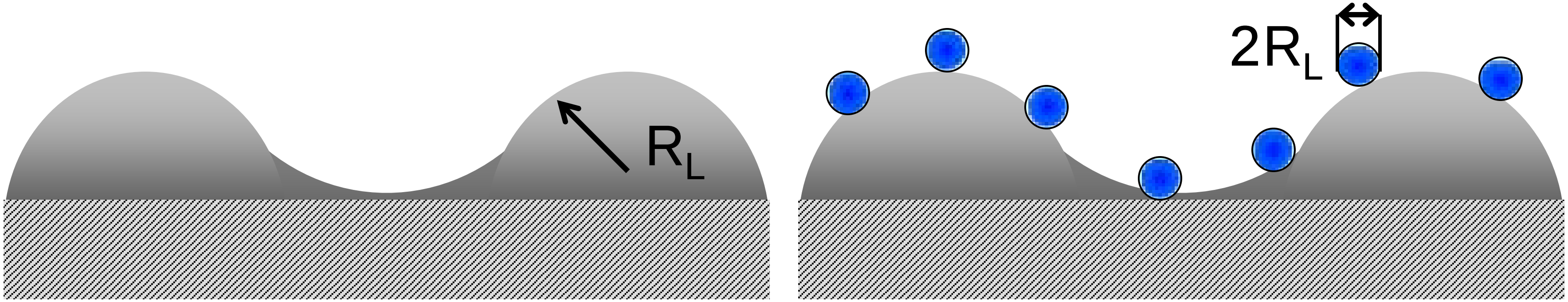
FFC versus Bulk Density of APAP (before and after dry coating)



How does dry coating work?

Naturally occurring asperities on the surface of the particles have sizes of the order of 100 nm



If the surface of the particle is coated with nanoparticles, we create “artificial” asperities with size of the order of 10 nm.

$$\frac{P_{coated}}{P_{uncoated}} = 2\frac{d}{D} \cong \frac{d}{D}$$

- **This is the first generation model**
- **The fourth generation model accounts for surface energy, surface roughness (size and spatial distribution of asperities), and mechanical properties of the contact.**

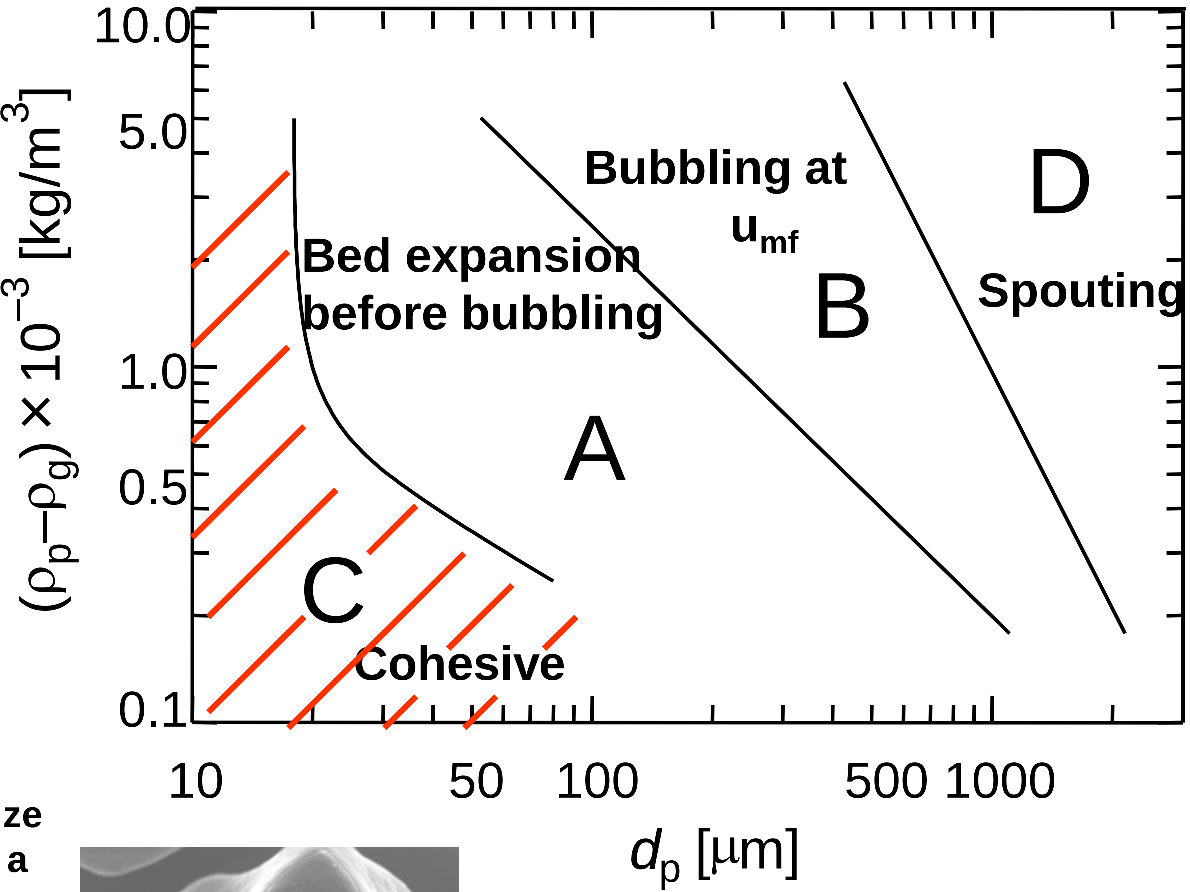
Yang, J., Sliva, A., Banerjee, A., Davé, R.N., Pfeffer, R. Dry particle coating for improving the flowability of cohesive powders, (2005) Powder Technology, Special Issue in Memory of Prof. Molerus,158 1-3, Pages 21-33. (40+ citations, many from pharma)

Particle Engineering Strategies for Improving Bioavailability

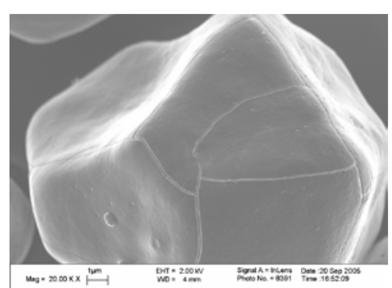
- APIs made as stabilized suspensions
  - *Not in dry form at nano size*
  - *Films, Spray drying, FB coating/granulation*
- Fluid-bed (FB) processing: API coated excipients
  - *Ease of handling, dosage uniformity, taste-masking and enteric coating at particle-scale, protective barrier, stability*
  - *Suitable for potent, low dosage formulations*

Geldart's Fluidization Map (Powder Technology, 7, 285 (1973))

Raw Cornstarch
Size: 15 micron



Fine cohesive powders (Group C) fluidize poorly, exhibiting channeling, lifting as a plug, and forming "ratholes" when aerated.



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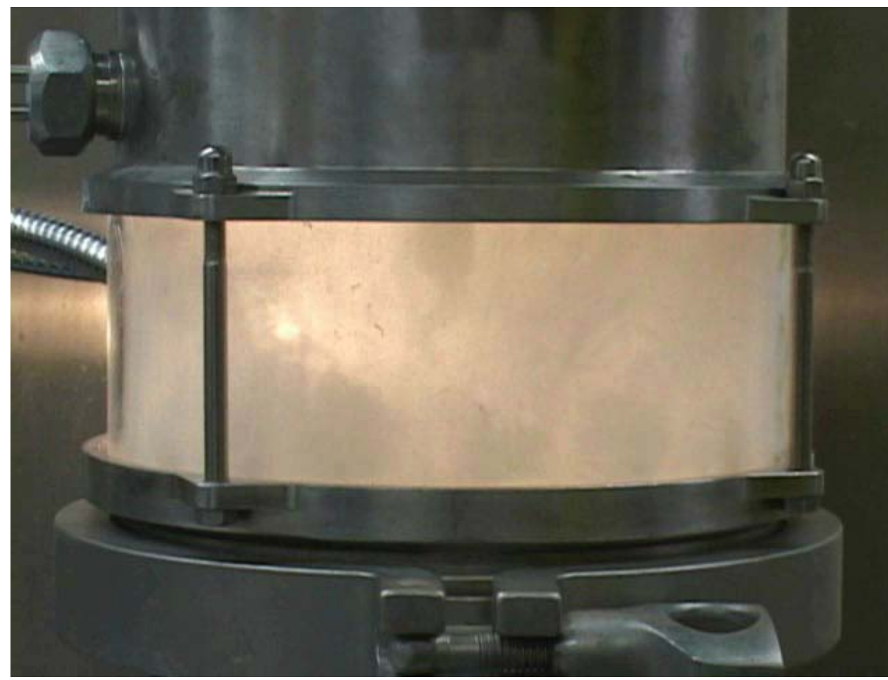
Project 8: Particle Engineering via Fluid Bed (FB) Processing: “Beating” the Geldart’s Law

$$\frac{\pi d_p^{\;3}}{6}(\rho_p - \rho_f)g(\varepsilon^{-4.8} - \varepsilon) = \frac{Al}{24\delta^2}$$

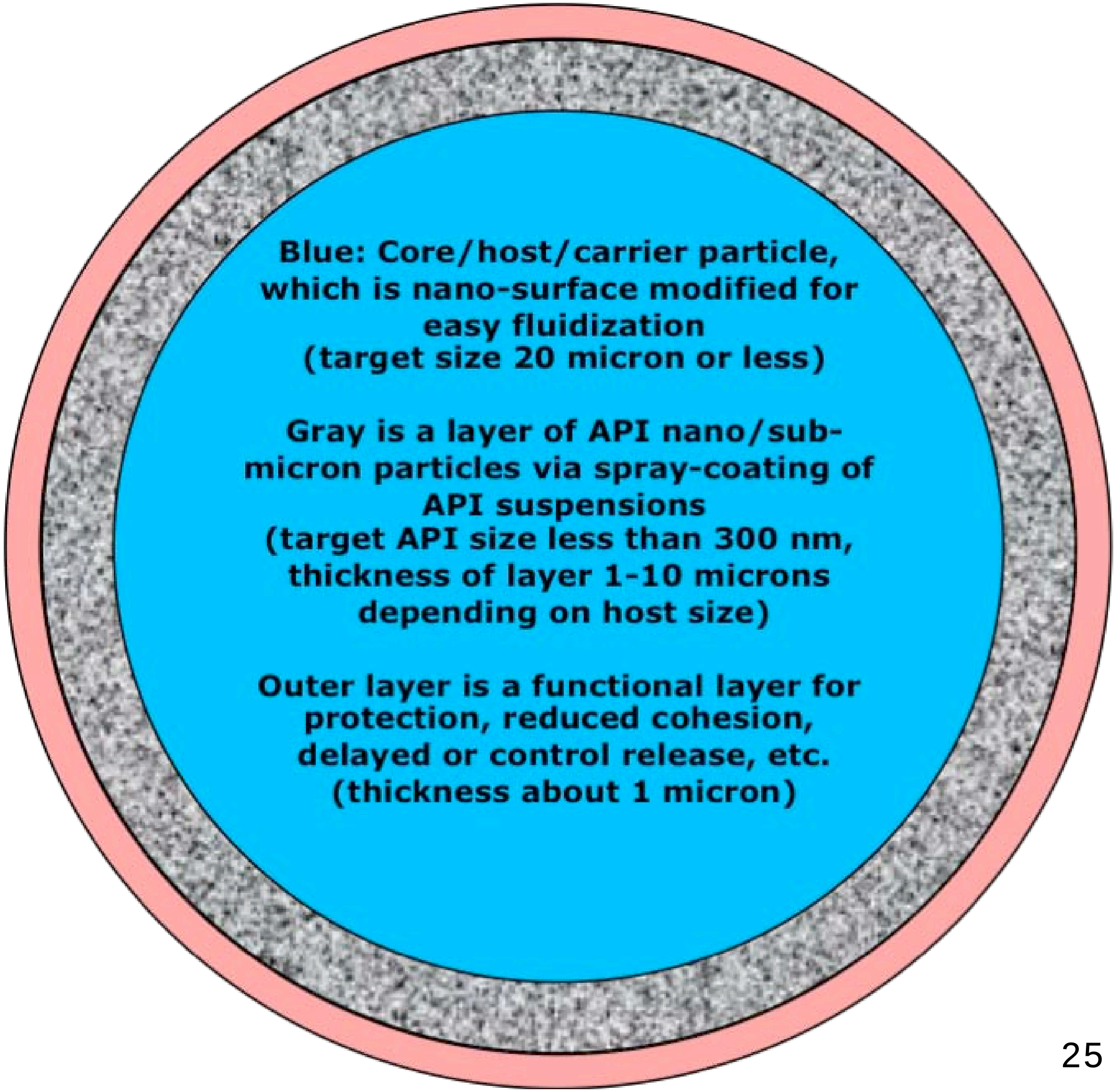
Mini-Glatt components after coating: negligible amount of powder is stuck to the walls



Surface Modified Powder may be fluidized and spray coated and/or granulated

Engineered Composite Particle

- Flexible, uniform drug content, ranging from 0.01% to 40%.
- Controlled dissolution characteristics via functionalization
- Uniform-composition across sample of capsule size scale
- Dust-free particles with minimum segregation tendency
- Controlled cohesion and good bulk density for speedy capsule filling



Recap and Discussion: Particle Engineering Strategy

- Novel particle engineering concepts
  - *Property enhancement via surface modification*
  - *Fluid-bed engineering for quick-to-market dosages*
  - *Nanotechnology via stable nano-suspensions (scalable, fast continuous methods)*
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  - *Correlating bulk-scale from particle scale characterization*
    - *AFM, IGC & mechanical properties*

Projects

1. Nanomilling of Active Pharmaceutical Ingredients and Crosslinked Polymers in a Wet Stirred Media Mill – Bilgili (1 RET + 1-pre)
2. Drop-on-demand printing of API on polymer films – Khusid (2 RETs + 1 Pre)
3. Characterization of Effects of Processing on API Polymorphism by Raman Spectroscopy – Iqbal (2 RETs)
4. Nanomaterials synthesis and characterization – Wang (2 RETs)
5. Optimization of Formulation of Griseofulvin Nanosuspensions for Long-term Stability – Bilgili (1 RET)
6. Formation of API loaded films for Oral Drug Delivery – Mitra (1 RET)
7. Surface Modification of Pharmaceutical Materials – Dave/Ghoroi/Marie (2 RETs + 1 Pre)
8. FB coating of API Suspensions on Surface Modified Excipient Particles Dave/Ghoroi/Marie (1 RET)

Projects are connected

- All projects deal with ERC mission – making better drug products
- Proj 1 provides materials for projects 6 and 8
- Proj 7 provides material to project 8
- Projects 3 and 4 are on characterization of complex drug materials
- Projects 2, 5, 6, and 8 deal with making drug products