The University Of Sheffield.

6th International Granulation Workshop

Granulation Course
Sheffield, UK, 24th – 25th June 2013

Acknowledgements

The organisers thankfully acknowledge the financial contribution of the following sponsors for supporting the 6th International Granulation Workshop:

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The organisers would also like to thank Shin Etsu and DFE Pharma for the provision of materials for the practical sessions.

ShinEtsu

DFE pharma

Course Timetable

Day 1 – Monday 24th June

Time	Topic	Presenter
08.00 - 08.50	**Registration**	
08.50 - 09.00	**Introduction**	Prof. Agba Salman
09.00 – 09.30	**Lecture 1** Introduction to Granulation	Mr James Cartwright *GSK*
09.30 - 10.30	**Lecture 2** Wet High Shear Granulation Regime Map	Dr Ian Gabbott *AstraZeneca*
10.30 – 11.00	Coffee Break	
11.00 - 12.00	**Lecture 3** Batch Granulation: Process and Formulation Variables	Prof. Agba Salman *University of Sheffield*
12.00 - 13.00	**Lecture 4** Continuous Processing in the Pharmaceutical Industry	Mr James Cartwright *GSK*
13.00 - 14.00	Lunch	
14.00 - 15.00	**Practical Session I (Group Rotation Basis)** 1. Continuous Granulation (Mr James Cartwright, *GSK*) 2. Roller Compaction (Dr Bindhu Gururajan, *Novartis* & Manfred Felder, *Alexanderwerk*) 3. Extrusion: Spheronisation (Dr Csaba Sinka, *University of Leicester*) 4. Batch Granulation (Dr Robert Sochon, *GSK* & Mr James Osborne, *Nestlé*) 5. Tabletting (Dr Vikram Chouk, *Addivant Global Technology*) 6. Finished Product Characterisation (Dr Yuen Sin Cheong, *Procter & Gamble*)	
15.00 - 15.30	Coffee Break	
15.30 - 16.30	**Practical Session II**	
16.30 - 17.30	**Practical Session III**	

Day 2 –Tuesday 25th June

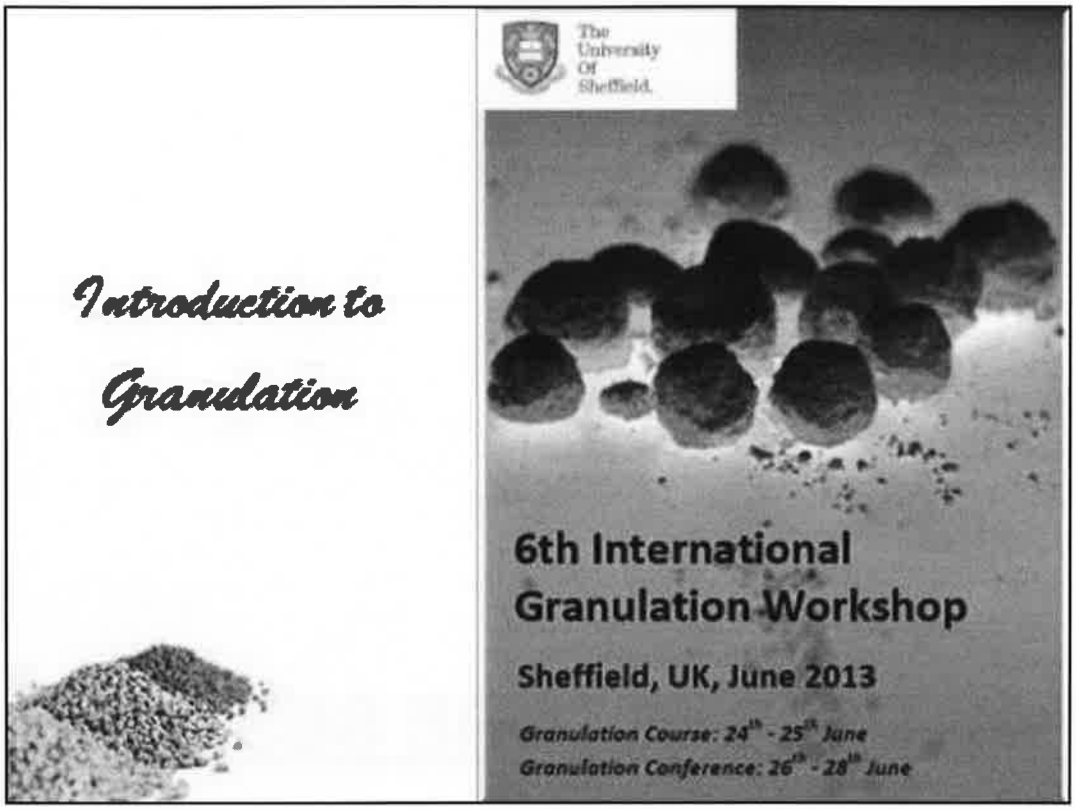
Time	Topic	Presenter
09.00 - 10.00	**Lecture 5** Troubleshooting in Granulation Processes	Mr Nigel Somerville Roberts *Procter & Gamble*
10.00 - 11.00	**Lecture 6** Mathematical Modeling of Granulation Processes	Prof. Jim Litster *Purdue University*
11.00 - 11.30	Coffee Break	
11.30 – 12.30	**Lecture 7** Powder Characterisation	Prof. Stefan Palzer *Nestlé*
12.30 - 13.30	**Lunch**	
13.30 - 14.30	**Practical Session IV**	
14.30 - 15.30	**Practical Session V**	
15.30 – 16.00	**Coffee Break**	
16.00 - 17.00	**Practical Session VI**	
17.00	**Wrap up session**	

CONTENTS

PART 1 - LECTURE SESSIONS

Lecture 1. Introduction to Granulation

Mr James Cartwright (GSK)



Presentation Purpose

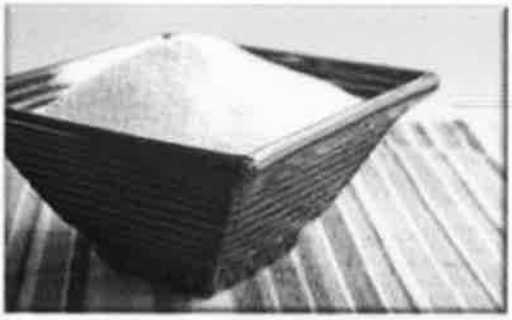
1. Raise awareness of granulation unit operations
2. Discuss High Shear Wet Granulation (HSWG)
3. Discuss Fluidised Bed Drying (FBD)
4. Discuss Roller Compaction (RC)
5. Discuss relationships between product and process

Presentation Outcomes

1. Increased understanding of HSWG and RC
2. Increased understanding of FBD
3. Increased awareness of granulation processes

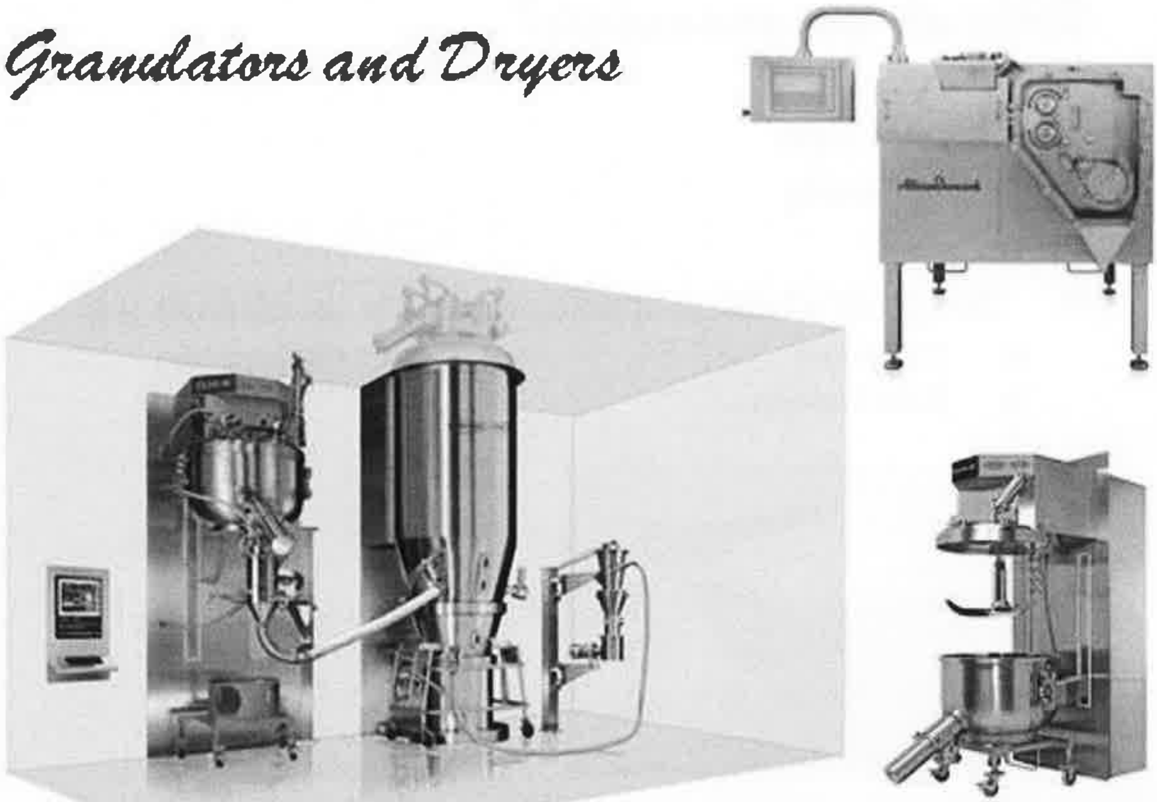
Why do we granulate?

1. Improve Flow
2. Homogeneity
3. Size
4. Design structural properties to deliver an attribute e.g.
   a) Dissolution
   b) Solid Fraction

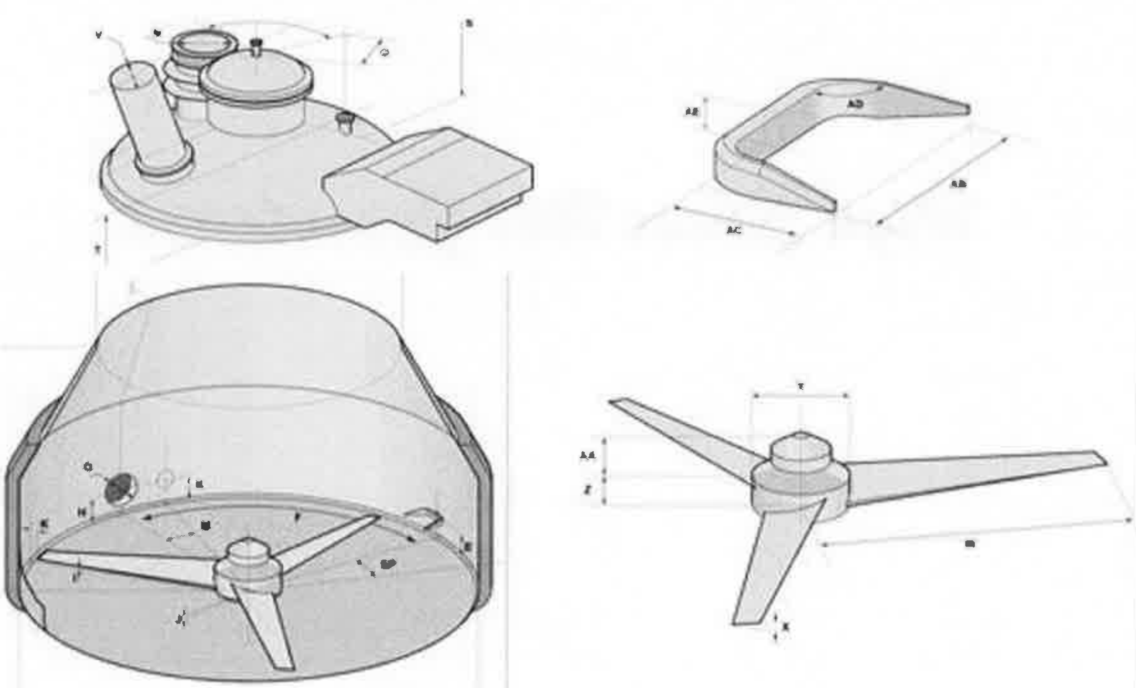


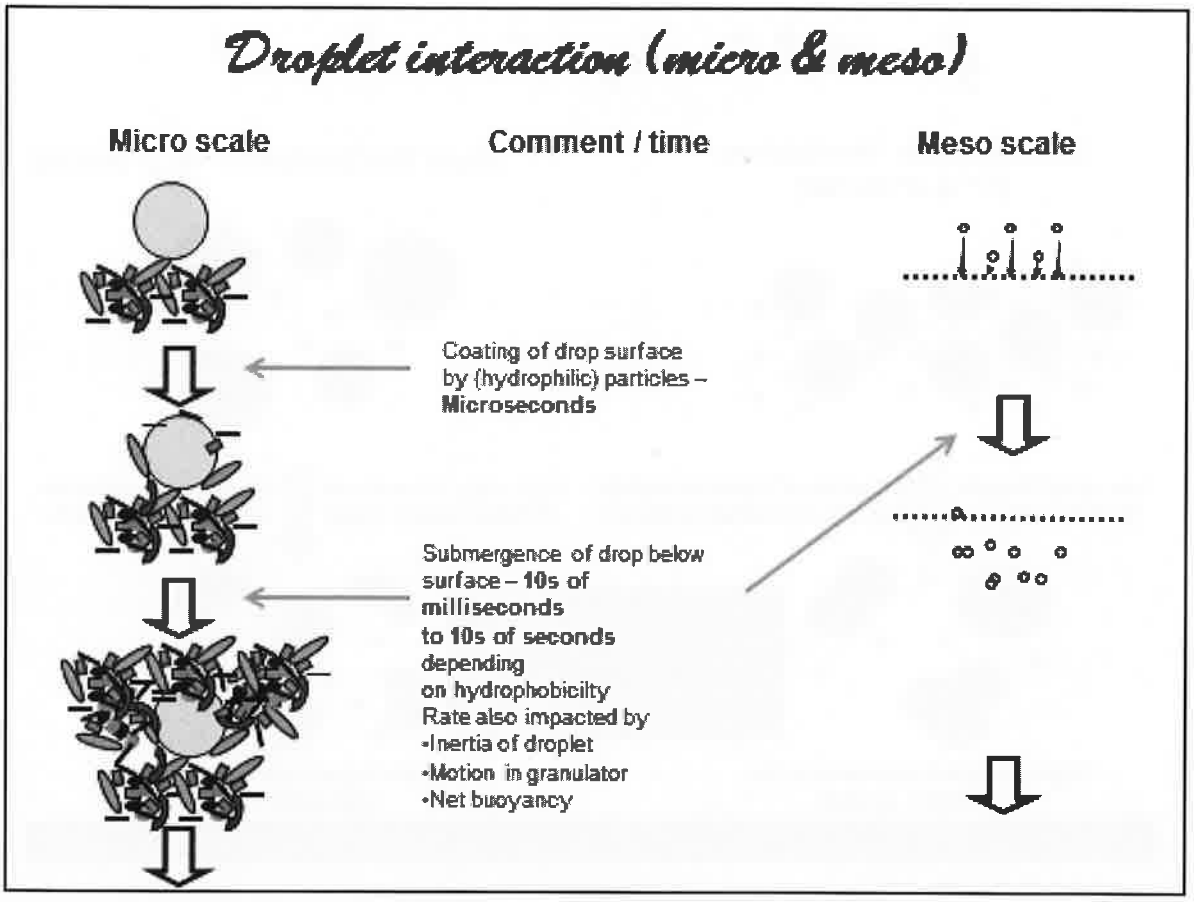
High Shear Wet Granulation

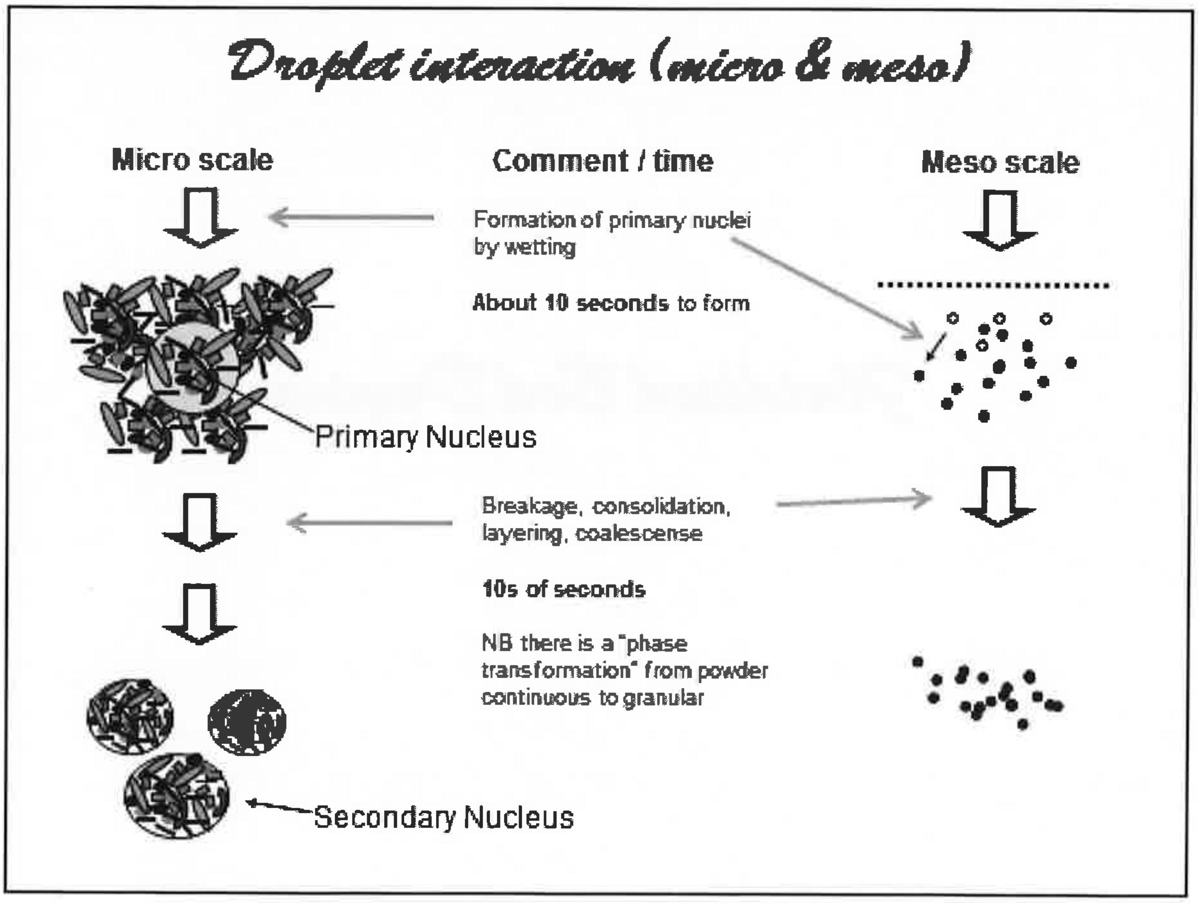
Granulators and Dryers

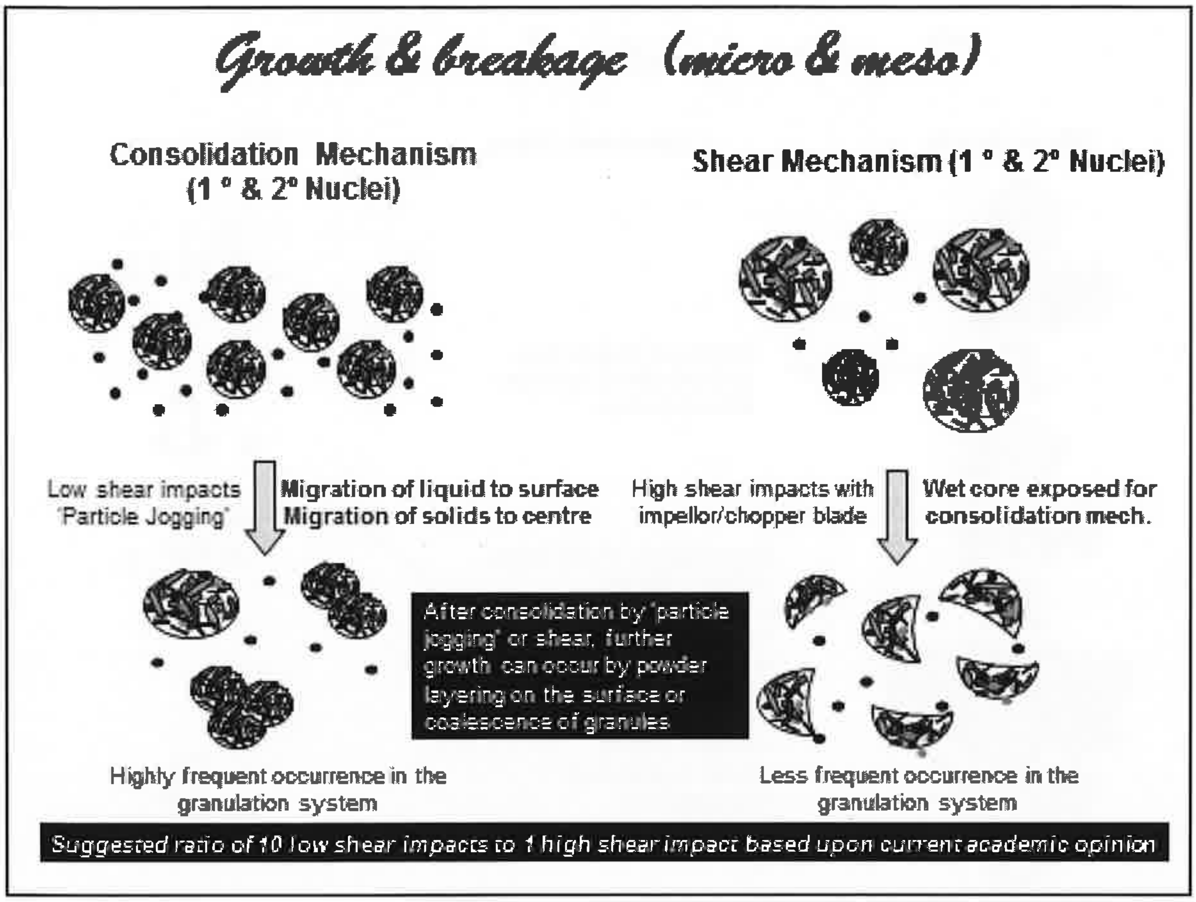


High Shear Wet Granulator (Bottom Driven)



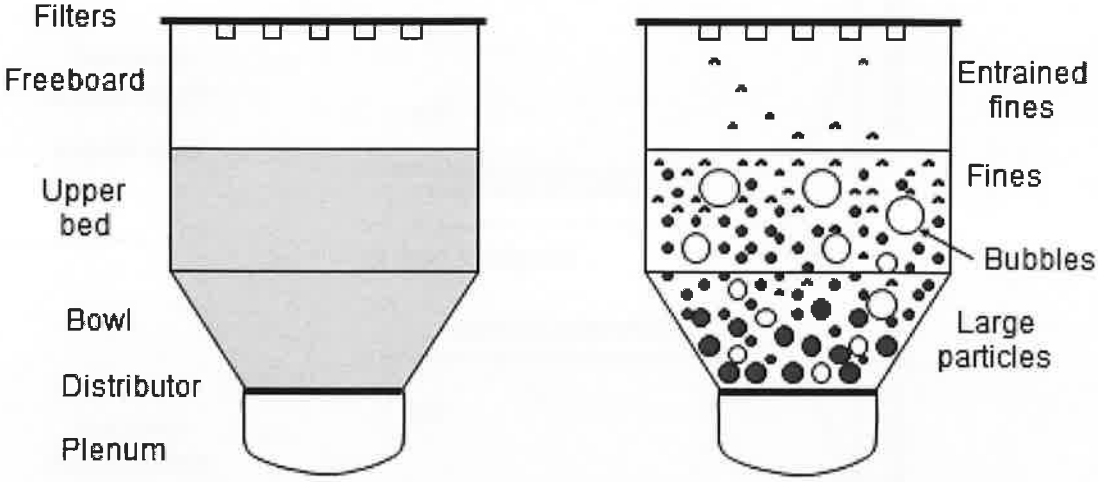

Droplet interaction (micro & meso)
Micro scale
Comment / time
Meso scale
Coating of drop surface by (hydrophilic) particles – Microseconds
Submergence of drop below surface – 10s of milliseconds to 10s of seconds depending on hydrophobicilty
Rate also impacted by
•Inertia of droplet
•Motion in granulator
•Net buoyancy


Droplet interaction (micro & meso)
Micro scale
Comment / time
Meso scale
Formation of primary nuclei by wetting
About 10 seconds to form
Primary Nucleus
Breakage, consolidation, layering, coalescense
10s of seconds
NB there is a "phase transformation" from powder continuous to granular
Secondary Nucleus



Fluidised Bed Drying

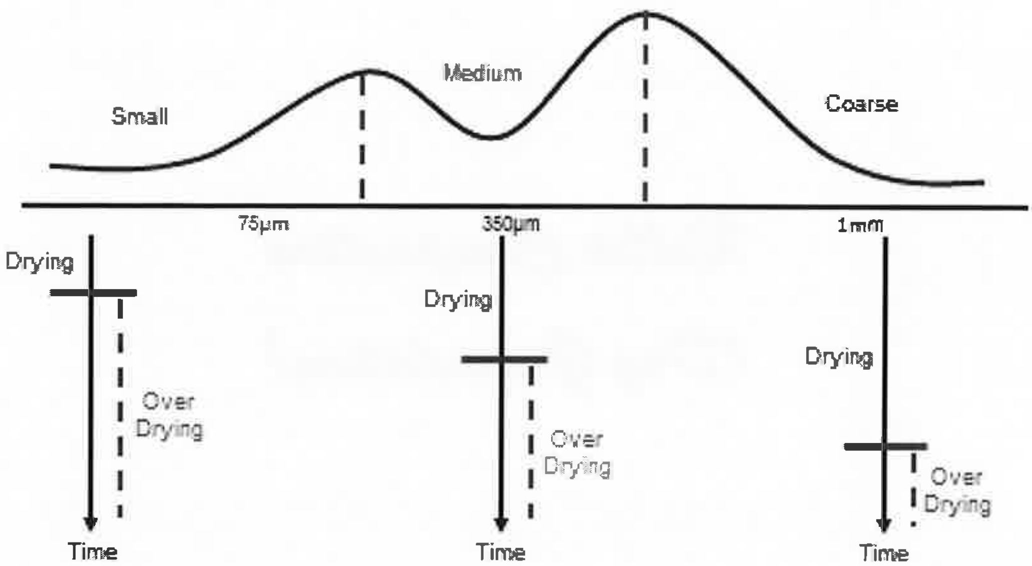
Equipment (Macro)



Some vertical segregation – fines near top, large particles near distributor

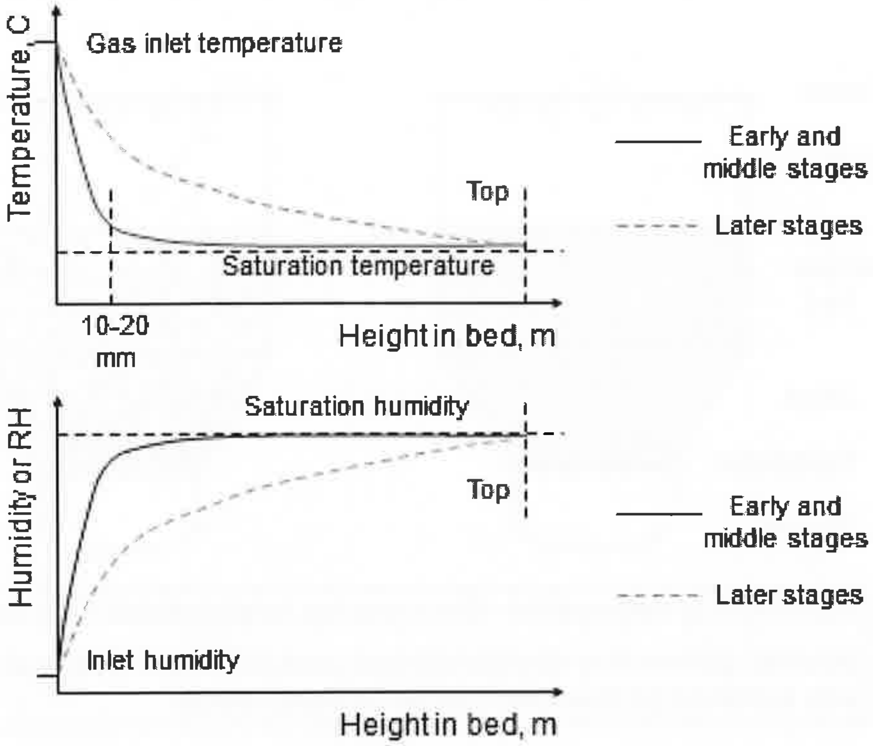
Bubbles grow as they rise through bed, particles are thrown up at top but only entrained permanently if above terminal velocity

Transformation Map - Size Relationship to Drying



Smaller material may be able to 'strip' moisture from larger granules. This may lead to A less clearly defined boundary between constant rate and falling rate drying mechanisms

Temperature and humidity profiles in fluid bed dryers

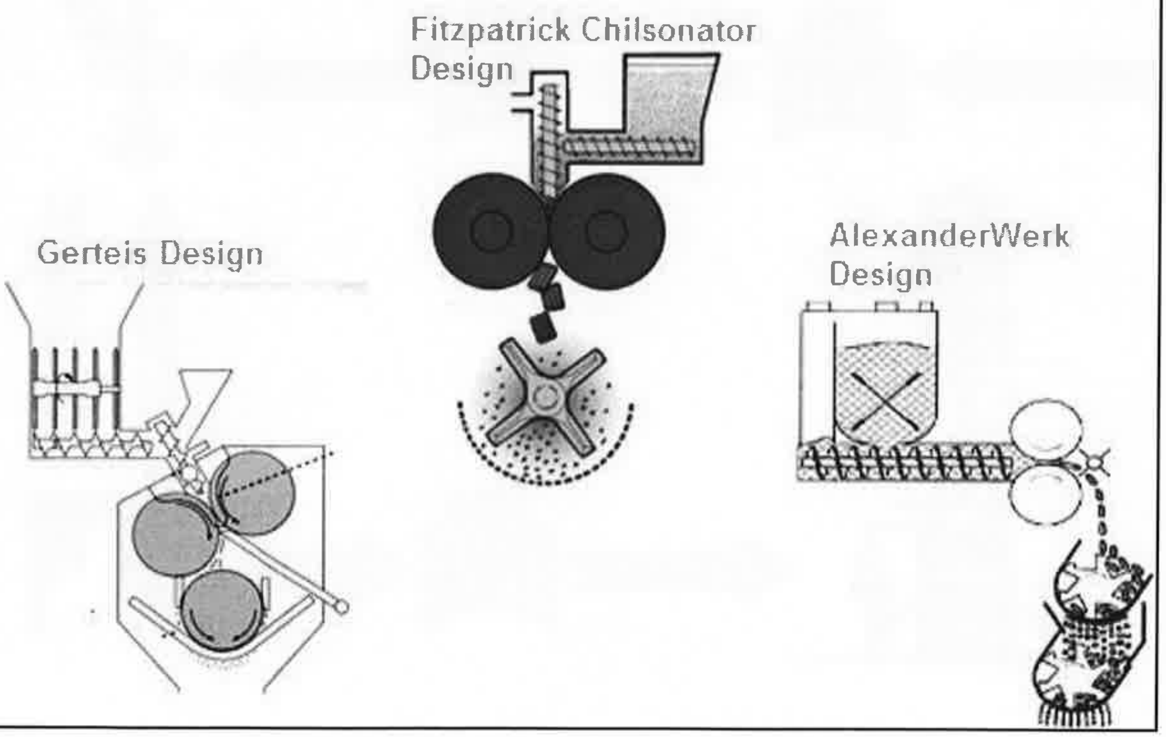


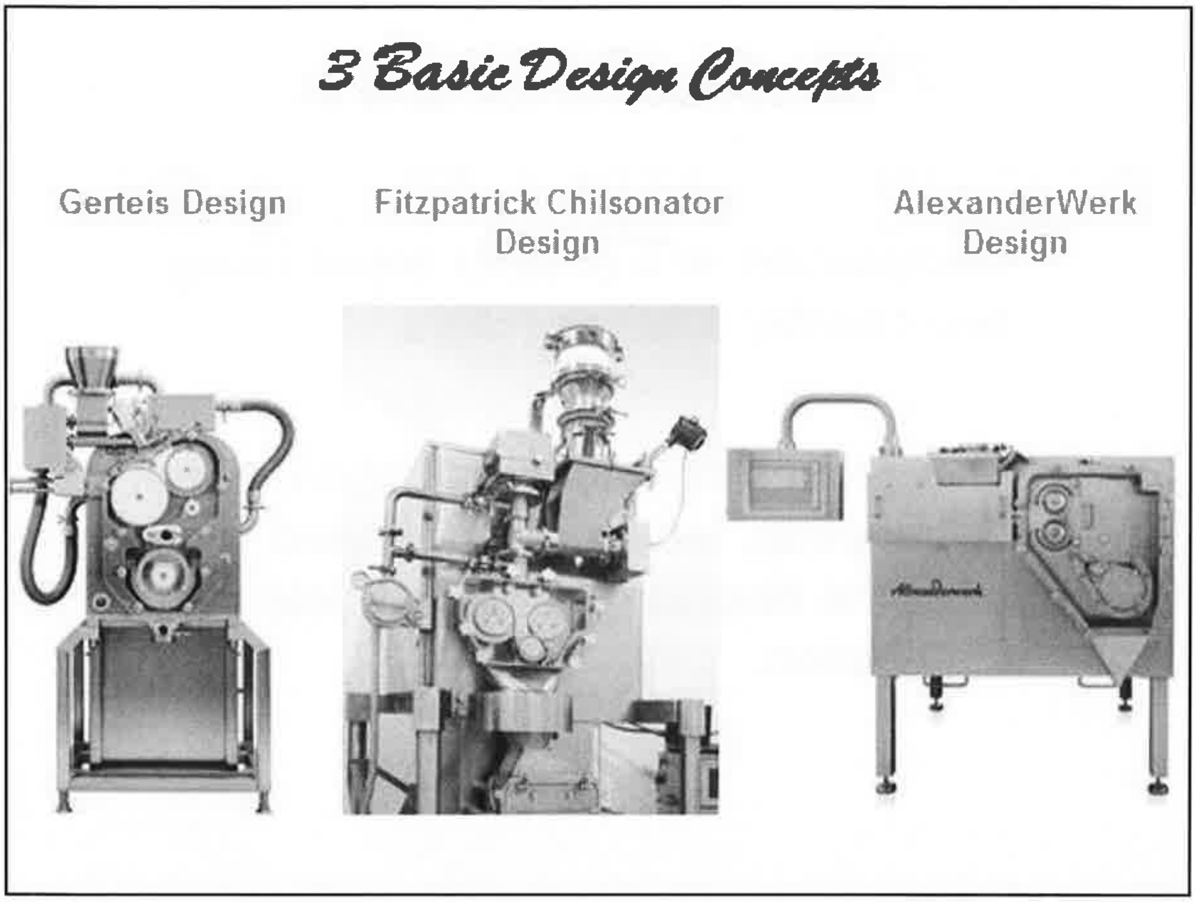
Roller Compaction
(Dry Granulation)

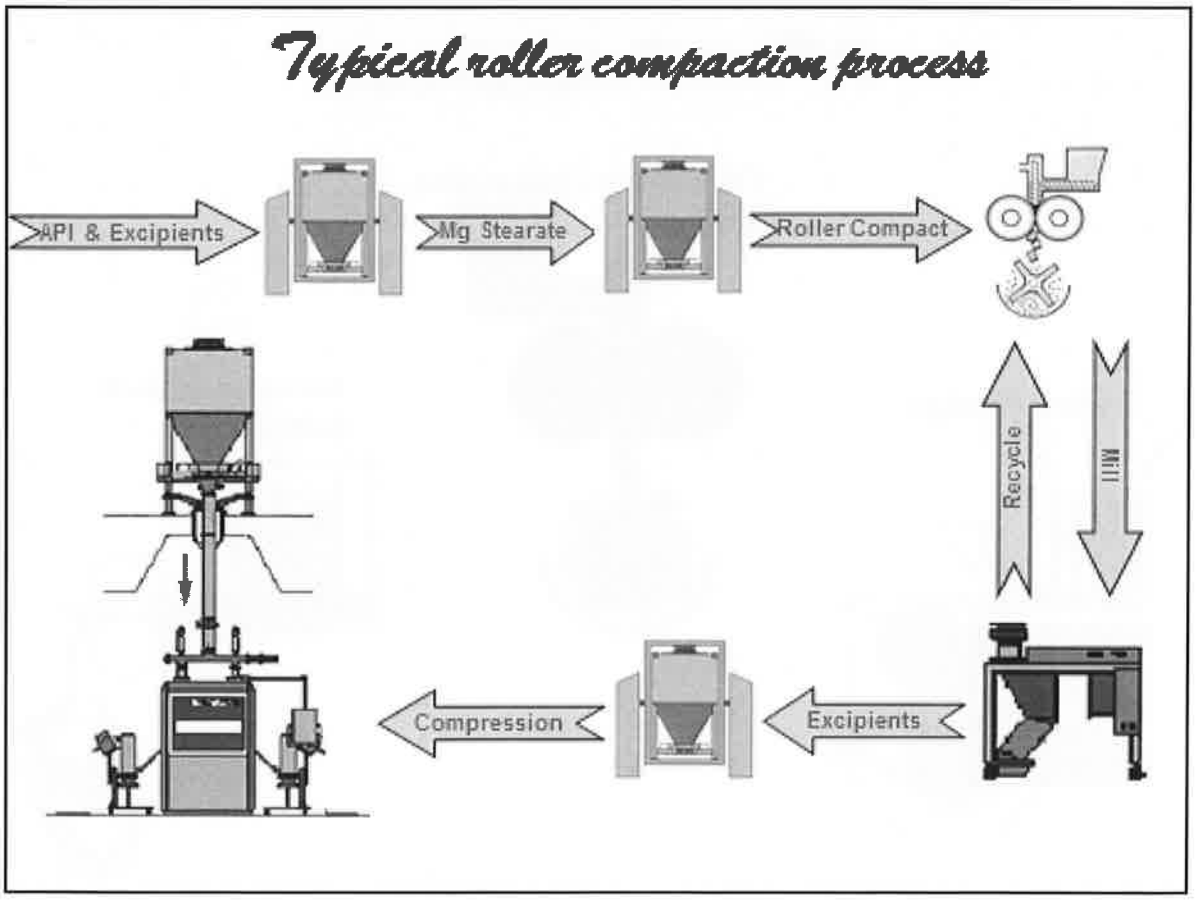
Roller Compaction: Definition

- Compaction of a powder blend using two counter rotating rollers.
- This process produces a ribbon, sheet or briquette, which can be milled to yield the desired granule particle size distribution.

3 Basic Design Concepts

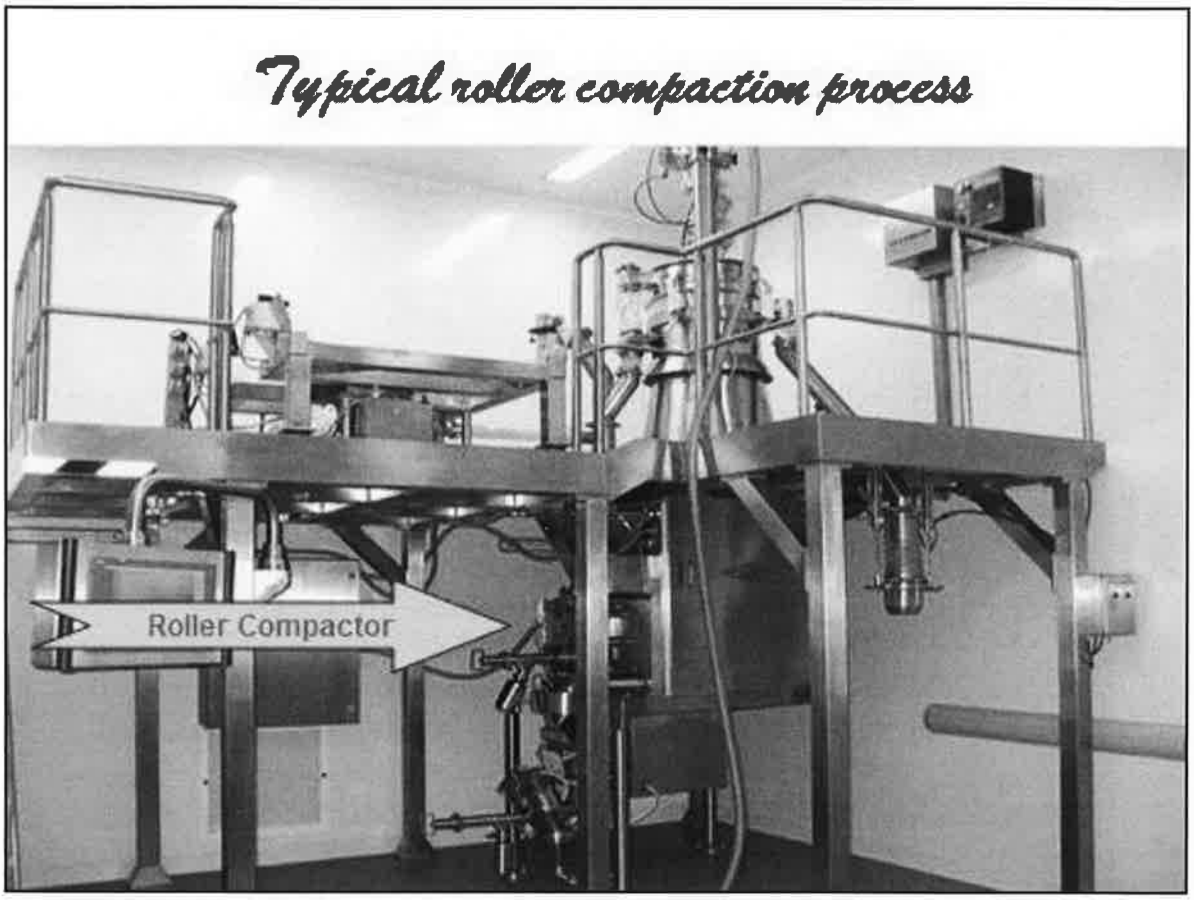


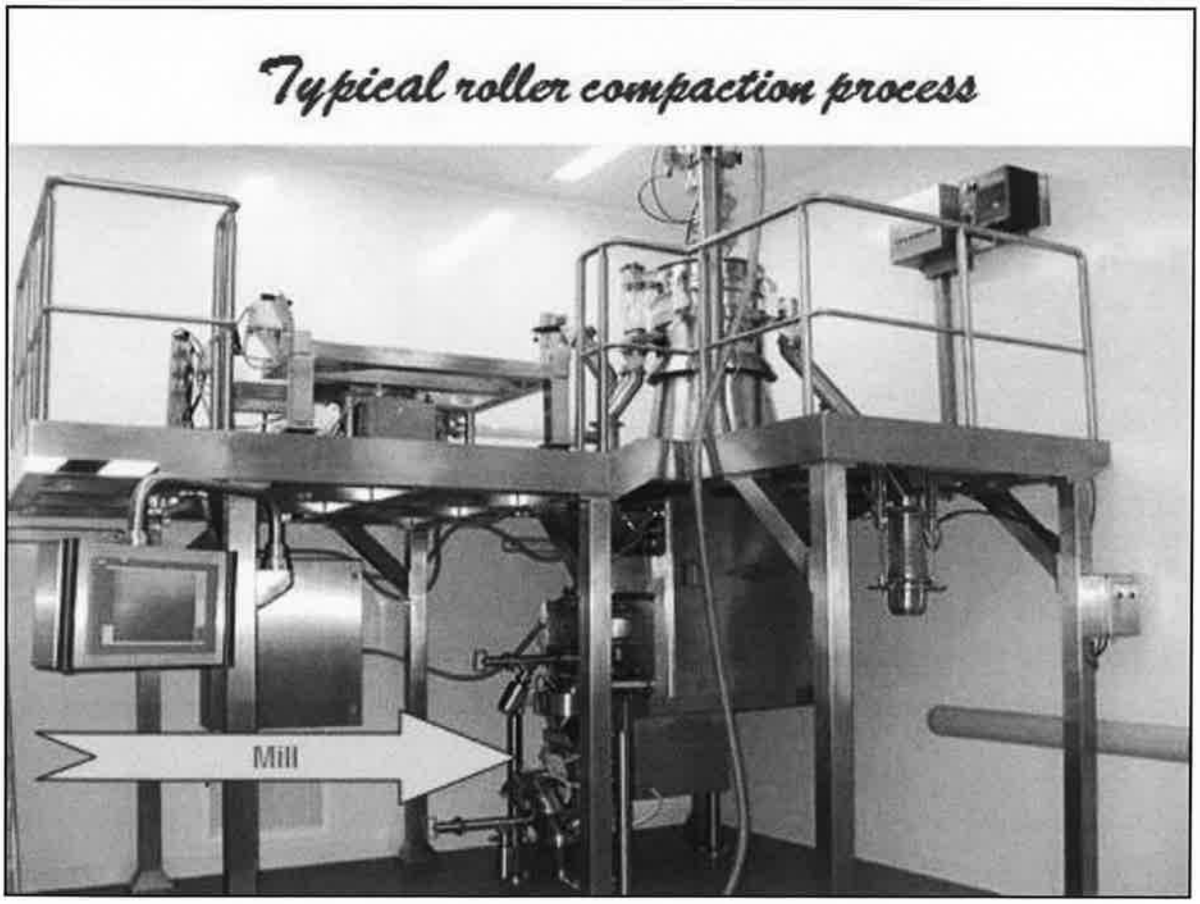

3 Basic Design Concepts
Gerteis Design
Fitzpatrick Chilsonator Design
AlexanderWerk Design


Typical roller compaction process
API & Excipients
Mg Stearate
Roller Compact
Recycle
Mill
Excipients
Compression

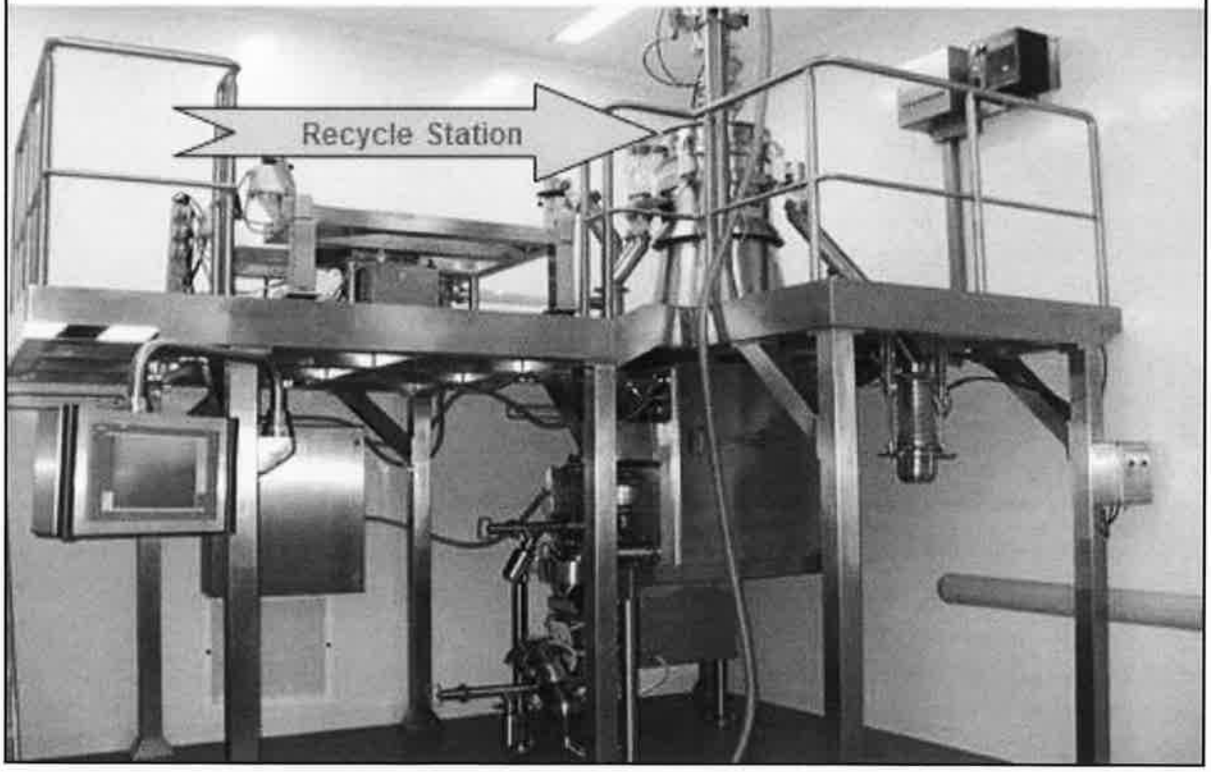
Typical roller compaction process

Typical roller compaction process

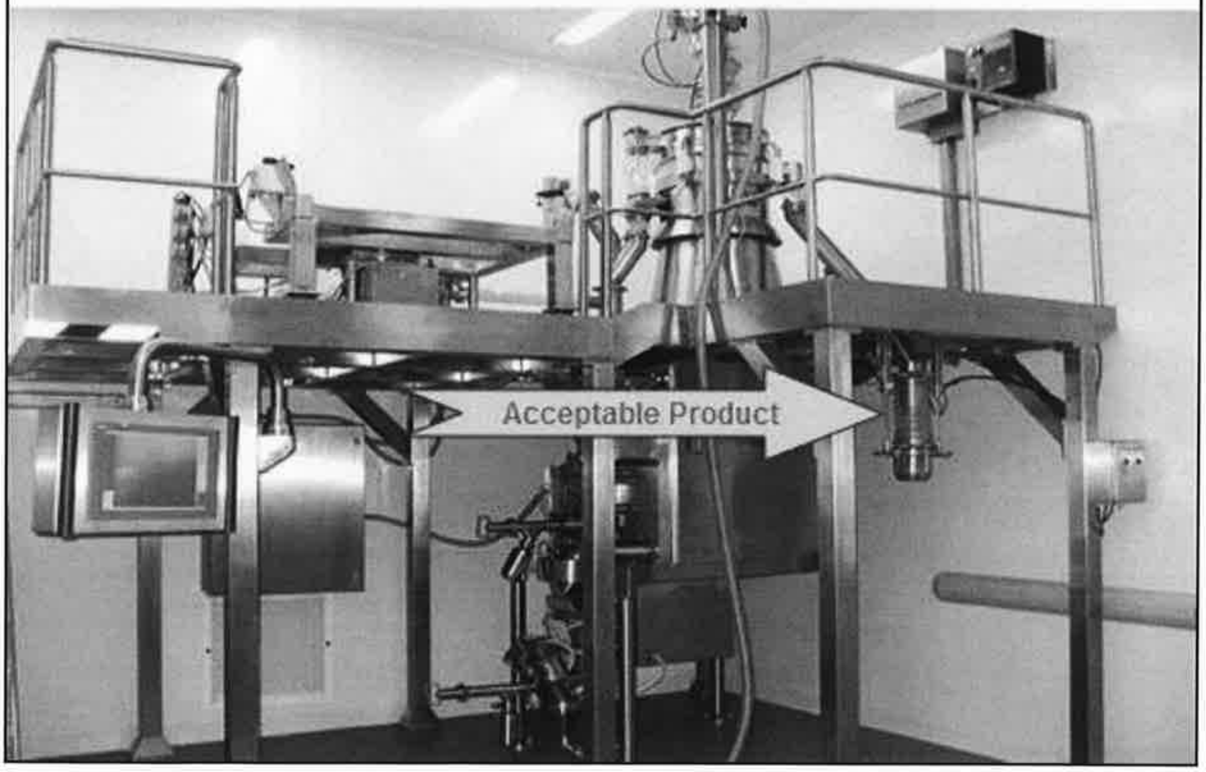

Typical roller compaction process
Roller Compactor


Typical roller compaction process
Mill

Typical roller compaction process

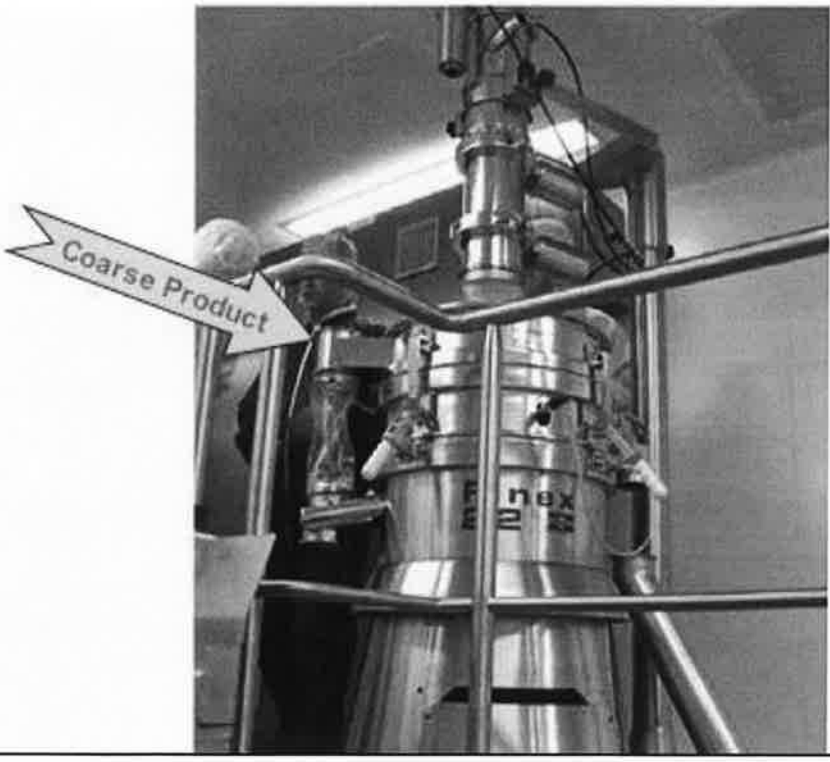


Typical roller compaction process

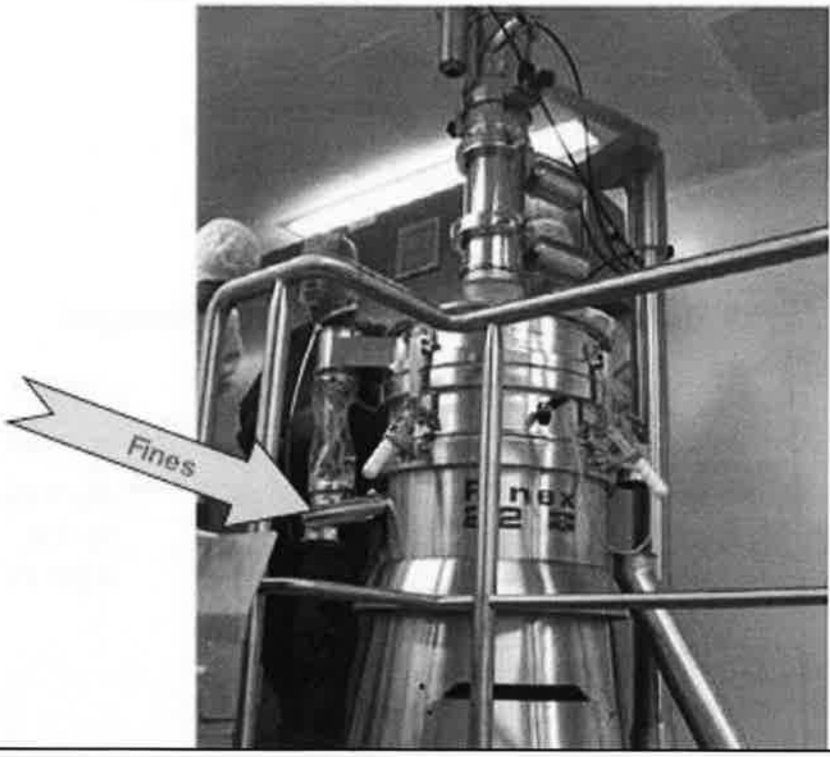


Recycling and Sieving

Recycling and Sieving



Recycling and Sieving

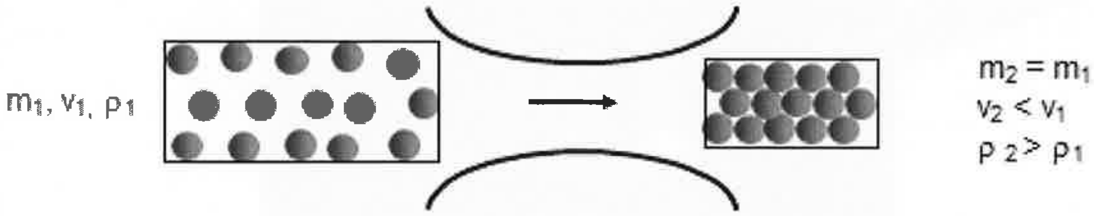


Recycling and Sieving

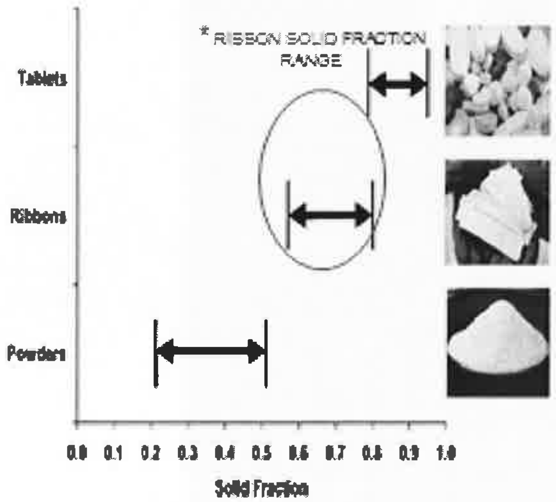
Roller Compaction Rationalisation

- Densification = Volume in/volume out
- The greater volume change, the greater the densification
- Mass in and out remains constant in a unit time

Hence density (Solid Fraction) is key parameter being changed



Solid Fraction during Roller Compaction



Zinchuk et al 2004

$$SF = \frac{\rho_e}{\rho_t}$$

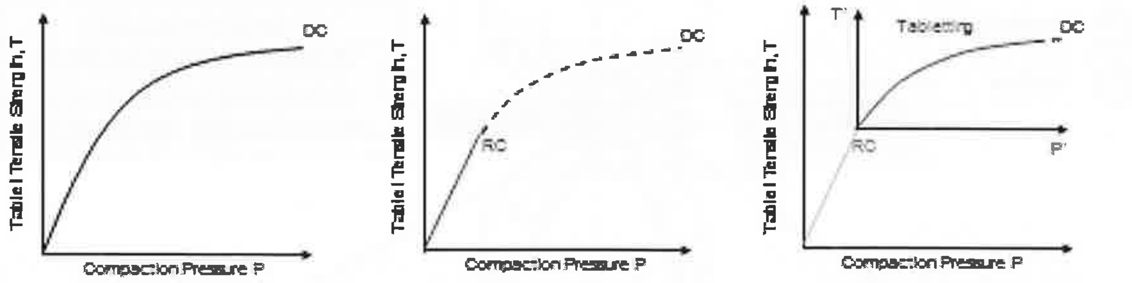
ρ_e = compact density (g/ml)

ρ_t = true density of material (g/ml)

True Density Definition:
The density of the particles that make up a powder or particulate solid.

Compact (or Bulk) Density:
The average density of a large volume of the powder in a specific medium (usually air)

Concept of Cumulative Compaction Pressure

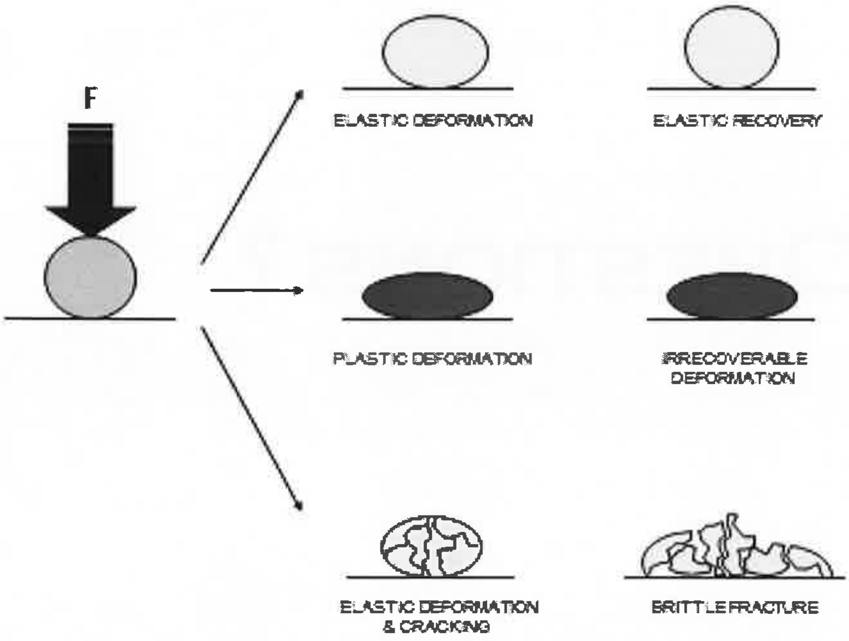


Direct Compression | Roller Compaction | Roller Compaction & Tabletting

Redrawn after Farber et al. (2008)

The powder blend can only be compressed to a finite extent, dictated by the formulation.

Deformation & Intrinsic Material Properties

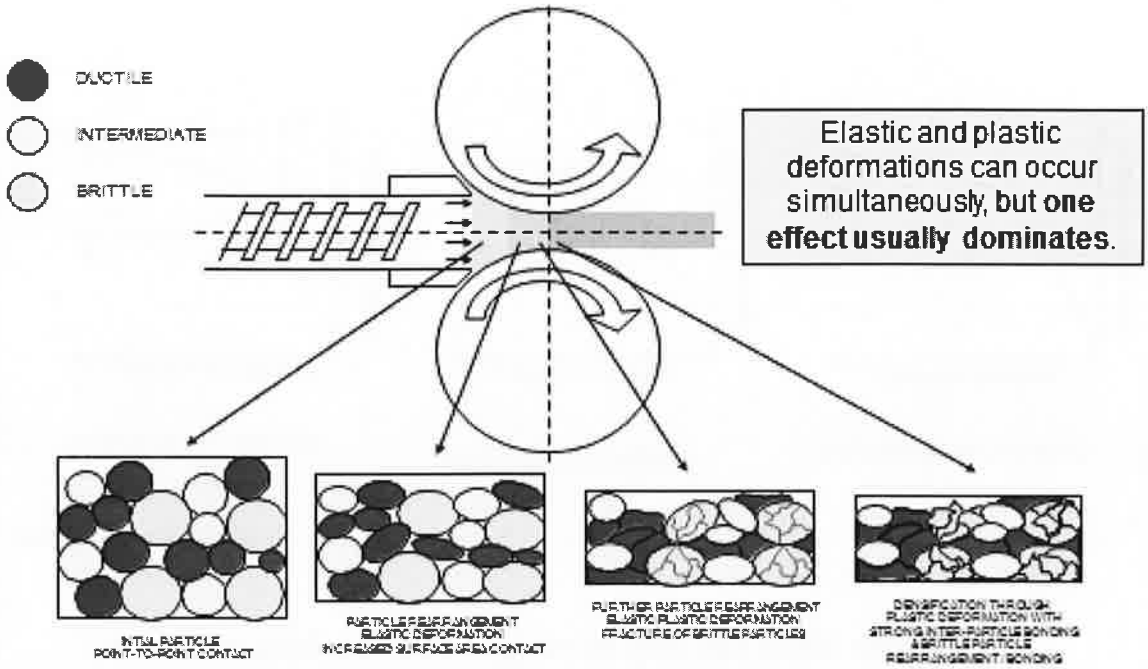


No real deformation
Not conducive to compact formation via compression

Easily deformed.
Time dependence.
Roller compaction reduces ability for further deformation during tablet compression – work hardening

Brittle fracture forms new surfaces for further bonding during tablet compression.
Insensitive to roller compaction speed

From Powder Densification to Ribbon



QUESTIONS ?

Further Reading

Roller Compaction Work

Paul Nkansah et al	*(Drug Dev and Ind Pharmacy, 2008 34:142–148)*
John Gamble et al	*(Pharm Dev and Tech, 2010, 15(3): 223–229)*
Stefanie Peter et al	*(Powder Technology, 2010 199: 165–175)*
Zinchuk et al	*(Int. J. Pharm, (2004) 269: 403-415)*

High Shear Wet Granulation Work

Paul Sirois et al	*(Pharm Dev and Tech, 2000, 5(3), 365–374)*
Karen Hapgood et al	*(Powder Technology, 2004, 141: 20–30)*
Gossett Campbell et al	*(Powder Technology, 2011, 1-3: 184–192)*
Simon Iveson et al	*(Powder Technology, 2001, 117: 3–39)*

Lecture 2. Wet High Shear Granulation Regime Map

Dr Ian Gabbott (AstraZeneca)

Wet High Shear Granulation

Regime Map

Ian Gabbott
Formulation Science, Pharmaceutical Development UK

AstraZeneca

Introduction
Why Granulate?

To produce larger agglomerates from fine powders

- Improve handling
- Improve product appearance
- Enhanced flow and mixing properties
- Control of solubility and porosity
- Increase bulk density for storage
- Creation of non-segregating blends

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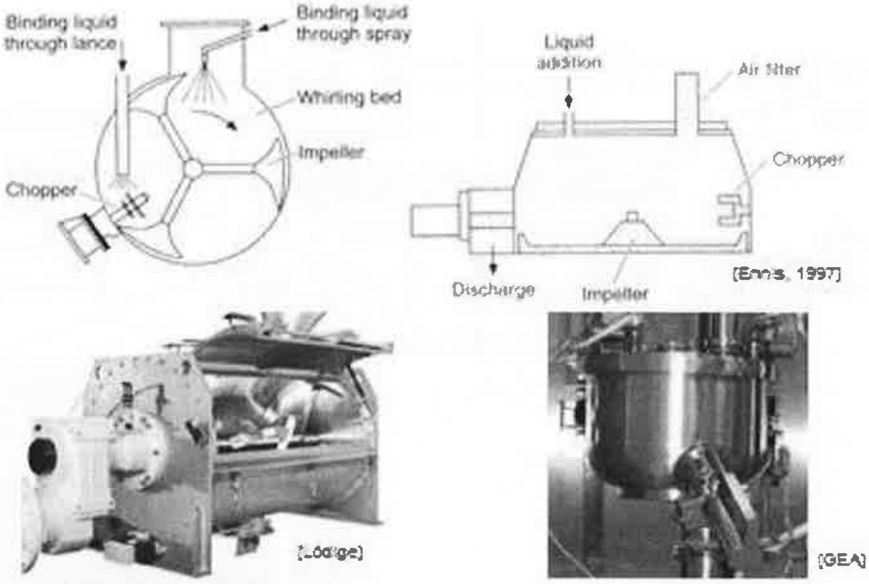
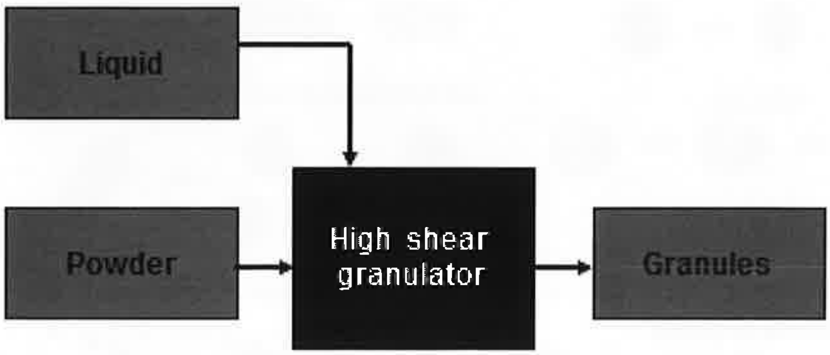
Introduction
High Shear Wet Granulators

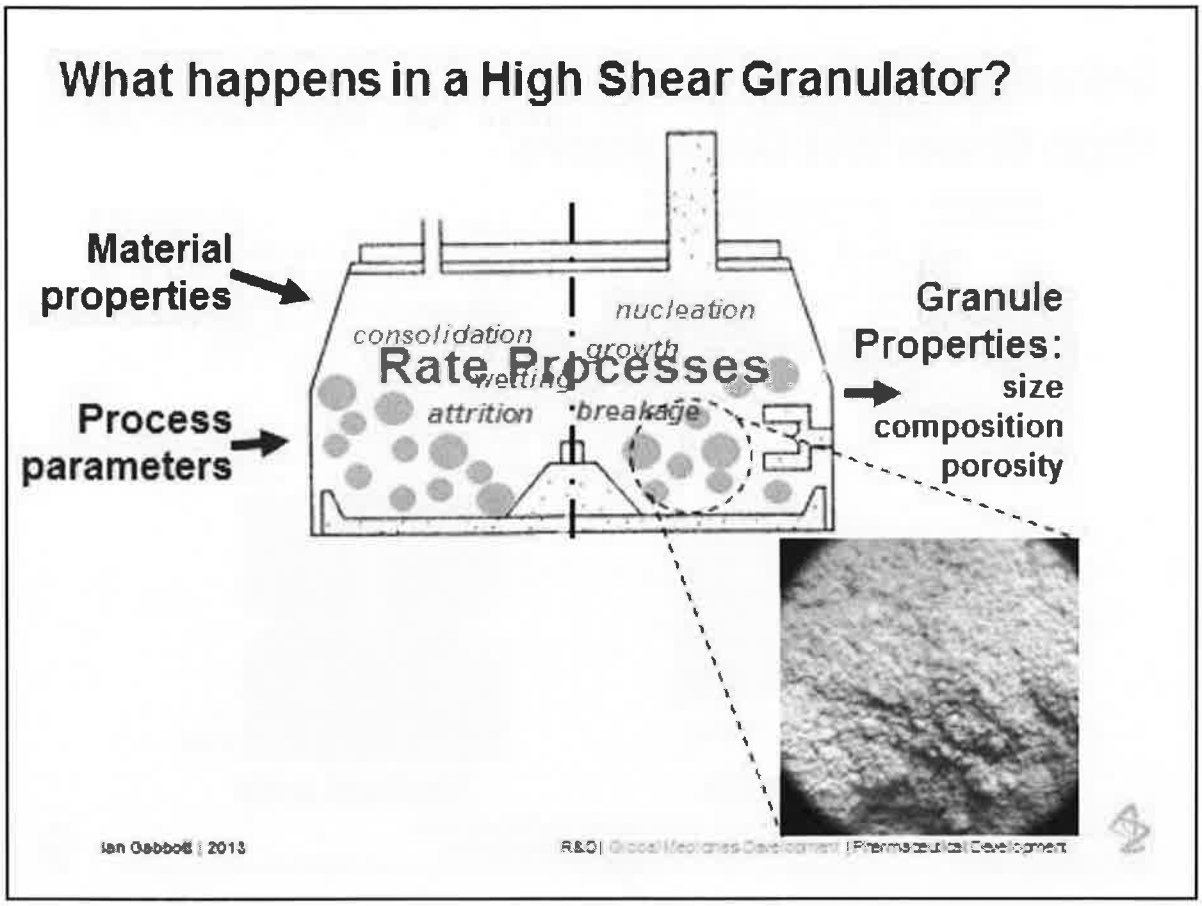


Horizontal axis **Vertical axis**

Terminology note: 'binder' and 'liquid' used interchangeably in this presentation

Introduction
High Shear Wet Granulation Process




What happens in a High Shear Granulator?
Material properties
Process parameters
consolidation
nucleation
Rate Processes
wetting
growth
attrition
breakage
Granule Properties:
size
composition
porosity
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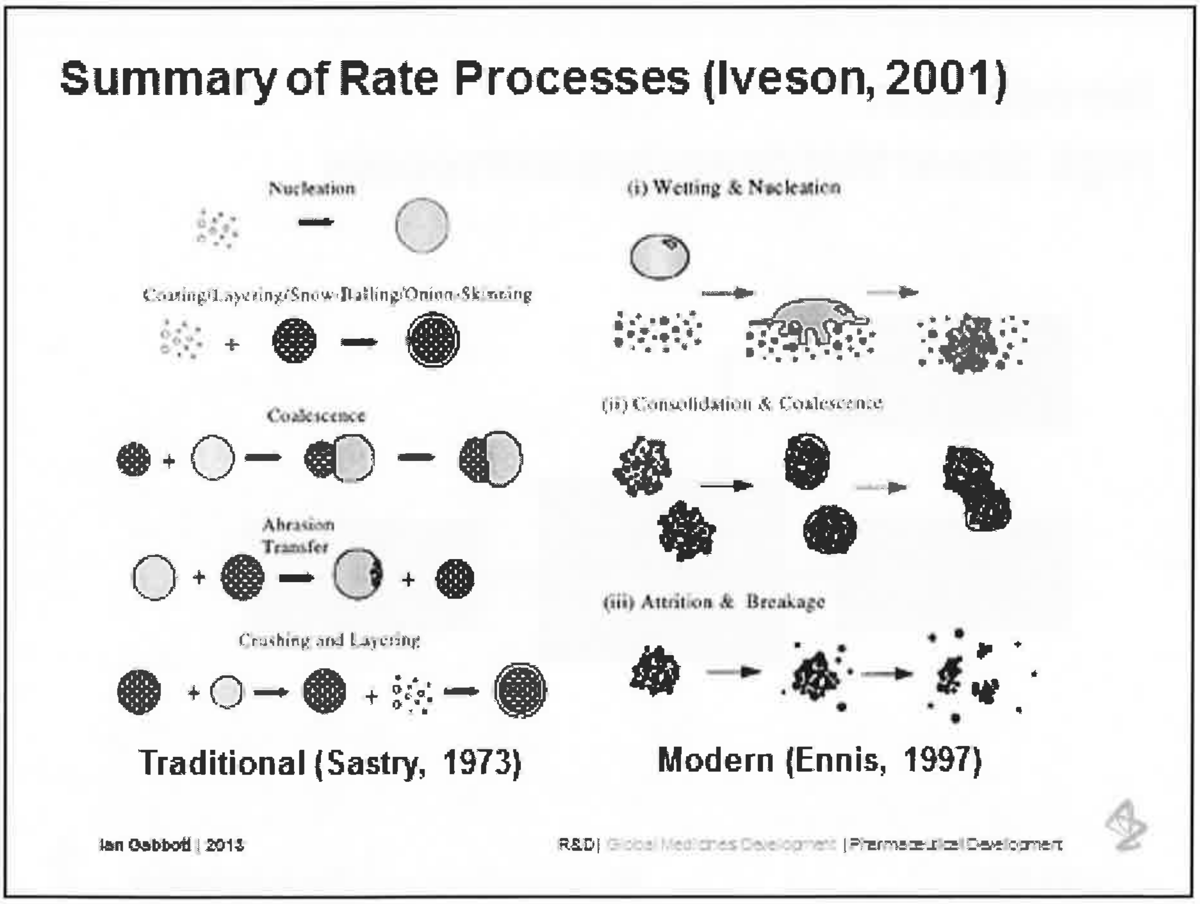
Summary of Rate Processes (Iveson, 2001)
Nucleation
Coating/Layering/Snow-Balling/Onion-Skinning
Coalescence
Abrasion Transfer
Crushing and Layering
(i) Wetting & Nucleation
(ii) Consolidation & Coalescence
(iii) Attrition & Breakage
Traditional (Sastry, 1973)
Modern (Ennis, 1997)
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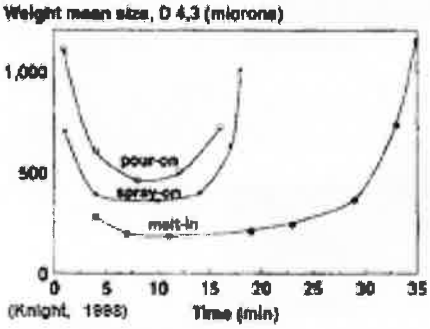
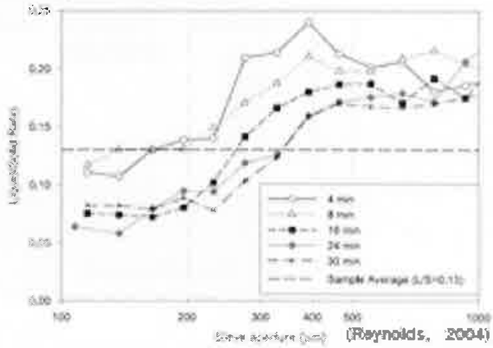
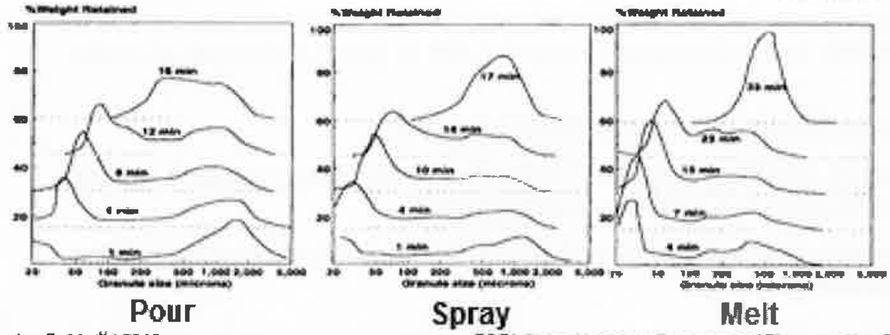
Mechanisms: Nucleation and Wetting Liquid/Binder Mixing and Distribution







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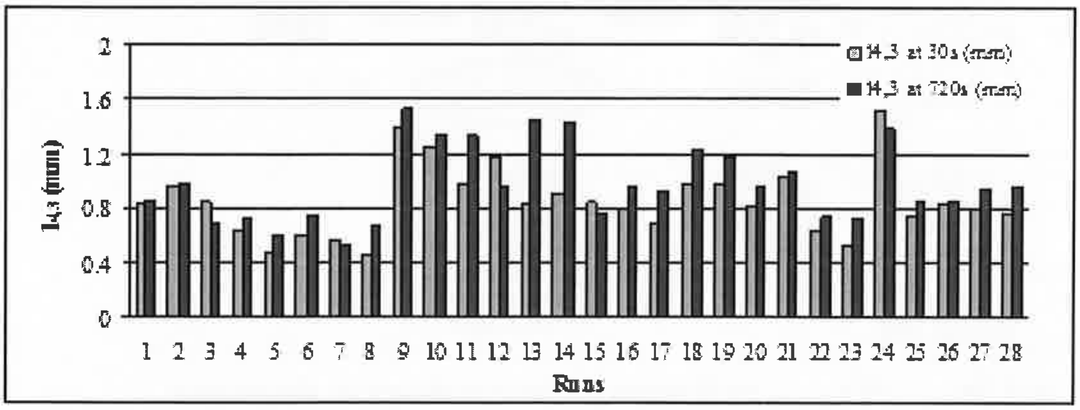
Importance of Nucleation

Properties of granules substantially imprinted during this stage



(Le, 2004)

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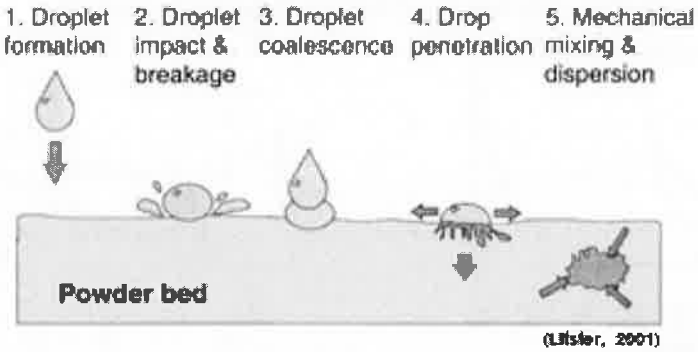
Mechanisms: Nucleation and Wetting



Wetting and nucleation, a process where the liquid binder is brought into contact with a dry powder bed, and is distributed through the bed to give a distribution of nuclei granules.

Two processes are important in the nucleation zone.

1) *nuclei formation*, which is a function of wetting thermodynamics (contact angle and spreading coefficients) and kinetics(penetration time).

2) *binder dispersion*, or effective mixing of the powder and binder, which is a function of process variables.

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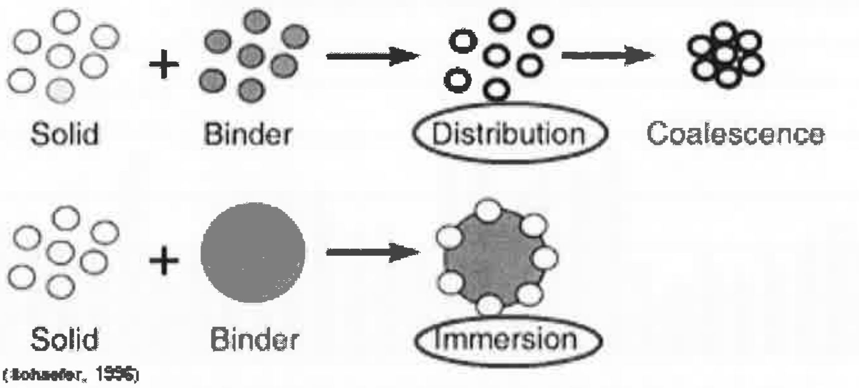
Nucleation mechanisms



(a) $D_{droplet}/D_{particle} >> 1$: immersion mechanism dominant
(b) $D_{droplet}/D_{particle} << 1$: distribution mechanism dominant

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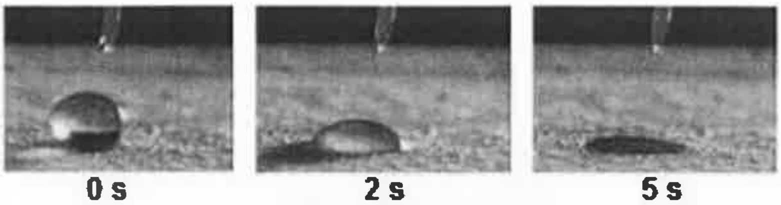
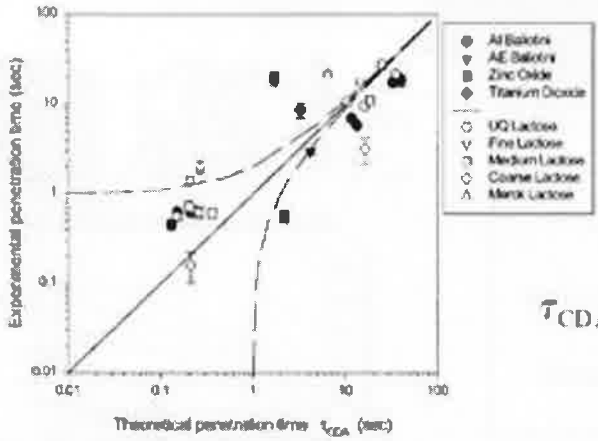
Nucleation kinetics – Penetration time prediction





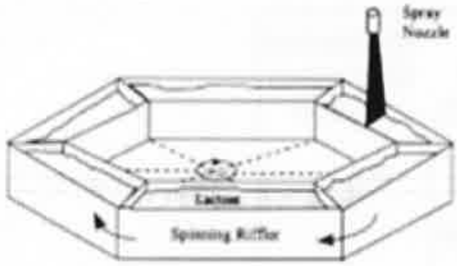
Penetration time depends on liquid and powder properties

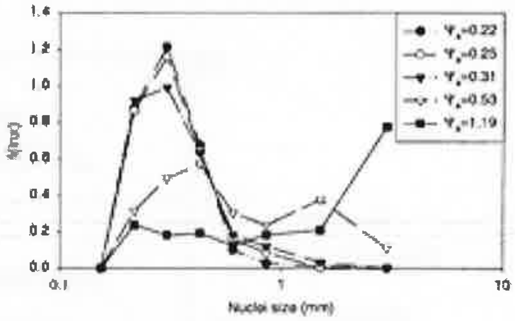
$$\tau_{CDA} = \frac{2V_0^2}{\pi^2 \varepsilon^2 r_d^4 R_{pore}} \frac{\mu}{\gamma_{LV} \cos\theta}$$

(Hapgood, 2002)

Quantifying Liquid Distribution - Dimensionless Spray Flux

Proposed by Litster et al. (2001)

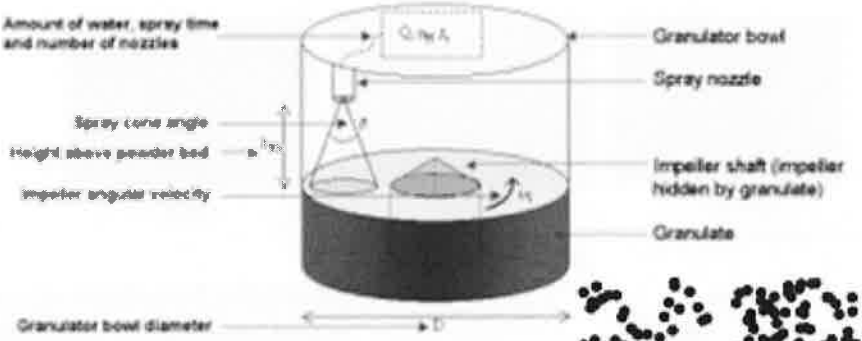


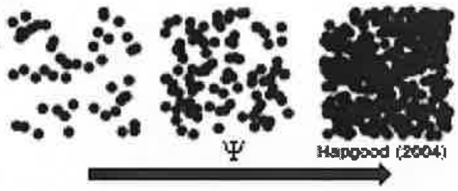


Experiments with carefully controlled liquid and powder flux.

- Quantified liquid density on powder surface using dimensionless spray flux:
$$\psi = \frac{\text{area flux of liquid}}{\text{area flux of powder}} = \frac{3\dot{V}}{2\dot{A}d_d}$$
- Found small values gave narrow monomodal distributions
  - Referred to as 'droplet controlled nucleation' i.e. a single droplet produces the 'nucleus' of a single granule

Spray Flux – Using real granulation parameters



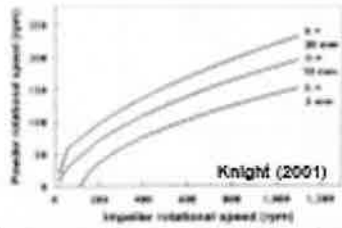


$\Psi =$

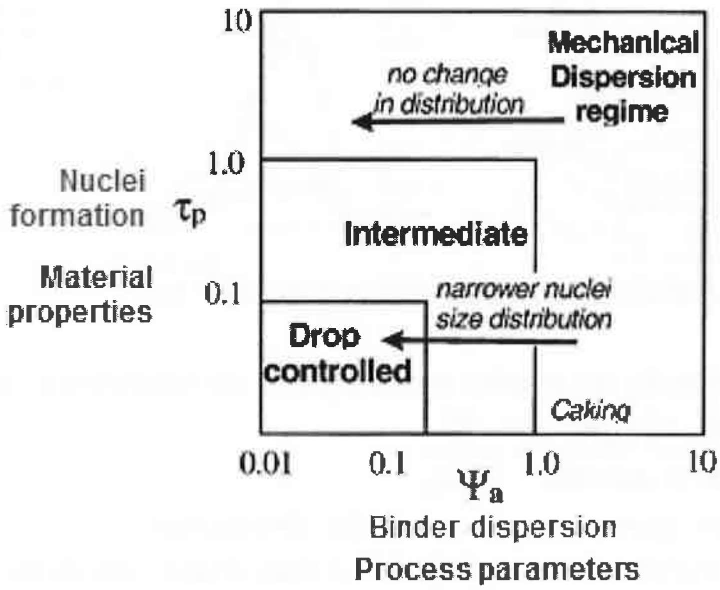
- Area flux of liquid
  - Liquid flowrate
    - Water quantity, Spray time, Number of nozzles
  - Droplet size

divided by

- Area flux of powder
  - Powder velocity
    - Slower than impeller speed
  - Projected spray width



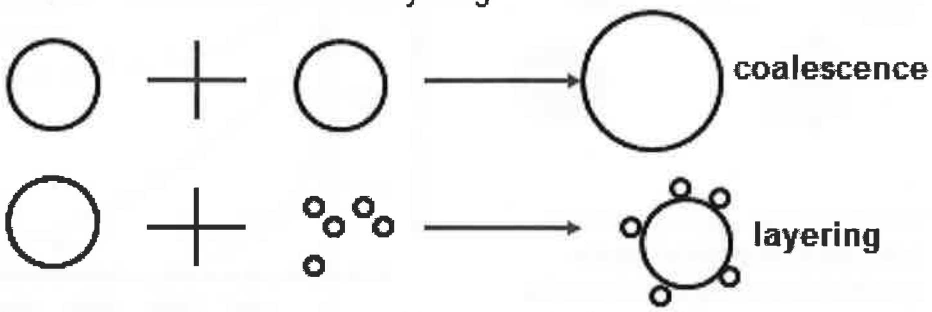
Summary – Nucleation regime map



(Hapgood, 2003)

Mechanisms: Consolidation & Coalescence Coalescence / Layering

- Process where collisions between two granules, granules and feed powder lead to granule aggregation
- Growth - coalescence and layering



- The success of granules coalescence is dependent on the **availability of the liquid on the granule surface** and **mechanical properties** (liquid bridge and inter-particle friction) of the granules.

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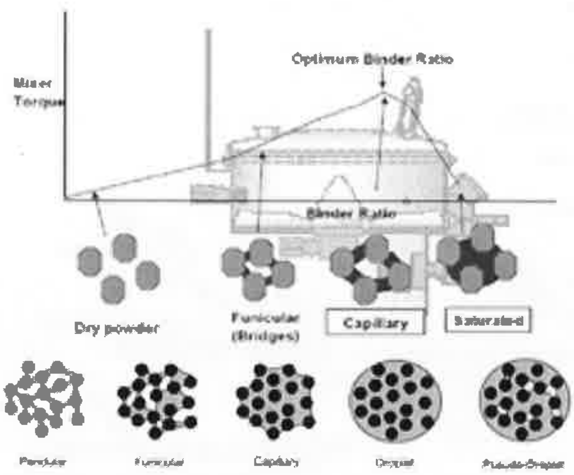
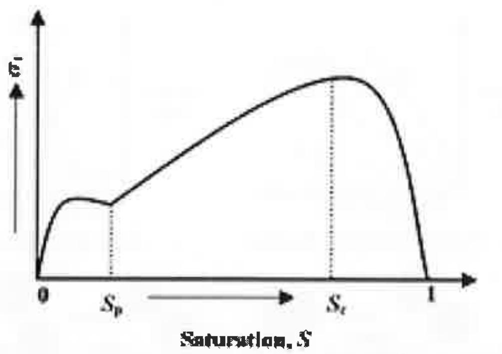
Saturation of liquid-bound granules

Wet Granulation Process



(Newitt & Conway Jones, 1958)



(Schubert, 1975)

Degree of saturation influences the mechanical properties of the granules

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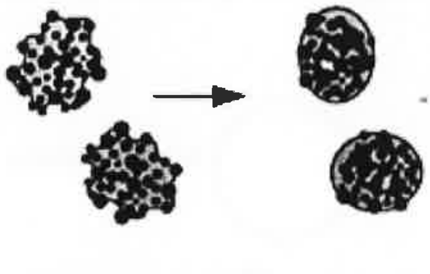
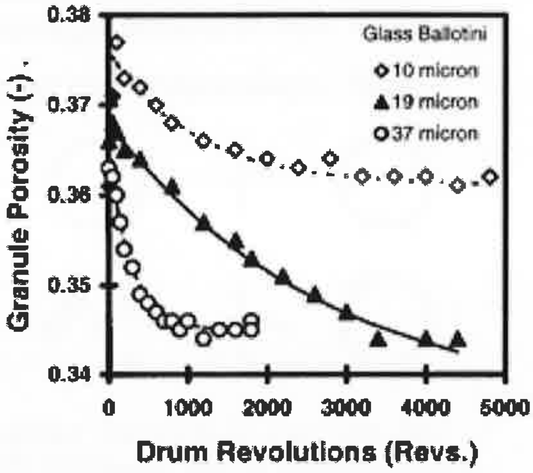
Consolidation



It is not just the total degree of saturation that determines coalescence, but also how the liquid is distributed.



Iveson (1998)

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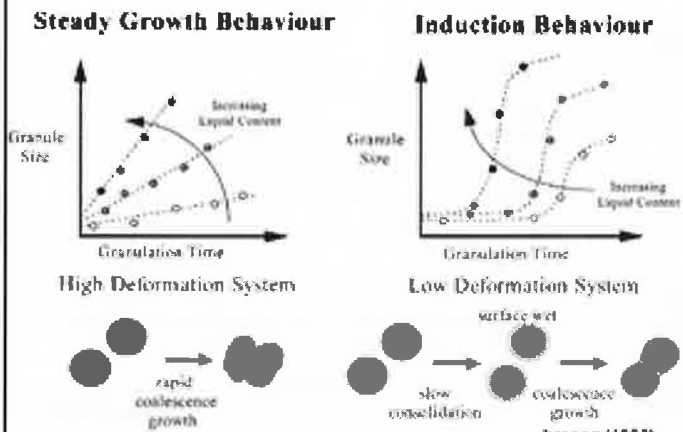
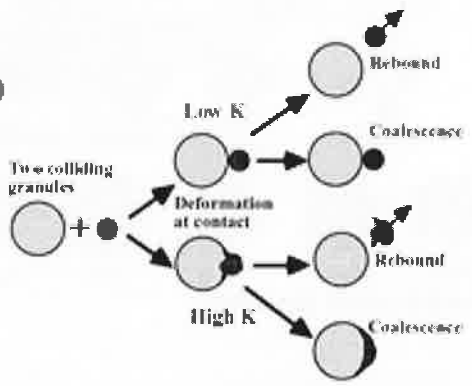
To coalesce or not to coalesce...



Iveson (1998)



Ouchiyama & Tanka (1982)
Perry's ChemEng HBk 8th Ed.

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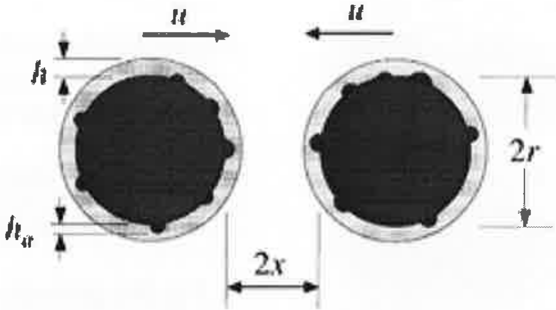
Non-deformable granules: Stokes number

The outcome of the collisions of two **liquid-covered** particles is determined by the ratio:



(Ennis, 1991)

$$St_v = \frac{\textit{Initial kinetic energy}}{\textit{viscous energy dissipation}} = \frac{8\rho r u}{9\mu}$$

$$St_v^* = \left(1 + \frac{1}{e}\right)\ln\left(\frac{h}{h_a}\right)$$

Critical stokes number
e is restitution coefficient

- For a given collision velocity and liquid viscosity, the theory predicts that there will be a limiting granule size beyond which coalescence will not occur

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Non-deformable granules: Stokes number Coalescence regimes

$$St_v = \frac{\textit{Initial kinetic energy}}{\textit{viscous energy dissipation}} = \frac{8\rho r u}{9\mu}$$

$$St_v^* = \left(1 + \frac{1}{e}\right)\ln\left(\frac{h}{h_a}\right)$$

Non-inertial regime ($St_v << St_v^*$)

- all collisions are successful

Inertial regime ($St_v \approx St_v^*$)

- collisions between two small or one small and one large granule are more likely to lead to coalscense

Coating regime ($St_v >> St_v^*$)

- all collisions between granules are unsuccessful

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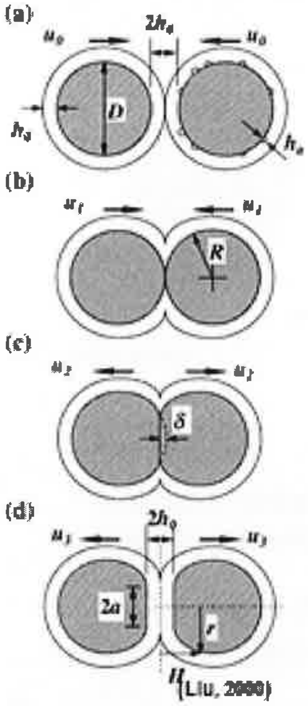
Deformable granules: Stokes deformation number



- Successful coalescence depends on ratio of kinetic energy of collision compared to energy dissipated during granule deformation

$$St_{def} = \frac{\textit{Impact kinetic energy}}{\textit{plastic energy absorbed}} = \frac{\rho u^2}{2Y}$$

- Y is the granule dynamic yield stress, which varies with formulation properties and granule porosity. Iveson recommends the 'end-point' porosity for measurement.
- Stokes deformation number takes into account
  - Process agitation intensity (related to collision velocity)
  - Granule rheology (related to formulation and material properties)

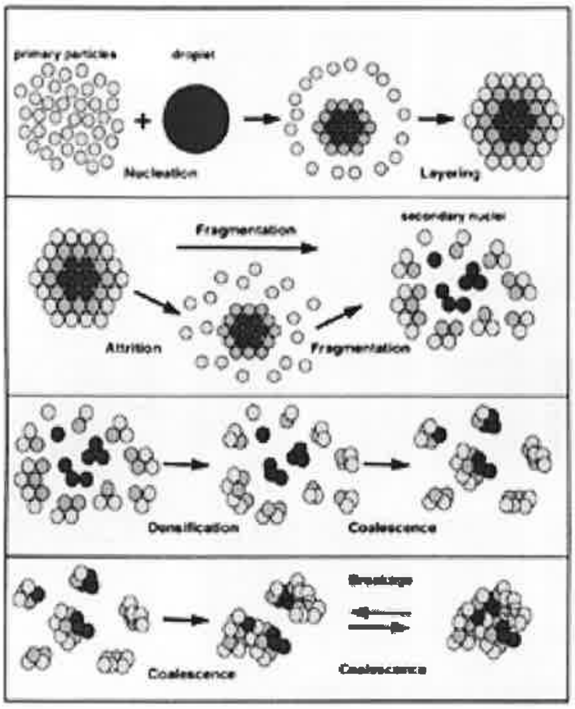
Granule dynamic strength

Powder-Binder Properties	Qualitative Prediction From Models (Equation 2.2 & Equation 2.5)	Experimental Results
Primary particle size, d_p	Increasing d_p decreases strength	Increasing d_p decreases strength (Iveson & Litster, 1998b; van den Dries et al, 2003) Increasing d_p increases strength (Gabbott, 2007)
Binder viscosity, μ	Increasing μ increases strength	Increasing μ increases strength (Iveson & Litster, 1998b; Eliasen et al, 1998)
Binder content, w (which affects granule saturation level, S)	Increasing w increases strength	Variable effect (Iveson & Litster, 1998b; Gabbott, 2007; Schubert, 1975)
Binder surface tension, γ	Increasing γ increases strength	Increasing γ increases strength (Iveson & Litster, 1998b)

(Chan, 2009)

- Some observations from literature on the influence of a range of material/formulation parameters on dynamic granule strength
- Linking these back to Stokes deformation number may indicate the influence on coalescence rates
- However, some observations can be conflicting and changes in materials may induce multivariate effects – need to be aware of competing effects

Mechanisms: Attrition and Breakage



(Vonk, 1997)

Granule homogeneity and liquid distribution

- Attrition dominated
  - Limited redistribution of granule components
- Fragmentation dominated
  - Extensive redistribution of granule components

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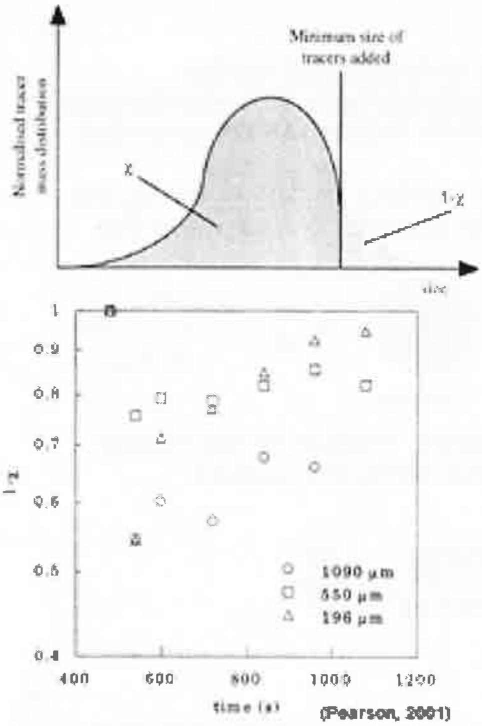
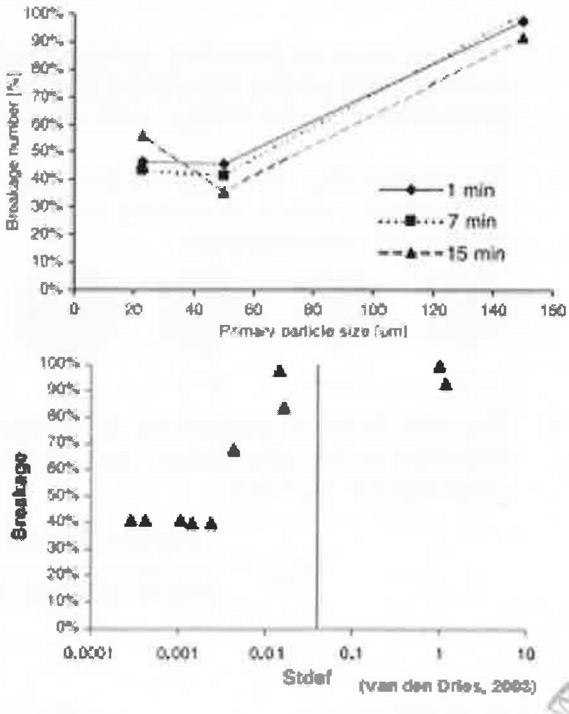
Evidence of breakage in high shear granulation



(Pearson, 2001)



(van den Dries, 2003)

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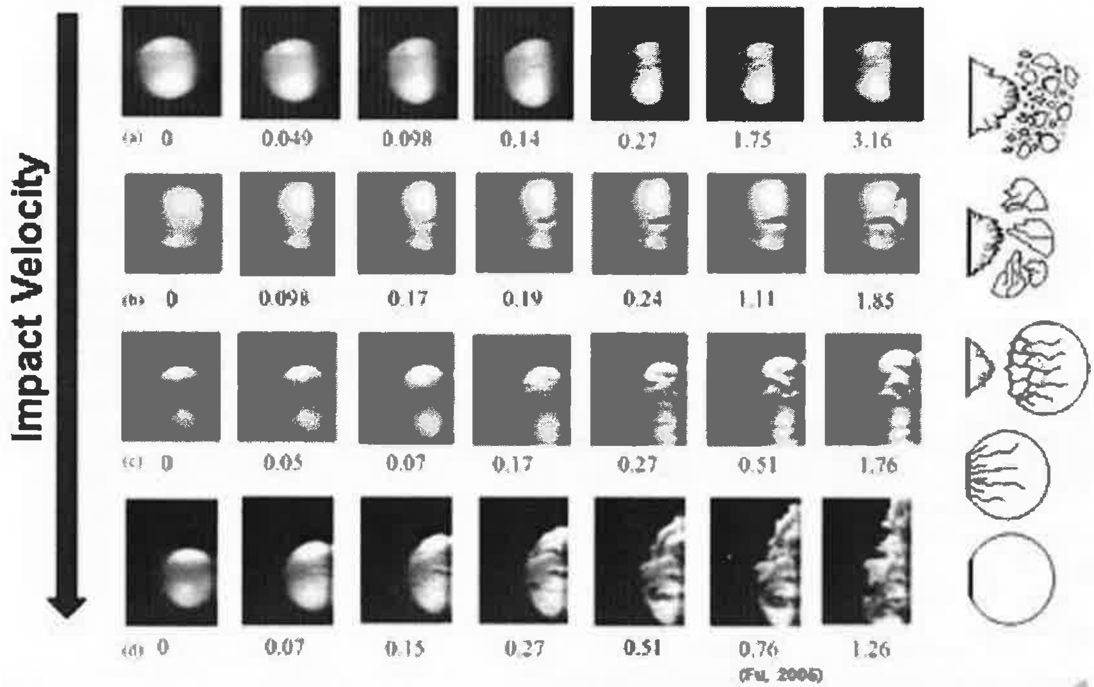
Breakage of wet agglomerates



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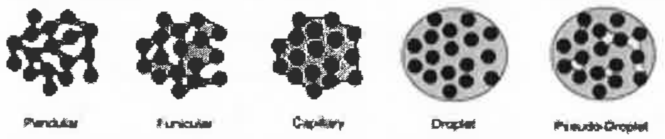
Definition of a Granule Growth Regime Map

- The success of granules coalescence is dependent on the **availability of the liquid on the granule surface** and **mechanical properties** (liquid bridge and inter-particle friction) of the granules.
- The availability of liquid on the granule surface is described by the 'saturation', which is related to both the quantity of liquid and the degree of consolidation



$$s_{max} = \frac{w\rho_s(1-\varepsilon_{min})}{\rho_l\,\varepsilon_{min}}$$

- The mechanical properties of the granules, relative to the mixing intensity in the granulator, are described using the Stokes deformation number

$$St_{def} = \frac{\textit{Impact kinetic energy}}{\textit{plastic energy absorbed}} = \frac{\rho u^2}{2Y}$$

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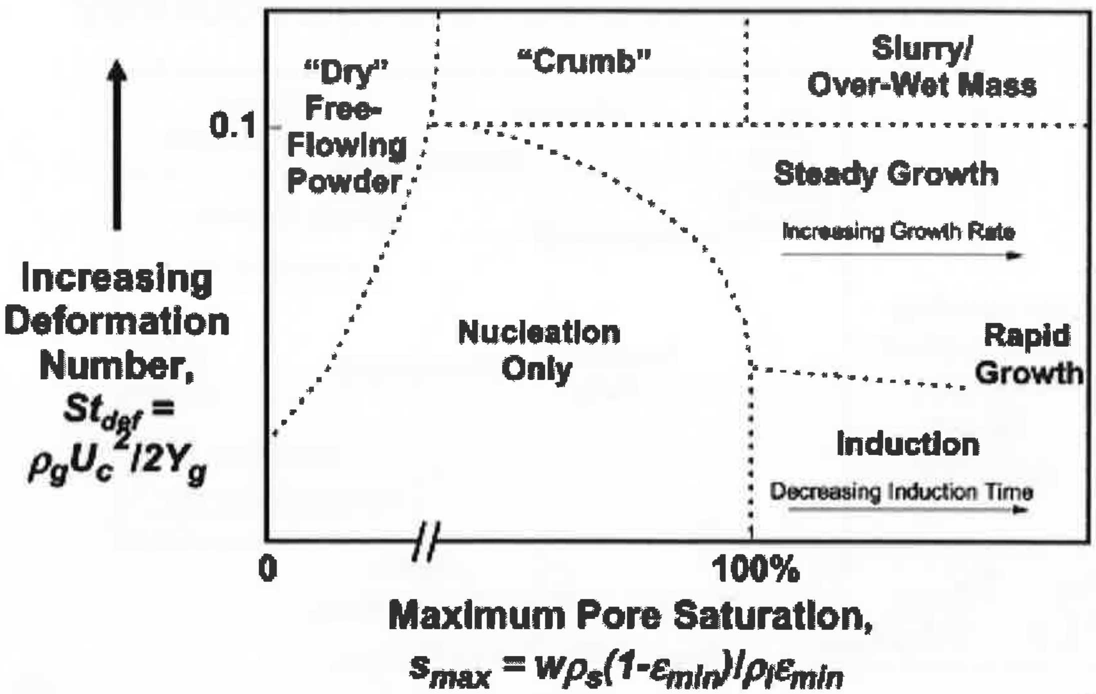
Granule Growth Regime Map (Iveson, 2001)



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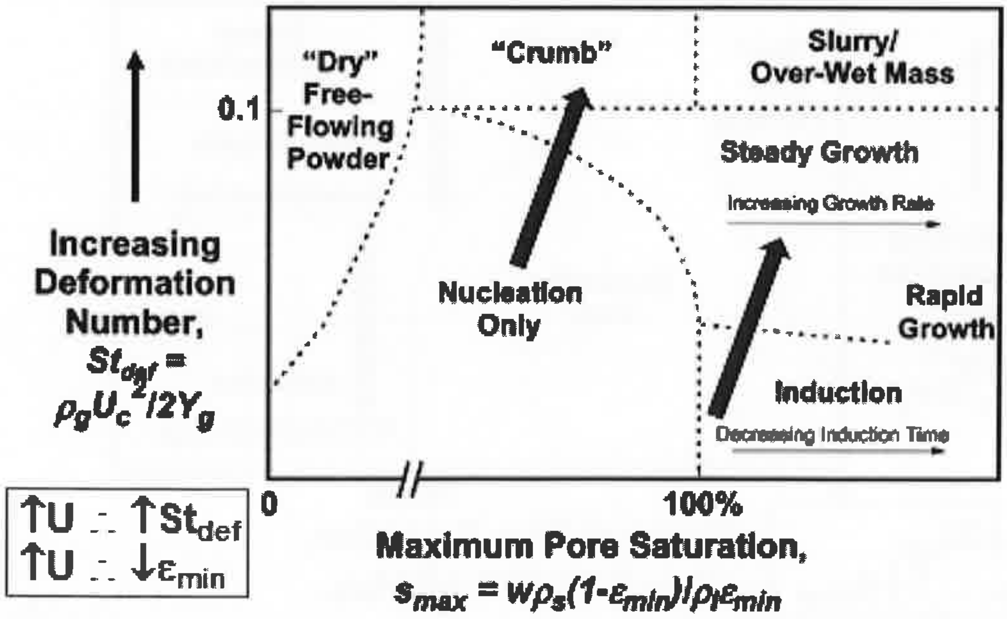
Granule Growth Regime Map
Qualitative movement: Increase impeller speed



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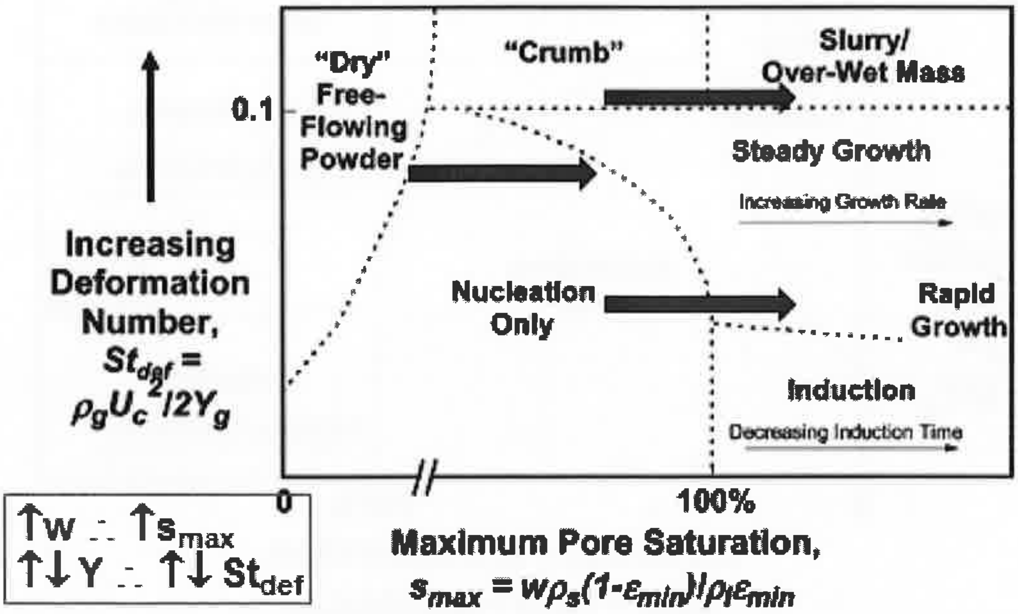
Granule Growth Regime Map
Qualitative movement: Increase liquid quantity



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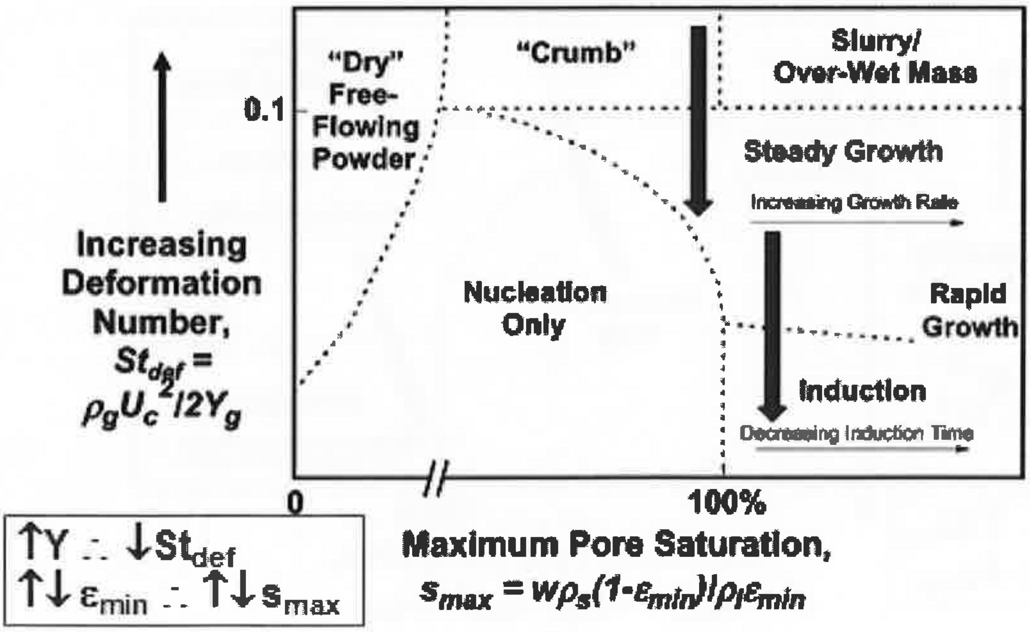
Granule Growth Regime Map
Qualitative movement: Decrease powder size



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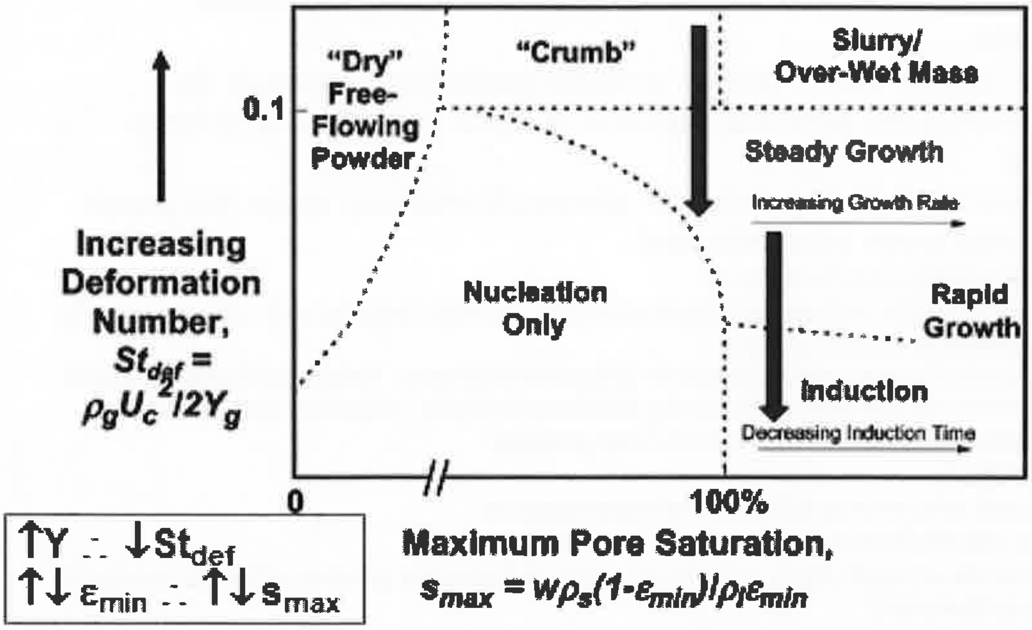
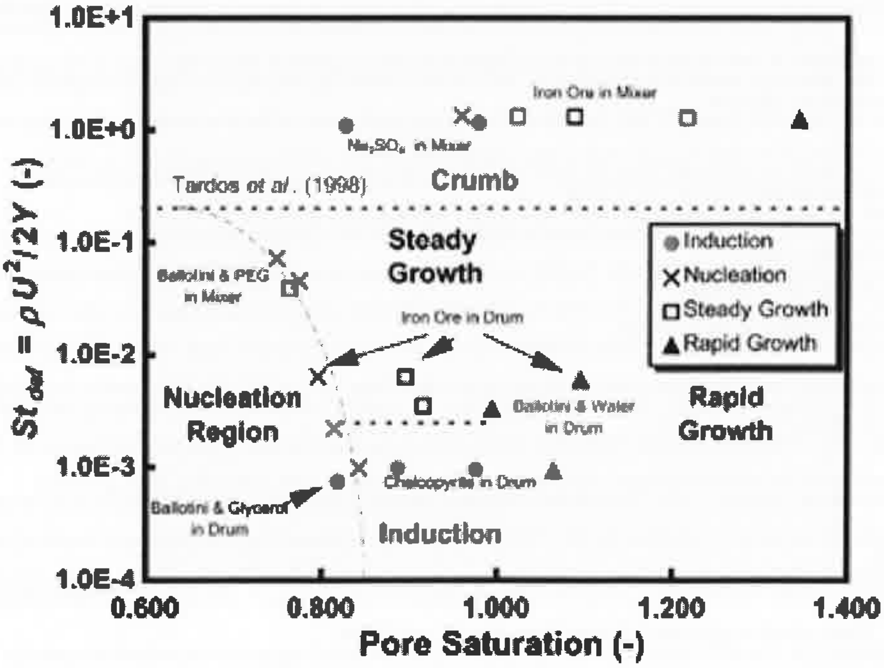
Granule Growth Regime Map
Qualitative movement: Increase liquid viscosity



Growth regime map validation (Iveson, 2001)



Conclusions/ Caveats

- Examined the key rate processes important during high shear granulation
- Use of 'regime maps' provide a useful qualitative framework for understanding the potential impact of material property and process changes
- Absolute location of a particular process/formulation within the growth regime map is not straightforward:
  - Stokes deformation number
    - Characteristic collision velocity is difficult to estimate (impeller and chopper speeds can lead to overestimation)
    - Granule dynamic yield strength is difficult to determine. Iveson performed this test at relatively low strain rates using hand-made pellets, which are unlikely to be representative of the structure of real granules
  - Saturation
    - Liquid saturation is difficult to estimate/measure
  - Time dependence
    - Granule strength, liquid content etc. change during the process rather than remain at a fixed point

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Lecture 3. Batch Granulation: Process and Formulation Variables

Prof. Agba Salman (University of Sheffield)

The University Of Sheffield.

Batch granulation: process and formulation variables

A. D. Salman
Department of Chemical & Biological Engineering
University of Sheffield
United Kingdom

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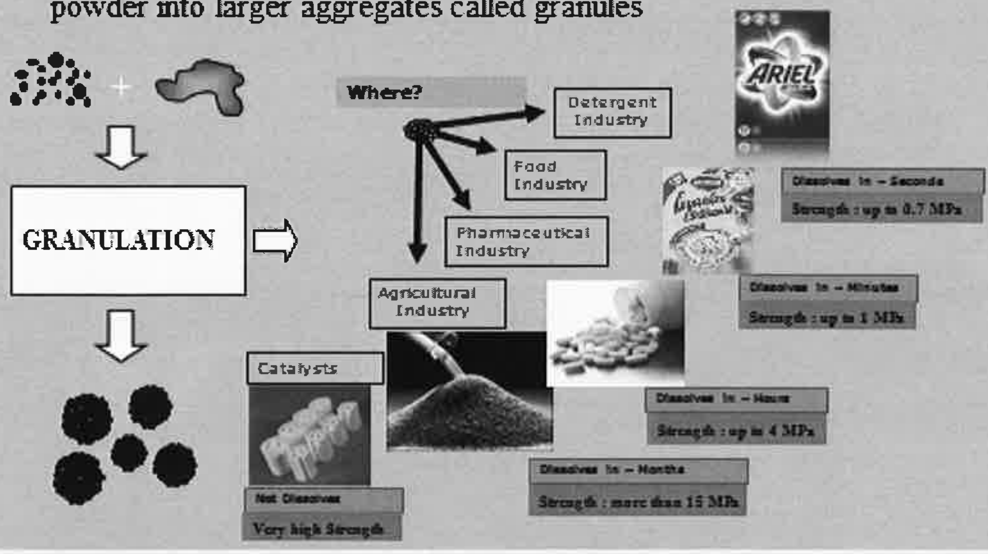
Granule Properties. It is not just Size anymore!
Dissolution time and Strength

Granulation is the name given to the process of agglomerating powder into larger aggregates called granules



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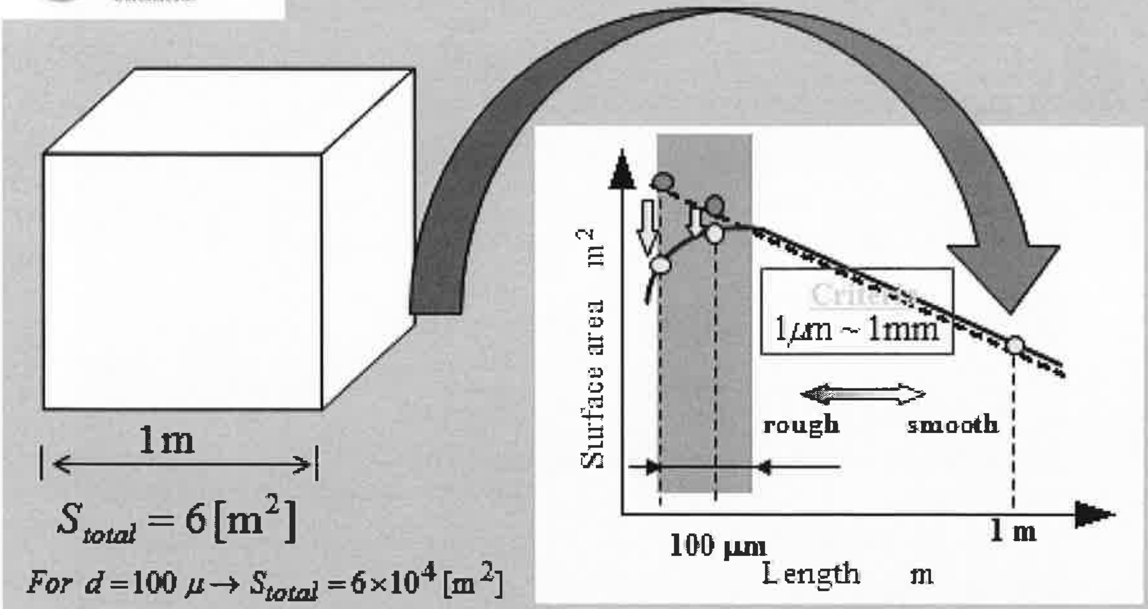
Why Particles: Large Surface Area



$S_{total} = 6\,[\mathrm{m}^2]$

For $d = 100\ \mu \rightarrow S_{total} = 6\times10^4\,[\mathrm{m}^2]$

For $d = 1\ \mu \rightarrow S_{total} = 6\times10^6\,[\mathrm{m}^2]$

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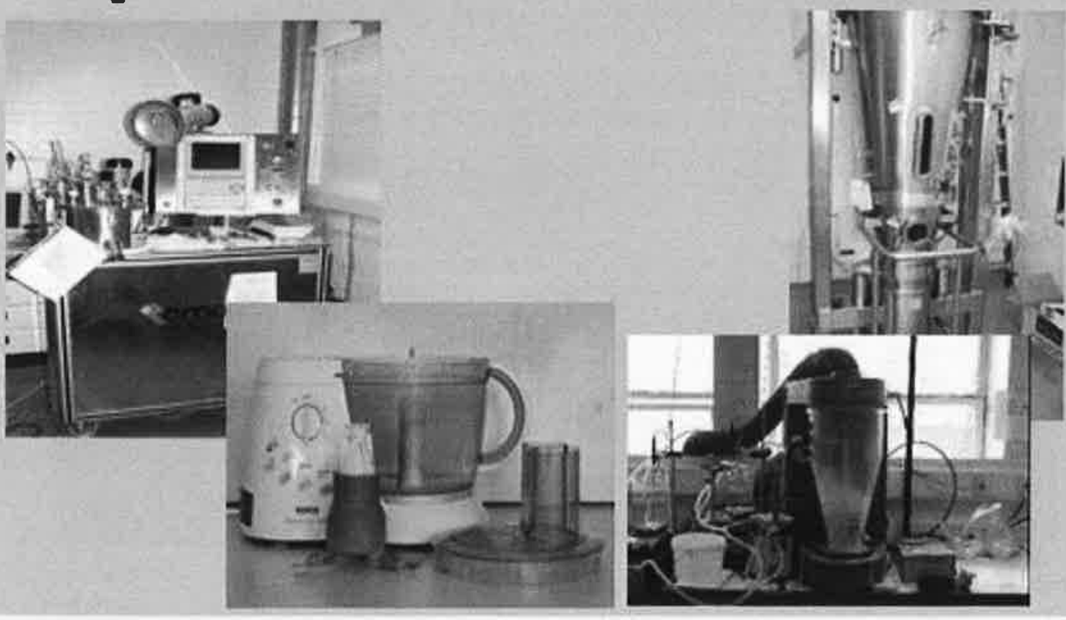
Common Equipment

- High Shear Granulation
- Fluidized Bed Granulation



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Magnitude of Shear Force


Fluidised bed granulation **High Shear Granulation**

Increasing impact force

∴ Different growth mechanisms!

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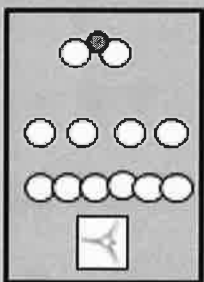
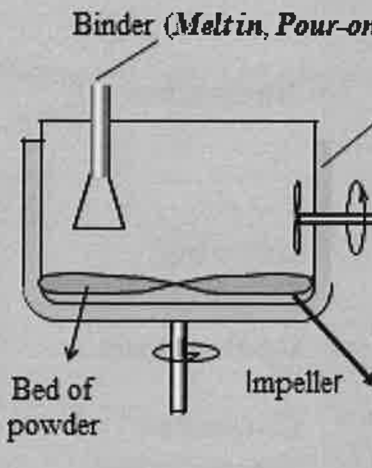
High Shear Granulation (HSG)

Process Variables:
Granulating time/ Binder amount
Impeller speed
Binder addition method

Formulation Variables:
Binder viscosity
Surface tension
Primary particle size
Droplet size





Granule Properties
Size, Structure, Porosity, Strength, Binder distribution

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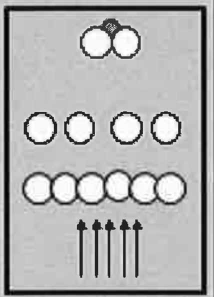
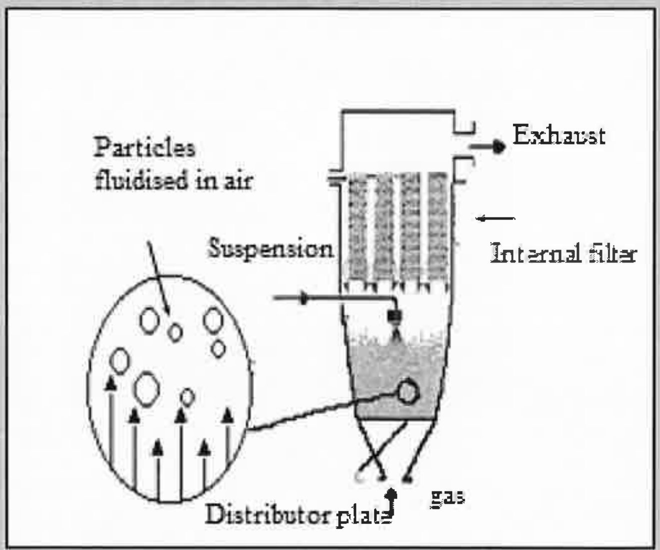
Fluidised Bed Granulation (FBG)

Process Variables:
Granulation time/Binder amount
Air velocity
Binder addition method

Formulation Variables:
Binder viscosity
Surface tension
Primary particle size
Droplet size





Granule Properties
Size, Structure, Porosity, Strength, Binder Distribution

Fluidised

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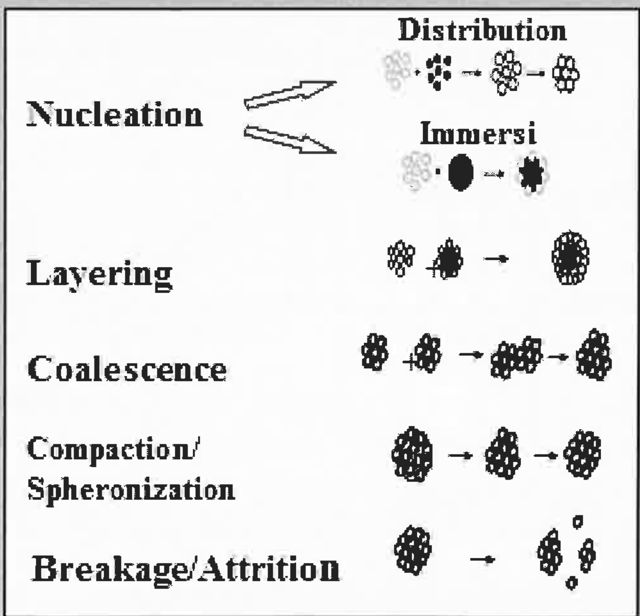
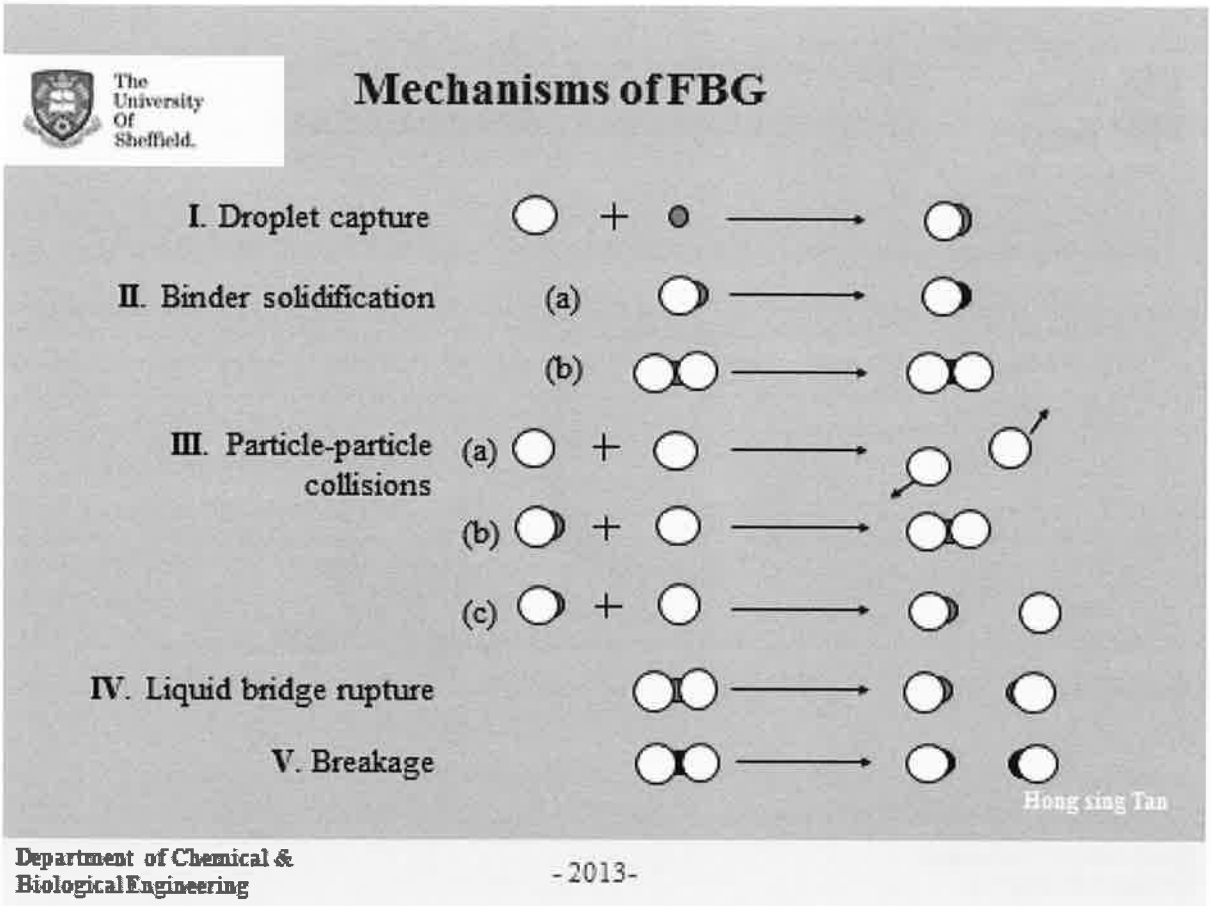
Granulation Mechanisms HSM



Iveson et.al., 2002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Mechanisms of FBG
I. Droplet capture
II. Binder solidification
(a)
(b)
III. Particle-particle collisions
(a)
(b)
(c)
IV. Liquid bridge rupture
V. Breakage
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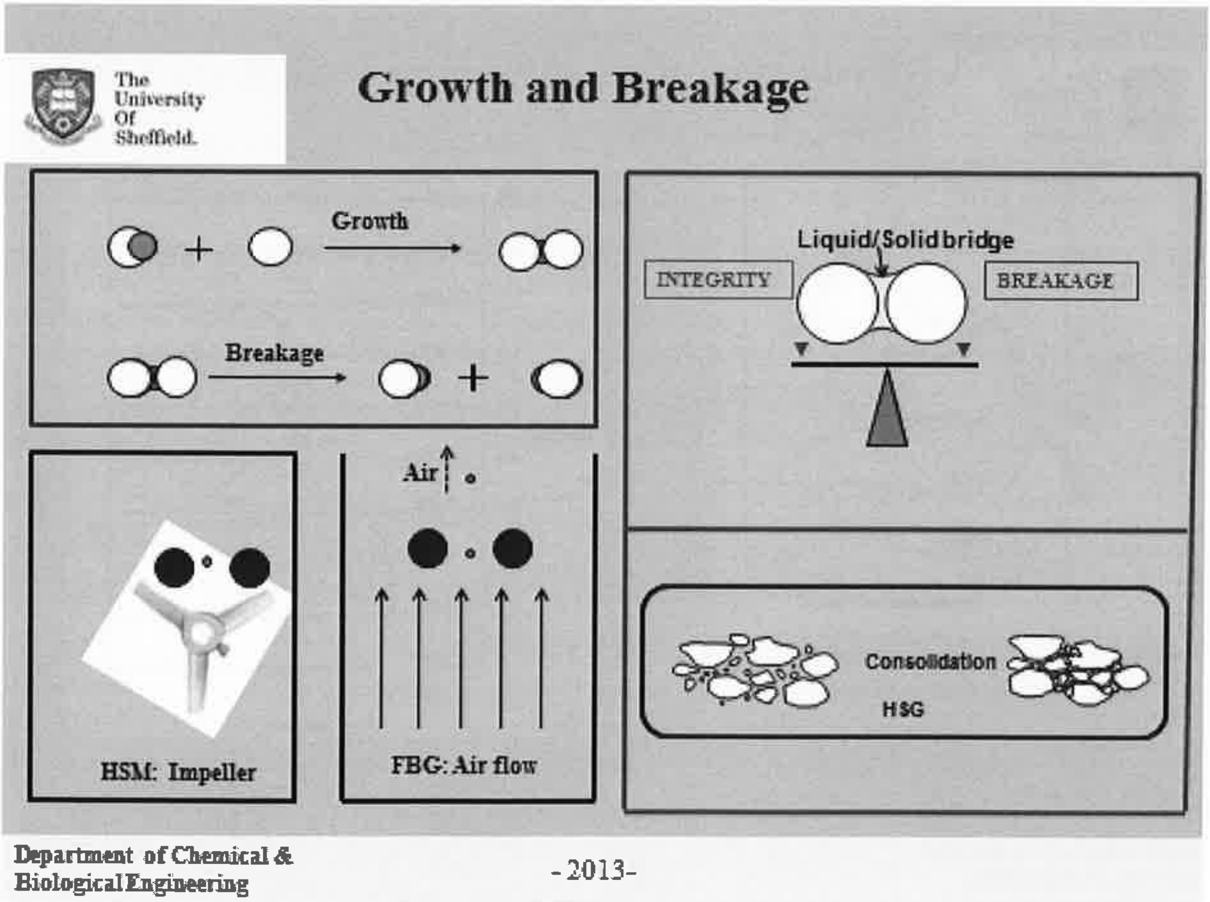
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Growth and Breakage
Growth
Breakage
Liquid/Solid bridge
INTEGRITY
BREAKAGE
Air
HSM: Impeller
FBG: Air flow
Consolidation
HSG
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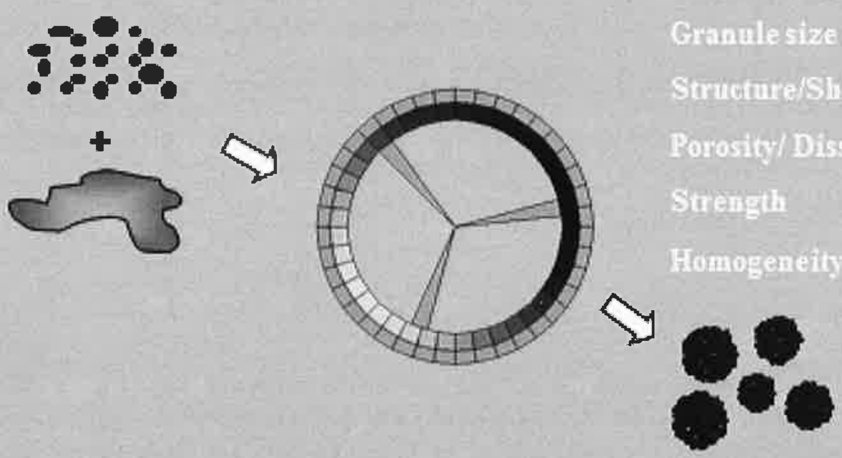
HSG and FBG
What are Attributes of High Quality Granulation?



Product Properties:

Granule size distribution

Structure/Shape

Porosity/ Dissolution

Strength

Homogeneity (Liquid/Solid ratio)

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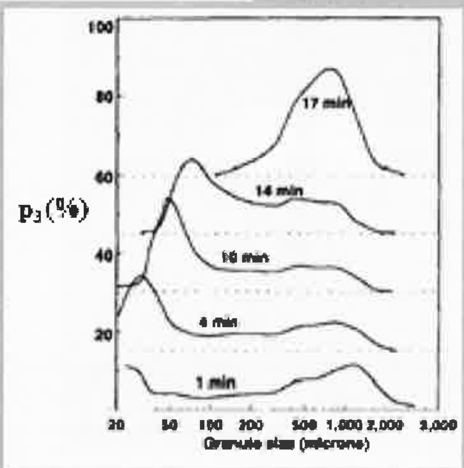
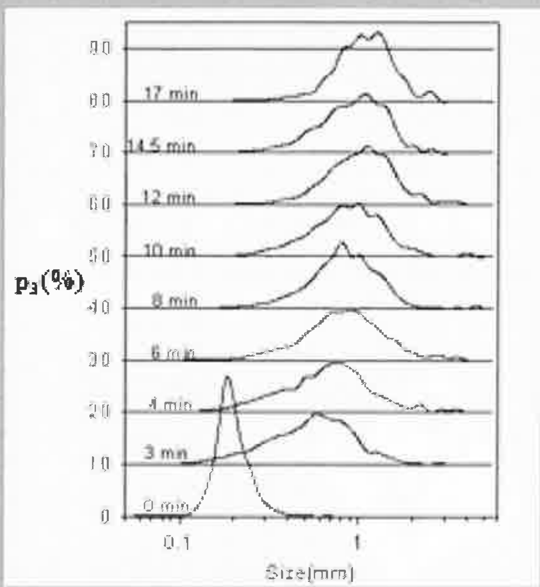
Evolution of Granule Size Distribution in FBG and HSG



Knight et.al 1998

High Shear Granulation

p_3 = normalized volumetric frequency distribution



Tan et.al 2006

Fluidised Bed Granulation

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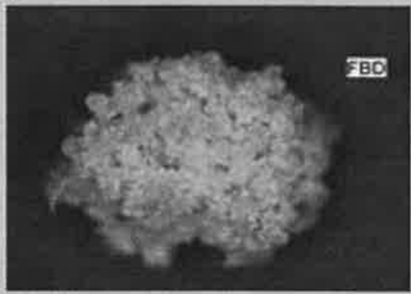
Granule Structures - SEM

High shear granules

- **Higher density**
- **Lower surface and interstitial porosity**
- **Porosity ≈ 0.008 - 0.02**
- **Lower dissolution rate**

Fluidised bed granules



- **Lower density**
- **Higher surface and interstitial porosity**
- **Porosity ≈ 0.1 - 0.3**
- **Higher dissolution rate**

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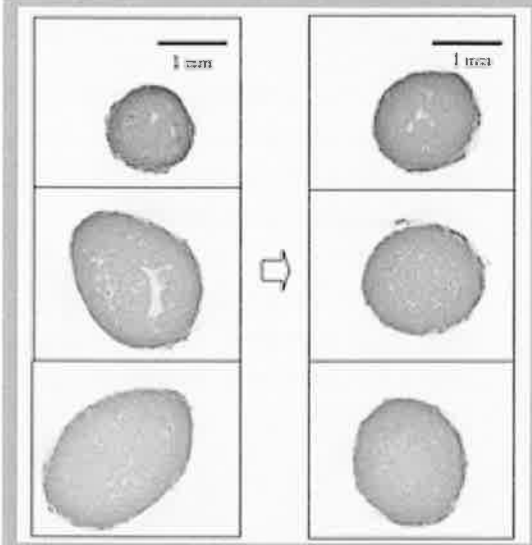
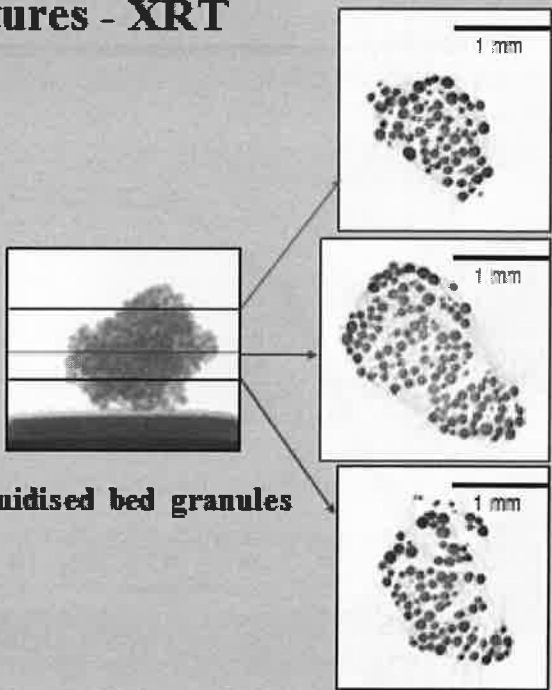
Granule Structures - XRT



400 rpm **600 rpm**

High shear granules



Fluidised bed granules

Daniel Barrera-Medrano, 2006

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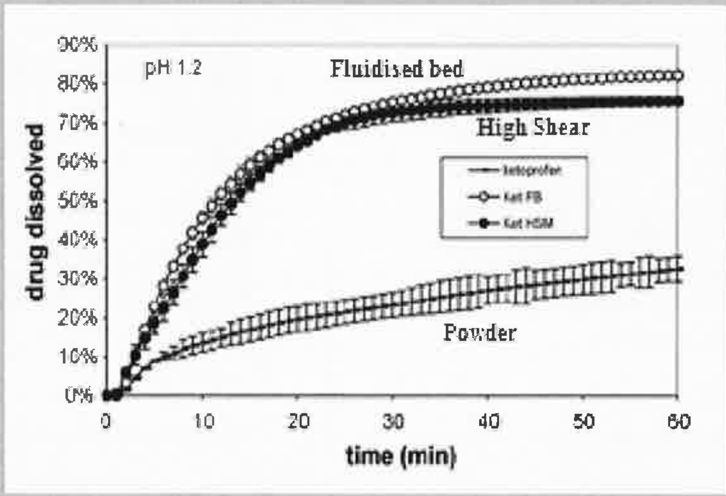
Dissolution of Granules



Passerini et al. 2010

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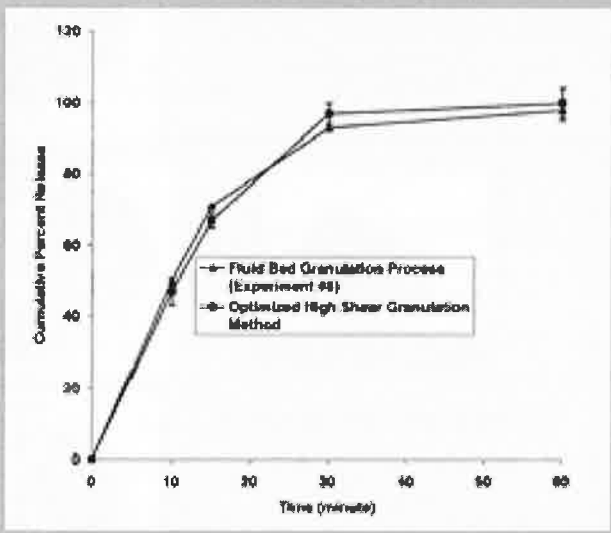
Dissolution Rate of Tablet



J.Z.H. Gao et al. 2002

Despite the granules having different shape and flow properties, the tablet dissolution rate achieved with compacts made by high shear granulation can also be duplicated by those made by fluidised bed granulation.

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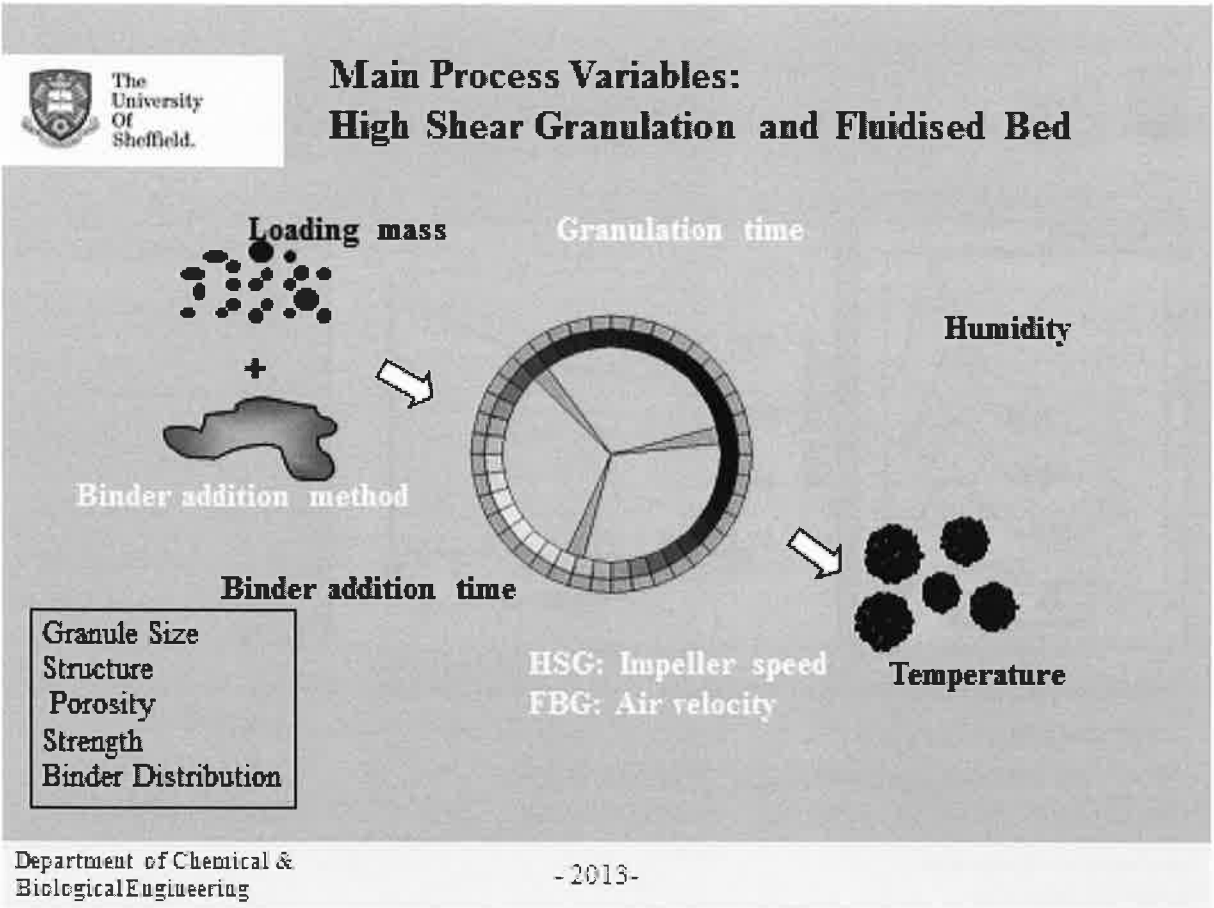
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Main Process Variables:
High Shear Granulation and Fluidised Bed
Loading mass
Granulation time
Humidity
+
Binder addition method
Binder addition time
Granule Size
Structure
Porosity
Strength
Binder Distribution
HSG: Impeller speed
FBG: Air velocity
Temperature
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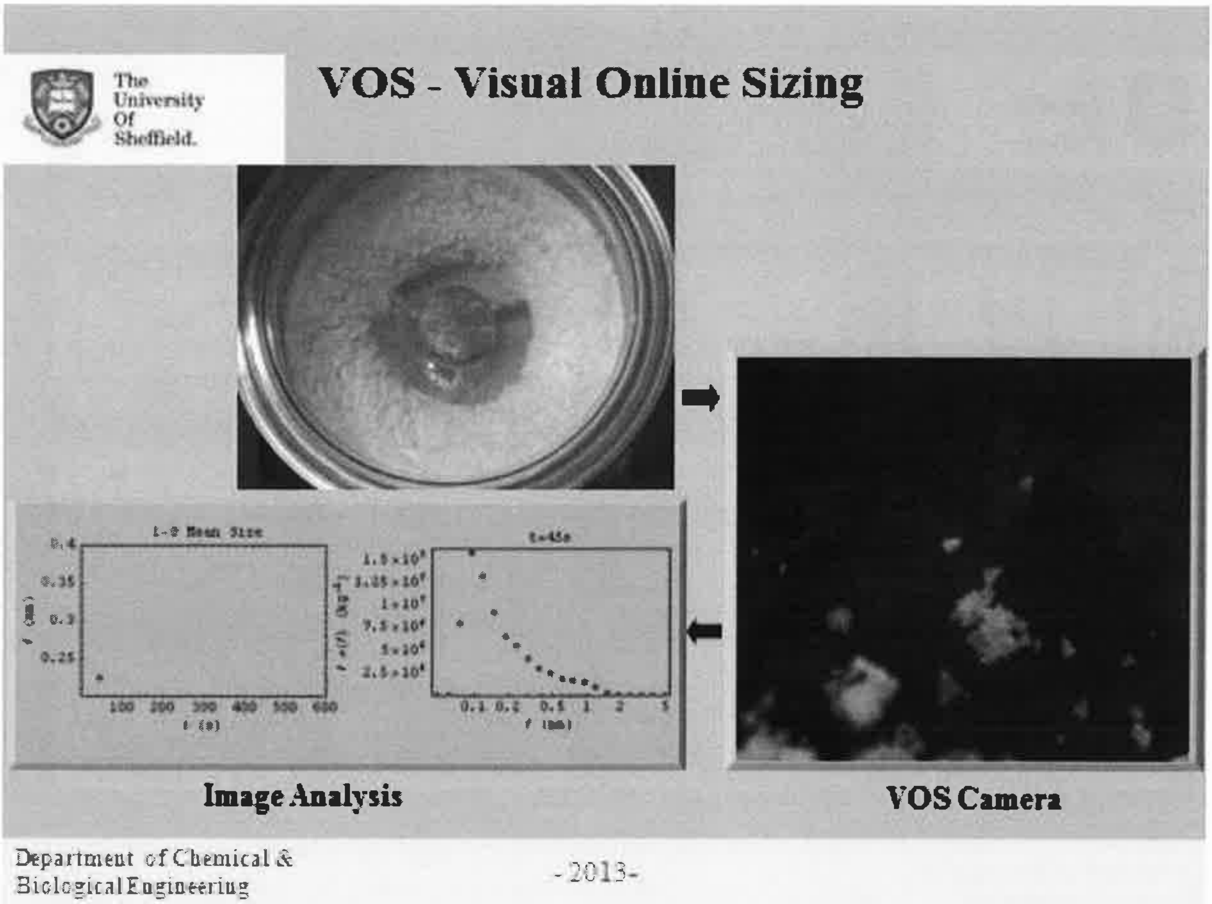
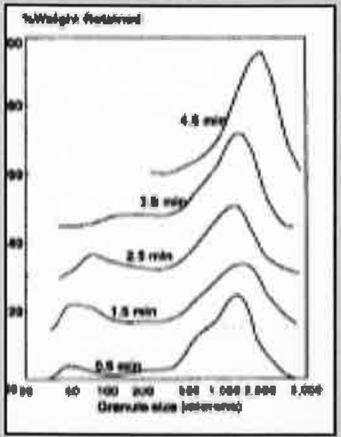
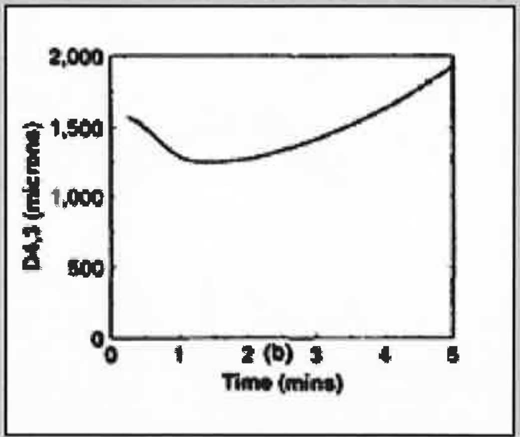

The University Of Sheffield.
VOS - Visual Online Sizing
Image Analysis
VOS Camera
Department of Chemical & Biological Engineering
-2013-

The University Of Sheffield.

Process Variables
1- Granulation Time on Granule Size





Materials
- **Calcium Carbonate ($D_{3,2}$= 4μm)**
- **Polyethylene glycol (PEG1500)**

X

Increasing the processing time **P.C. Knight et al., 1998**
➔homogenization
⇒ narrow granule size distribution

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Effect of Granulation Time on: Granule Size

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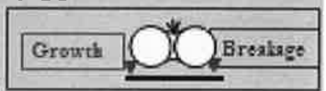
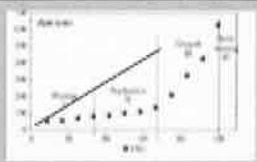
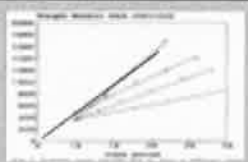


Increasing the granulation time: increasing the amount of binder
Increasing the growth
For low viscosity binder: increasing the breakage
More granulation time: increasing the consolidation and growth

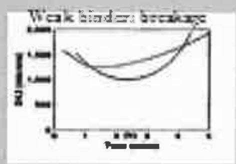
Kristensen, 1996



Benali et al, 2009

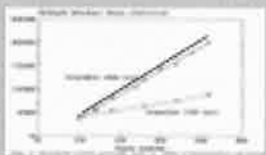


P.C. Knight, 1993

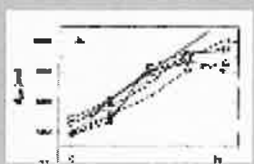


P.C. Knight et al, 1998

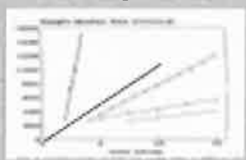
X



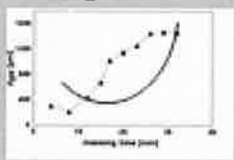
P.C. Knight, 1993



Schaefer et al, 1996

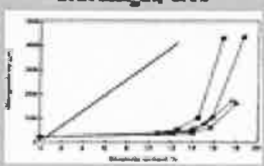


P.C. Knight, 1993

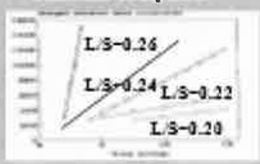


R. Thies et al, 1999

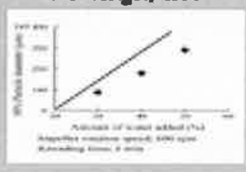
X



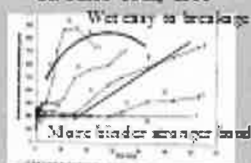
Kristensen, 1996



P.C. Knight, 1993



Ikumasa Ohno, 2007



Hoornaert, et al 1998

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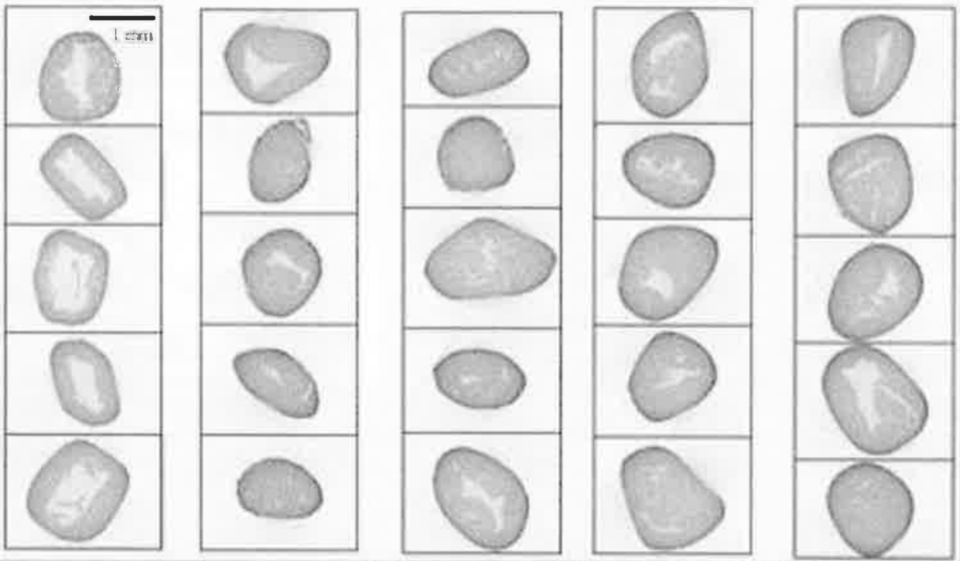
Effect of Granulation Time on: Structure (Solid Binder)



2 min | 4 min | 6 min | 10 min | 15 min

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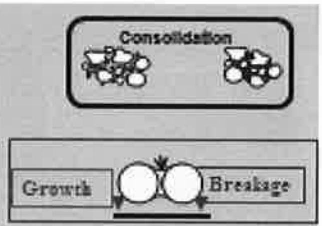
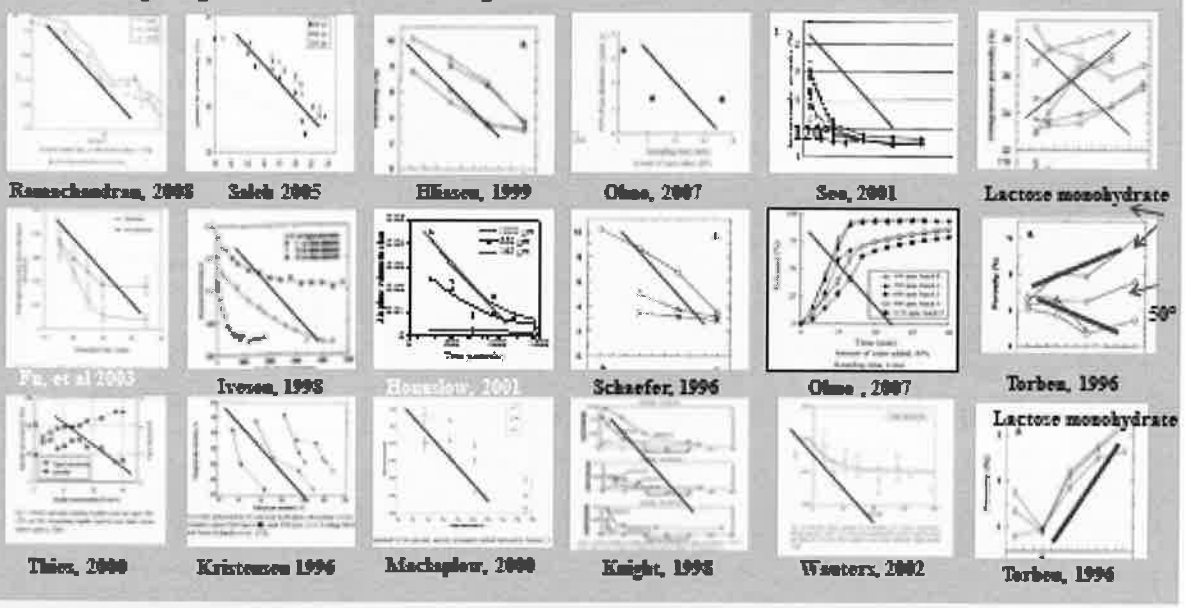
Effect of Granulation Time on Porosity

Porosity = The ratio of the volume of pores to the total volume of the granule



Increasing the granulation time increasing the consolidation



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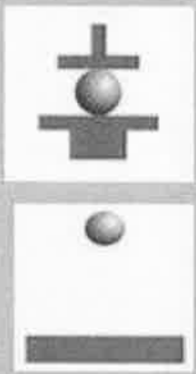
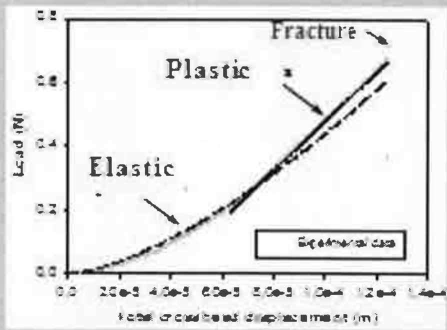
Strength Parameters: assuming Elasto-Plastic Contact Mechanics for Spheres Dry Granules





Elastic $P = \frac{\sqrt{2}}{3} R^{1/2} E^{*} \delta^{3/2}$ $\quad E^{*} = \frac{E_s}{1-\upsilon_s^2}$

Plastic $P = \pi R H \delta$ Johnson (1985)

Fracture $\sigma_f = 2.8 \frac{P_f}{\pi D^2}$

Hiramatsu & Oka (1966)

σ_f fracture stress, P_f fracture load, υ Poisson's ratio, δ displacement, H hardness, E* effective Young's modulus, R granule radius, D granule diameter

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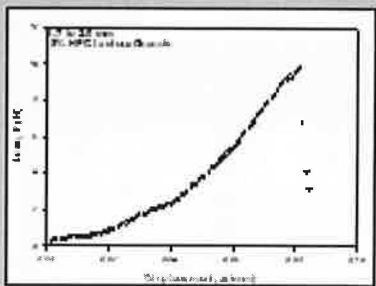
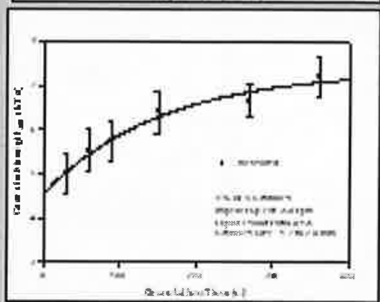
Effect of Granulation Time on: Granule Compression Strength

$$\sigma = \sigma_{max} - (\sigma_{max} - \sigma_o)\exp(-t/\tau)$$

Where
- t is granulation time (s)
- σ_{max} is maximum granule strength
- σ_0 is the initial granule strength
- τ is the characteristic time of the strengthening process

σ_{max} (MPa)	7.4 ± 0.3
σ_0 (MPa)	4.5 ± 0.4
τ (s)	164±66





- **Granule strength obtained from diametric compression is well described by the rate equation**

Mangwandi, 2008

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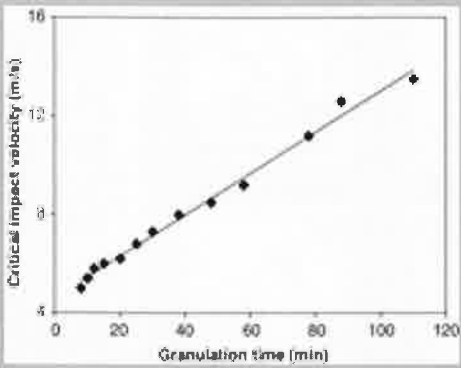
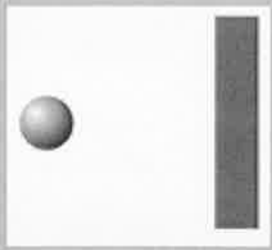
Effect of Granulation Time on: Impact Strength



J. Fu et al., 2005



- Critical impact velocity is the minimum velocity required to break the pellet in impact test.
- Higher critical impact velocity means the stronger the pellet.

It can be inferred from this result that granule strength increases with granulation time. This could be due to the fact that granules become more denser with time due to consolidation.

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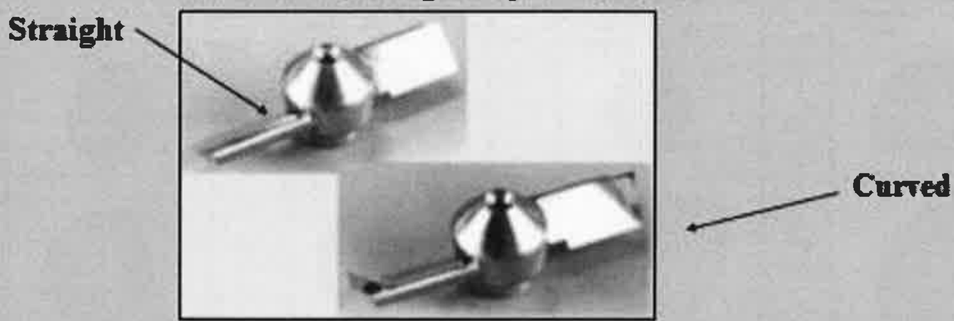
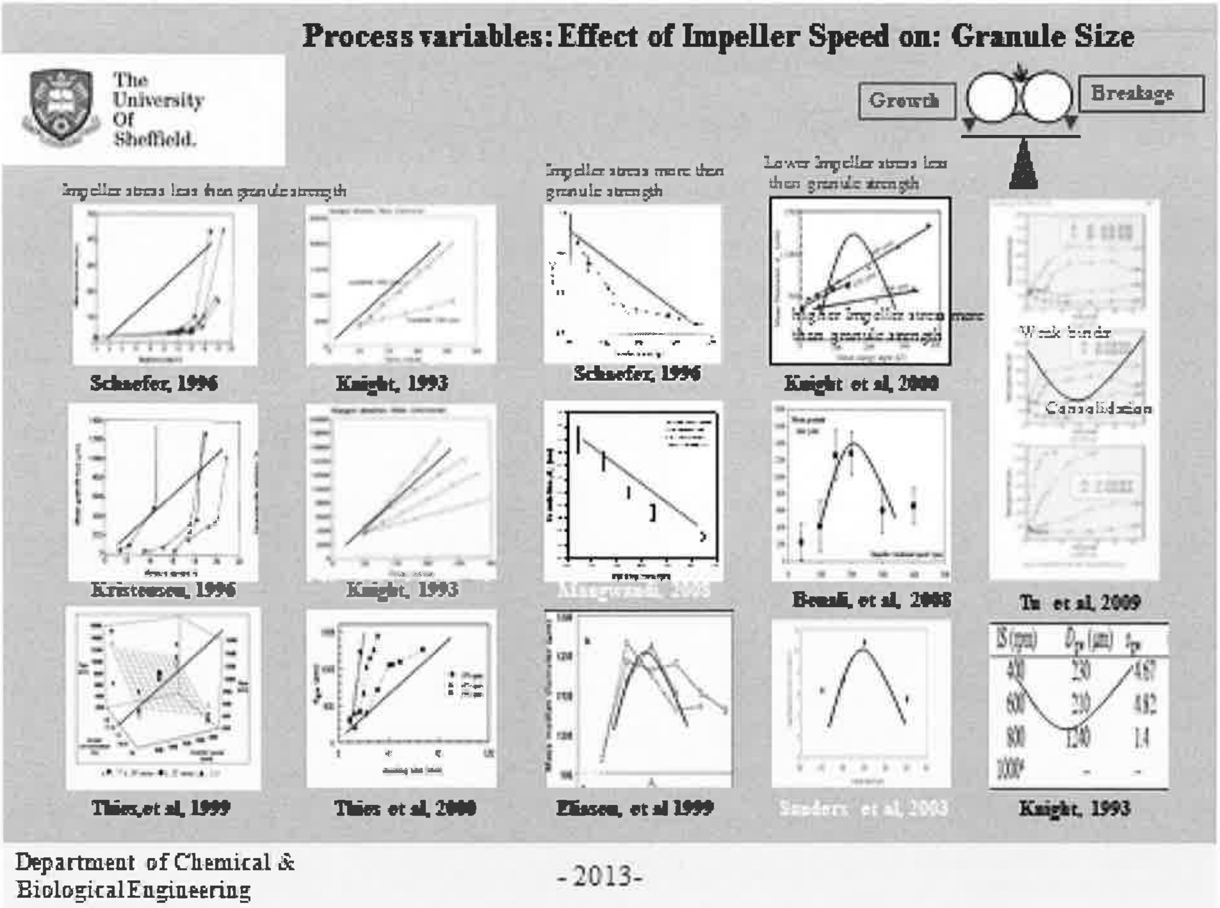
Operating Conditions: 2- Impeller Speed

Granulator Design: Impeller Blade



Curved Blades
Helix-like movement of the mass
More spherical agglomerates
Narrower PSD
Better reproducibility
Lower intra-granular porosity

"High Shear Pelletization", T. Schaeffer, TTC


Process variables: Effect of Impeller Speed on: Granule Size
The University Of Sheffield.
Growth
Breakage
Impeller stress less than granule strength
Impeller stress more than granule strength
Lower impeller stress less than granule strength
Higher impeller stress more than granule strength
Weak binder
Consolidation
Schaefer, 1996
Knight, 1993
Schaefer, 1996
Knight et al, 2000
Kristensen, 1996
Knight, 1993
Benali, et al, 2008
Tu et al, 2009
Thies, et al, 1999
Thies et al, 2000
Eliasen, et al 1999
Knight, 1993
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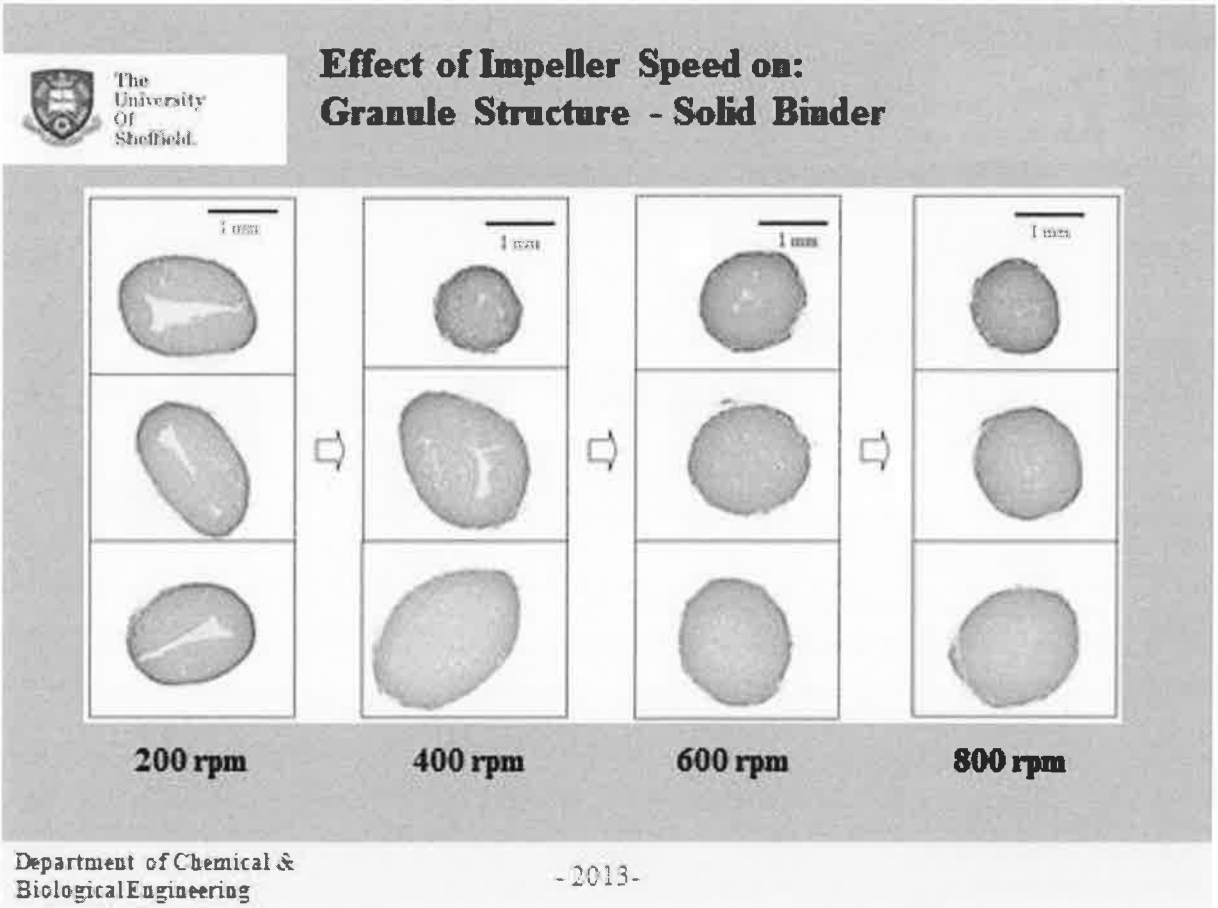
Effect of Impeller Speed on:
Granule Structure - Solid Binder
The University Of Sheffield.
1 mm
200 rpm
400 rpm
600 rpm
800 rpm
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The University Of Sheffield.

Effect of Impeller Speed on: Shape

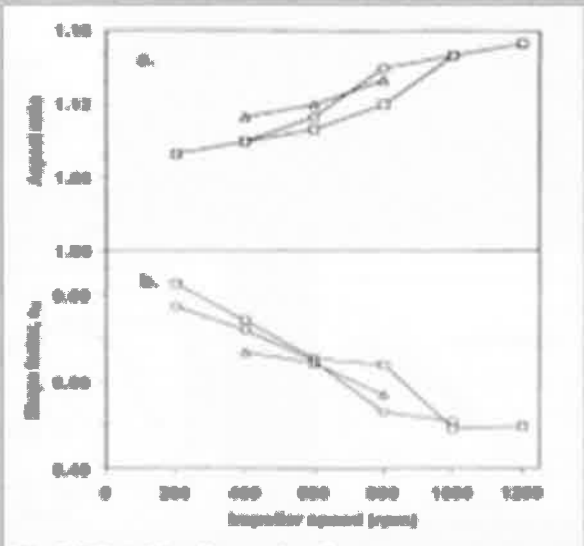
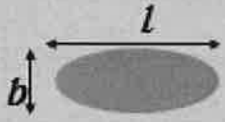


Fig. 9. Effect of impeller speed on the aspect ratio (a) and the shape factor (b) of the agglomerates at different jacket temperatures.

Aspect ratio, AR is given by

$$AR = \frac{l}{b}$$

l is the longest distance
b the shortest distance



Helle, 1999

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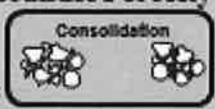
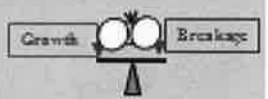
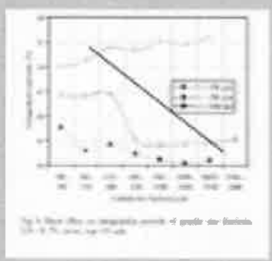
Effect of Impeller Speed on: Granule Porosity

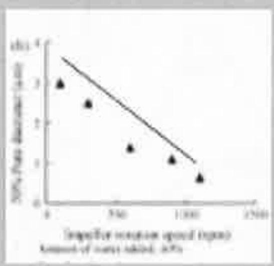
Increasing the impeller speed:
Increase the consolidation; decrease porosity
For low viscosity binder: increasing the breakage: increase porosity



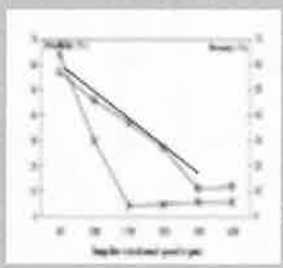




Oulaha, 2003

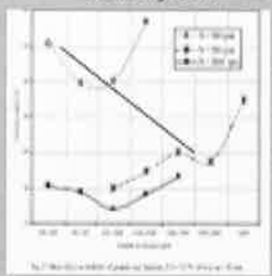


Ohno, 2007

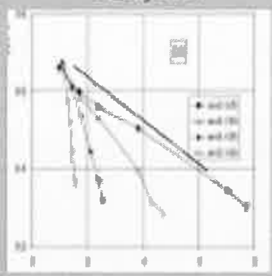


M. Benali, 2009

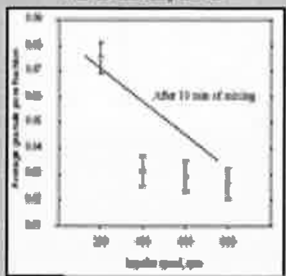
Déray et al., 2006



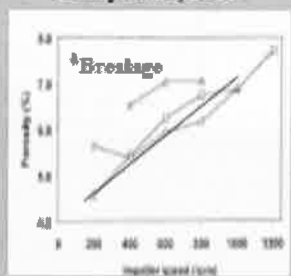
Oulaha, 2003



Gluba, 2005



Gabbot, 2007



Eliasen, 1999

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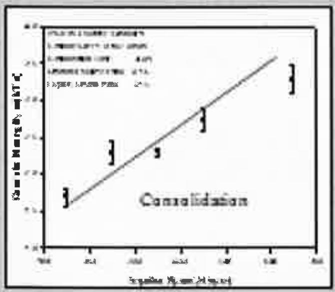
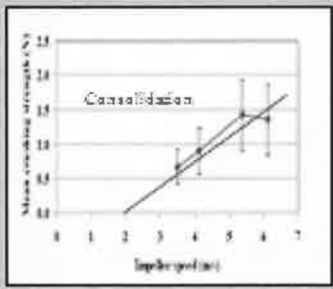
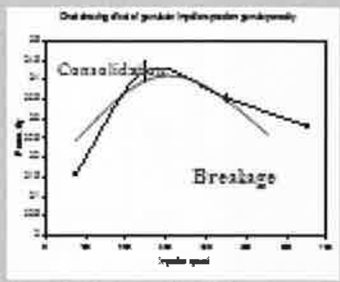
Effect of Impeller Speed on: Strength of Granules



Mangwandi, 2008



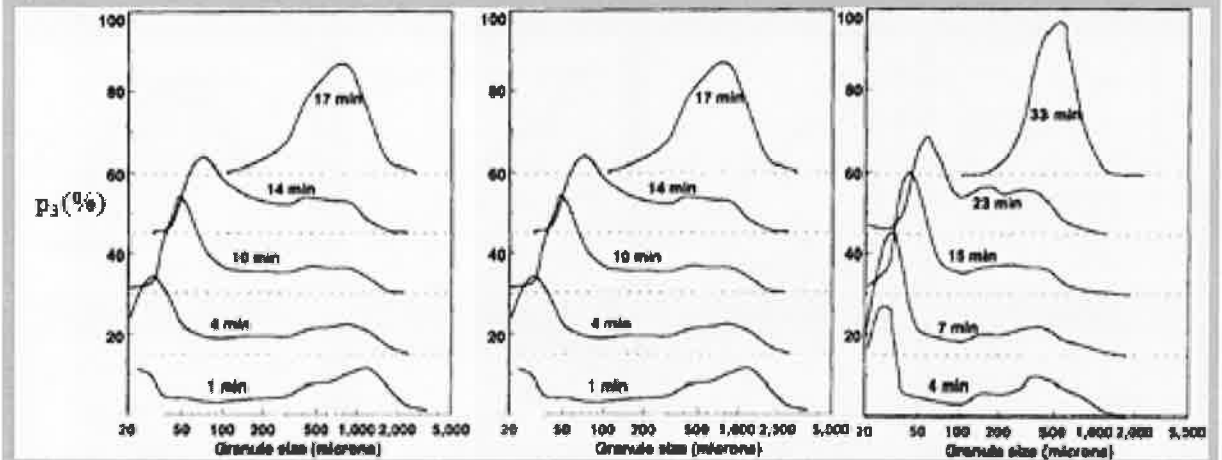
Rahmanian et al, 2007



Drovlo, 2008

The University Of Sheffield.

3- Effect of Binder addition method on Size



Pour on | Spray on | Melt in

Knight et.al 1998

Data for granulation in a 600 mm diameter vertical axis granulator.
Impeller speed: 150 rpm, chopper speed: 3000 rpm

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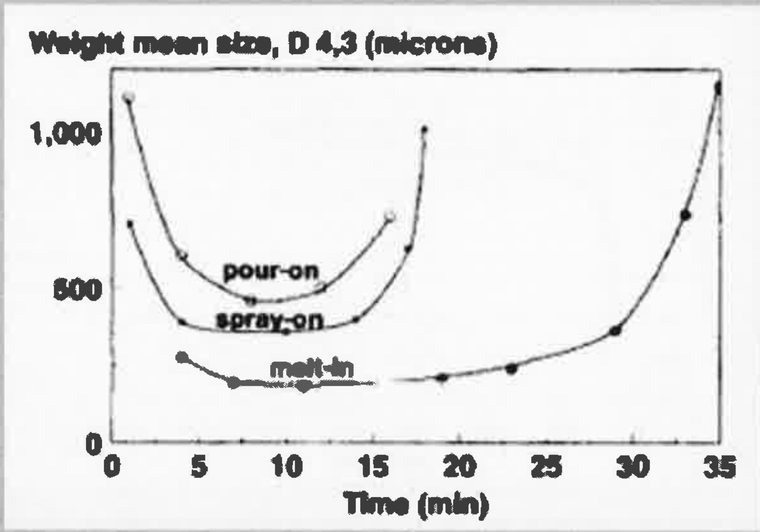
Process Variables
Effect of Binder addition method on Size



Knight et.al, 1998

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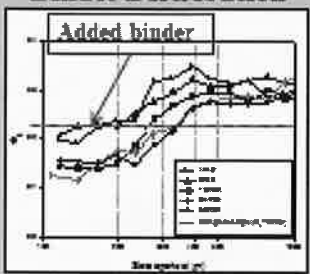
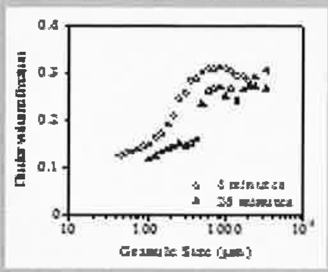
Granule Properties. It is not just Size anymore!
Binder Distribution

Binder Distribution



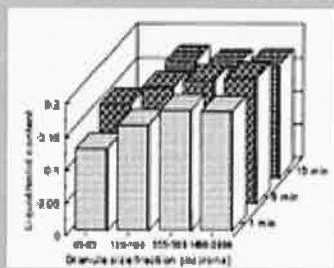
Reynolds et al, 2004

Binder Distribution



Scott & Hounslow, 2000

Binder Distribution



Knight et al, 1998

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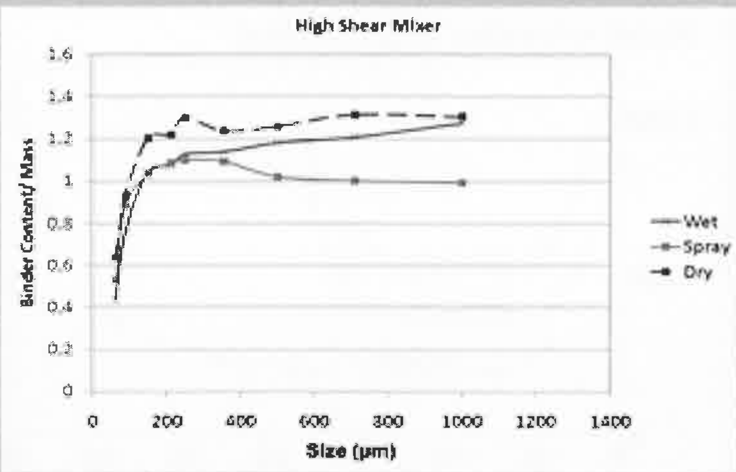
Binder Distribution

Spray addition, Wet addition and Dry addition



Binder distribution curves for each of the procedures in the High Shear mixer Dry addition; Wet addition and Spray addition

J Osborne, 2009

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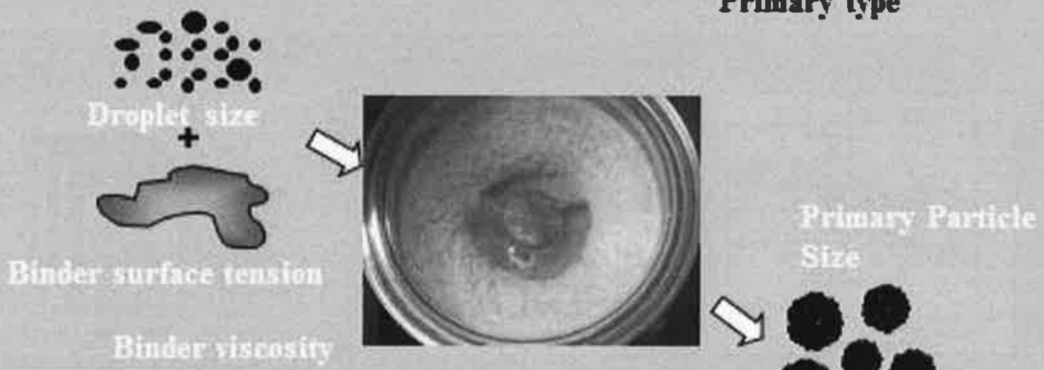
Main Formulation Variables

Binder type

Primary type



Granule Size
Structure
Porosity
Strength
Binder Distribution

Binder-Particle interactions

Materials Variables

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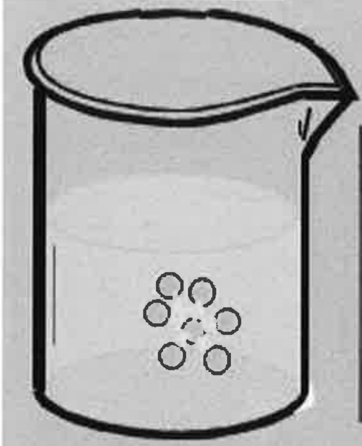
Viscosity



Viscosity is the measure of how "thick" a fluid is. It is a property of the fluid and defines its internal resistance to flow or stresses placed upon it. It can also be considered fluid friction.

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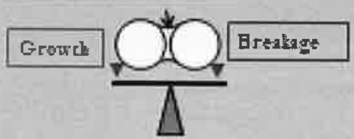
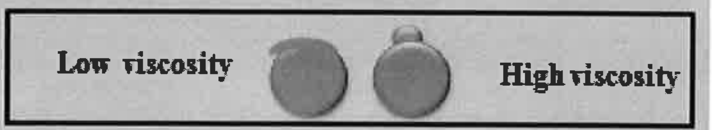
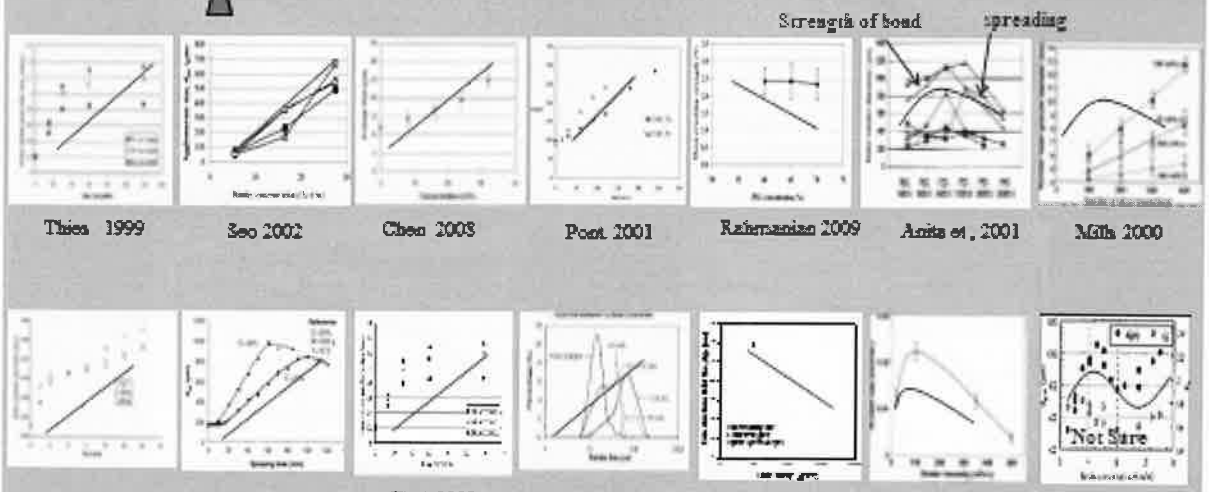
1- Effect of Binder Viscosity on Granule Size







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Effect of the Binder Viscosity on: Structure

High Viscosity

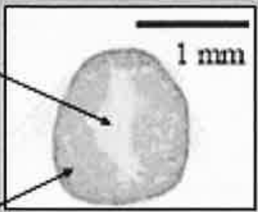
➔ **Promotes *Immersion***

Low Viscosity

➔ **Promotes *Distribution***

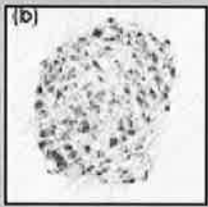
X-Ray tomograph of a Durcal Pellet obtained with PEG

Liquid Core



Dense Solid Shell

X-Ray tomograph of a Pellet obtained using water



Homogeneous liquid distribution
High intragranular porosity

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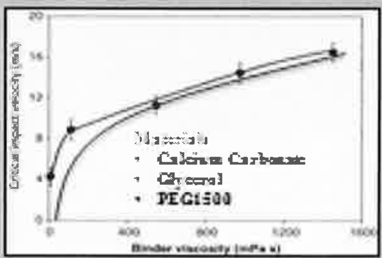
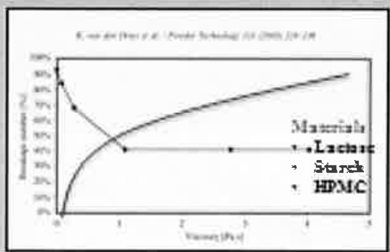
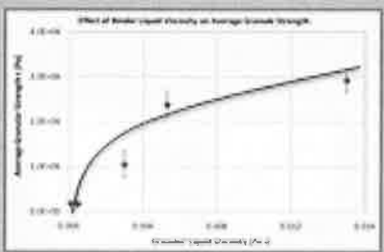
Effect Binder Viscosity on: Granule Strength



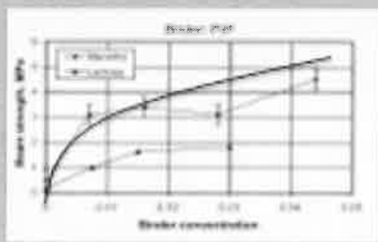
J. Fu et al., 2005



van den Dries et al, 2003



Drovlo, 2008



Bika et al, 2005

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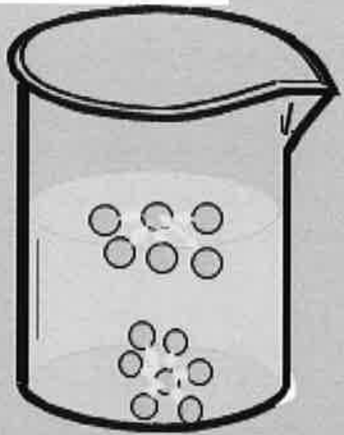
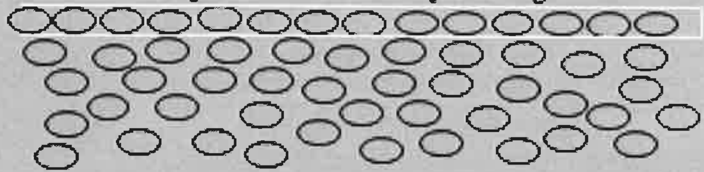
Formulation Variables: Surface Tension



What's going on at the surface of a liquid?

Surface molecules also form a much smoother surface than one would expect from randomly moving molecules



When the cohesion between the molecules of liquid is strong but between the liquid and air it is weak

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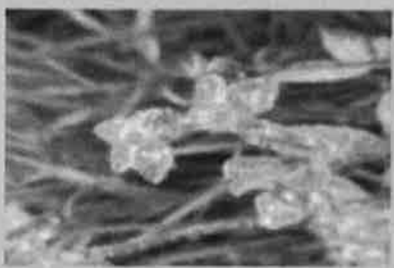
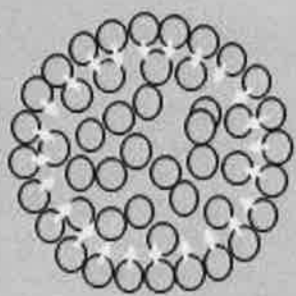
This explains the characteristic rounded shape that liquids form when dropping through the air: The molecules are all being pulled toward the centre





Staple

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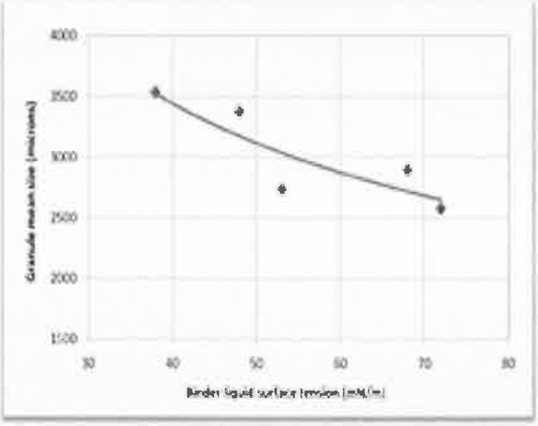
2- Effect of Surface Tension on: Granule Size



Difficult to consolidate the granules; and difficult to push the binder to the surface

Drovlo, 2008

The mean Granule size decreases with increasing surface tension

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3- Effect of Primary Particle Size: Strength

Rumpf (1962):

$$\sigma = \frac{8}{9}\frac{1-\varepsilon}{\varepsilon}\frac{F_{bond}}{d_{3,2}^2}$$

High shear: Strong, dense
Fluidised bed: Weak, porous

- Suggests that high Porosity granules will have low Strength

σ Granule strength
F_{bond} Bonding force between particles
ε Intra-granular porosity
$d_{3,2}$ Surface mean diameter of the primary particles

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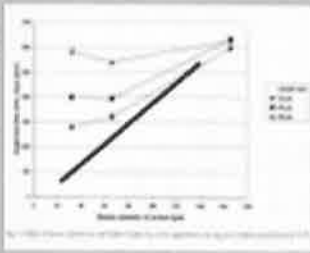
Effect of Primary Particle Size

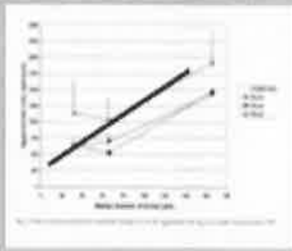
Increasing the primary particle size:
For strong and well spread binder: increase

Strong binder

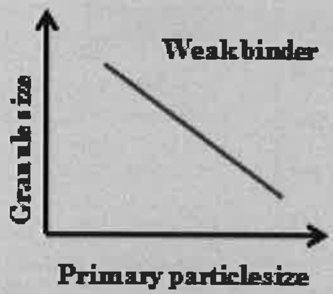


Alberger et al, 2002

Strong binder



Alberger et al, 2002



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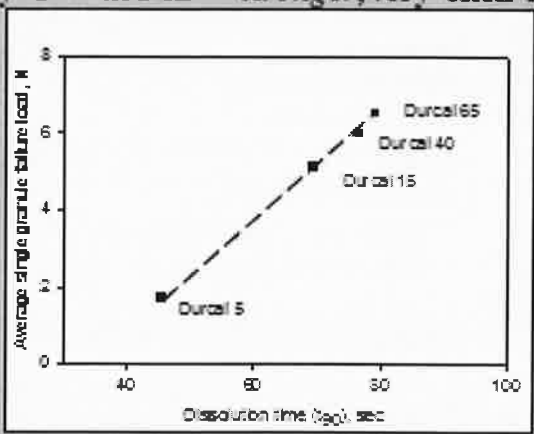
Effect of Primary Particle Size on Strength

Strength

⇒**Mono-sized** ➔ **model (Rumpf) predict** *smaller = stronger*

⇒**Reality** ➔ *wide PSD = stronger*, **very often larger mean size**



I. P. Gabbot, 2007

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4- Effect of Droplet Size/Solid Binder size on Granule Size

Liquid Binder

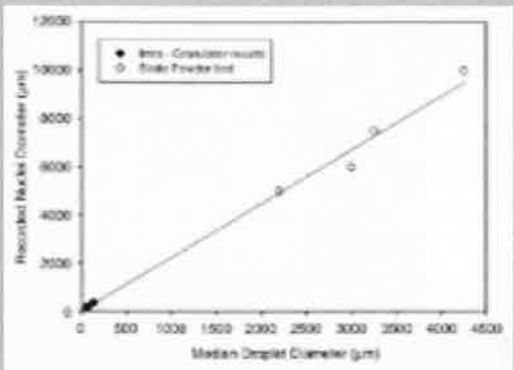

Fig. 11. Produced nuclei size as a function of droplet size.

K Ax, 2008

Solid Binder

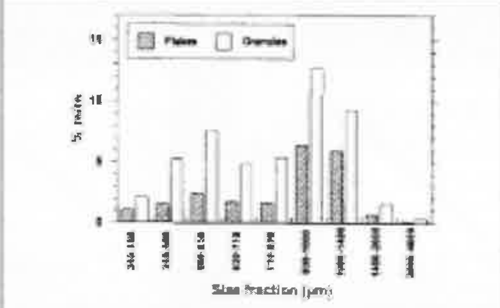

Fig. 6. Comparison between the particle size distribution of PEG 20000 flakes at 1 min before melting and the granule size distribution at 1 min of massing.

Schaefer, 1996

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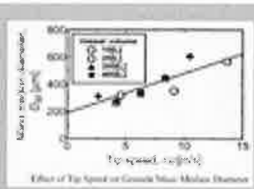
Scale-Up High Shear Granulation

Tip Speed of Impeller:

The product of the rotational speed and the radius of impeller

$$v_t = r \times \omega$$

ω Rotational speed
r Impeller radius

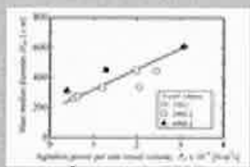


Watano et al., 2005

Agitation Power per unit Vessel Volume

$$P_v = \frac{\omega T}{V}$$

T Impeller torque
V Volume of vessel
ω Rotational speed



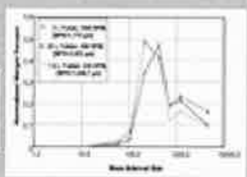
Sato et al., 2005

Shear Stress

Scale-up rule which insures that the particles receive the same stress in which case n = 0.8, for constant tip speed, n = 1

$$\frac{N_x}{N_y} = \left(\frac{D_y}{D_x}\right)^n$$

N_x Rotational speed, diameter D_x
N_y Rotational speed, diameter D_y



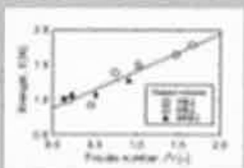
P.D. Hede et al 2008

Froude Number

Dimensionless number giving the ratio of the centripetal forces to gravitational forces

$$N_{fr} = \frac{\omega^2 D}{g}$$

ω Rotational speed
D Impeller diameter



Watano et al., 2005

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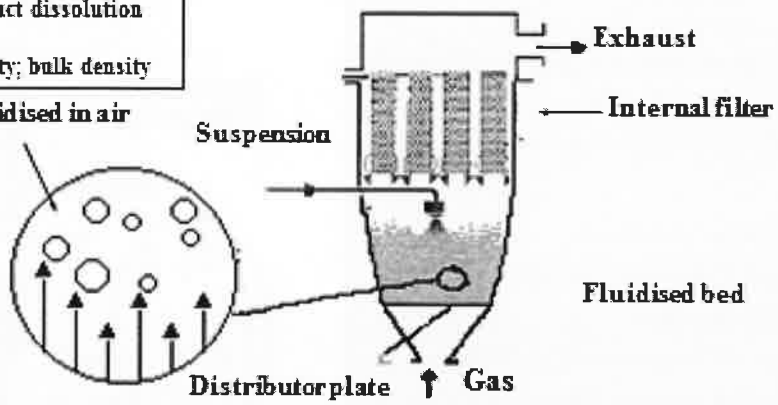
Fluidised Bed Granulation (FBG)

To improve flowability
To improve product homogeneity
To control product dissolution characteristics,
strength; porosity; bulk density



Process Variables:
- Effect of Granulation Time/ Amount of Binder on Granule Size/Shape
- Effect of Fluidizing Air Velocity

Formulation variable:
- Effect of Binder Viscosity/ Binder Concentratio
- Effect of Primary Particles Size
- Effect of Droplet Size

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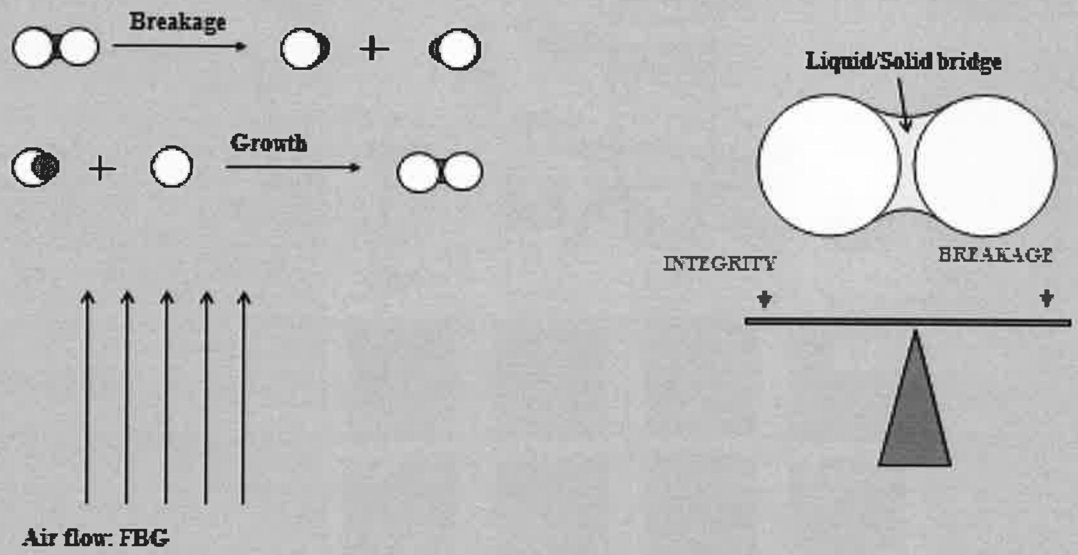
Growth and Breakage



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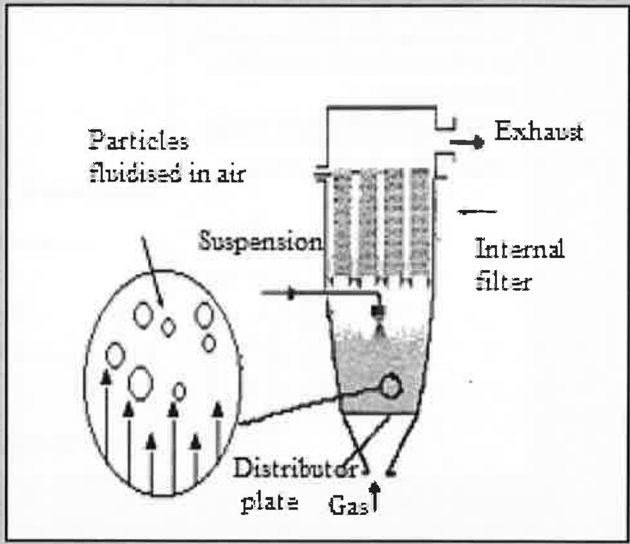
Fluidised Bed Granulation (FBG)

Process Variables:

- **Effect of Granulation Time/Amount of Binder on Granule Size/Shape/ Porosity**
- **Effect of Fluidizing Air Velocity**

Formulation variables:

- **Effect of Binder Viscosity/Binder Concentration**
- **Effect of Primary Particle Size**
- **Effect of Droplet Size**



Fluidised

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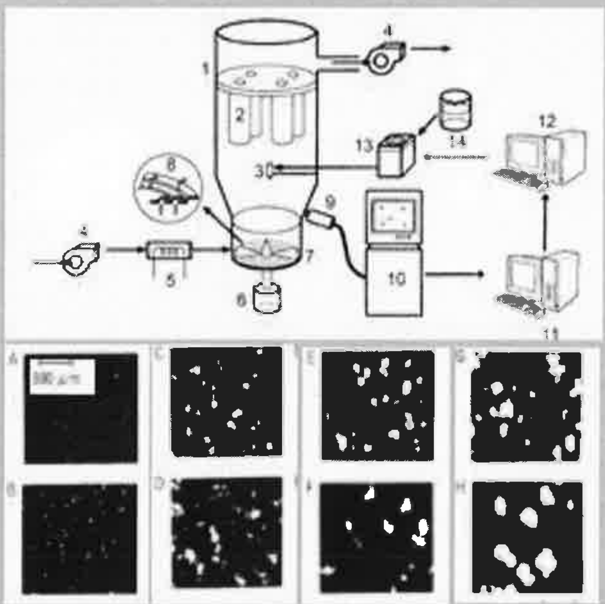
Direct Control of Granulation Processes by Image Processing System



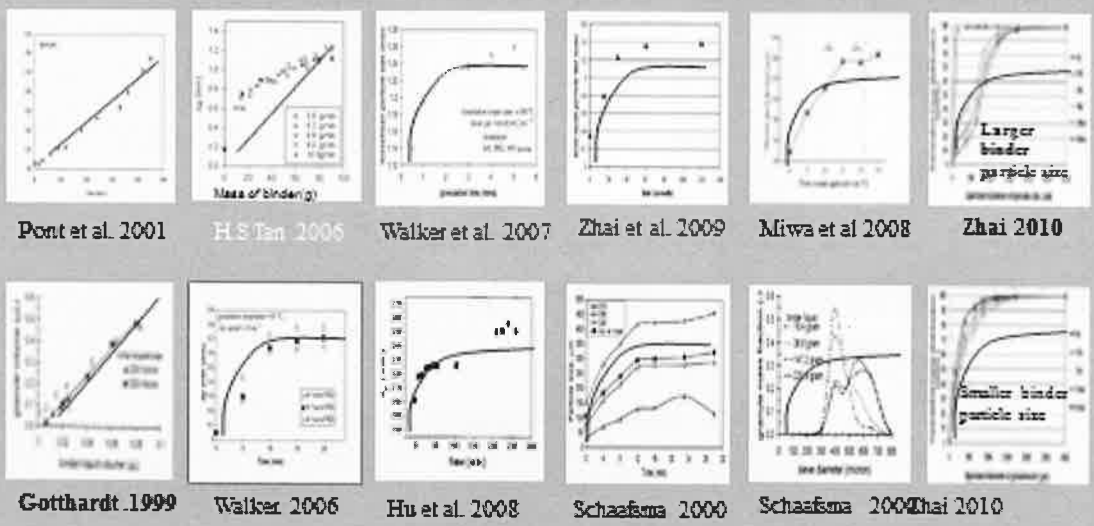
Pictures of granules taken by the developed image processing system.

S. Watano 2001

The University Of Sheffield.

Process Variables:
1- Effect of Granulation Time/ Binder Content on: Granule Size

More binder = more sticking of particles



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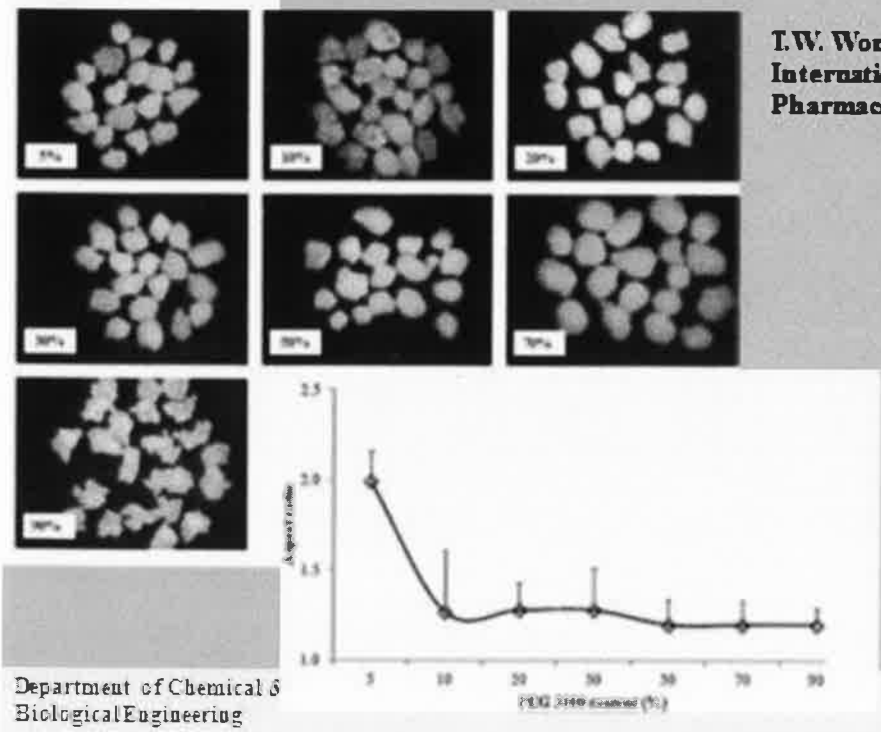
Process Variables:
Binder Content on: Granule Shape



T.W. Wong, N. Musa/ International Journal of Pharmaceutics *430 (2012) 184–196*

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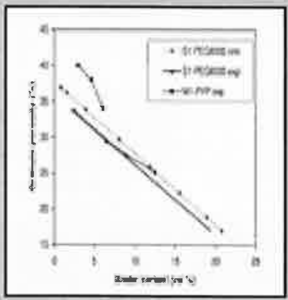
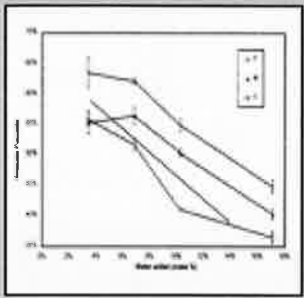
Effect of Binder Amount on Porosity

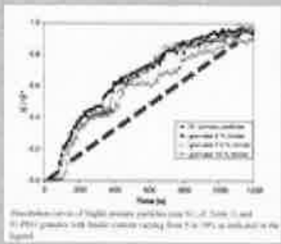
Increasing the binder content :
Increase the size of bond between particles: reducing porosity



Ansari et al. 2008



Mackaplow et al. 2000



Ansari et al. 2009

Effect of Binder Amount on Dissolution:

The higher the binder content results in granules which take longer to dissolve

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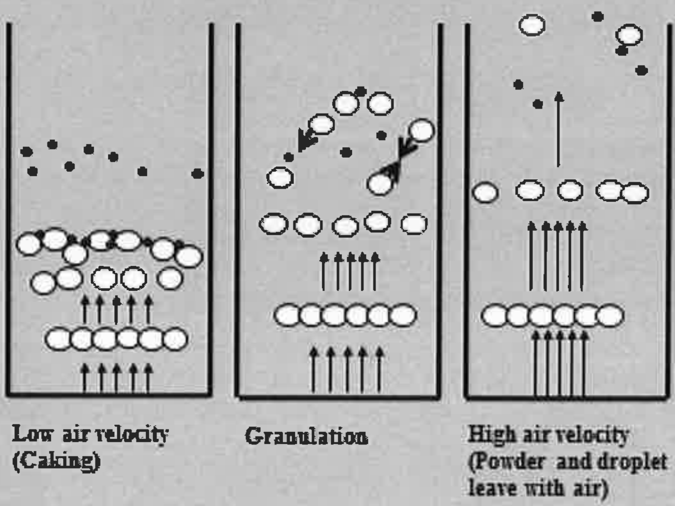
Granulation: Air Velocity



• Droplet ○ Particle

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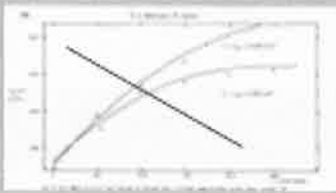
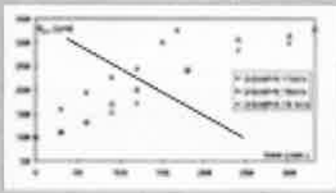
Process Variables
2- Effect of Fluidising Air Velocity on: Granule Size

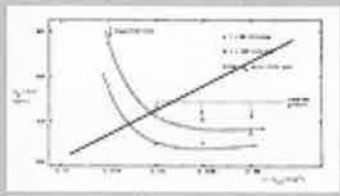
Increasing the air velocity:
Improve the collision rate: increase in size
Increasing the number of droplets leaving with the air



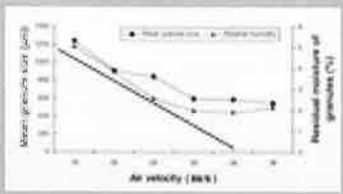
Smith & Nienow 1983



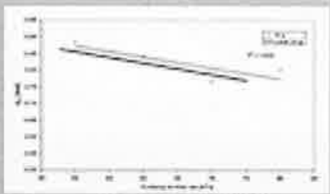
M. Hemati et al 2003



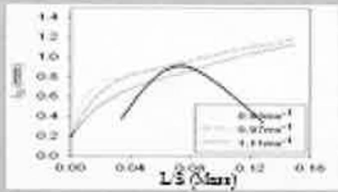
Smith & Nienow 1983



Behzadi et al. 2005



Mangwandi 2004



H.S. Tan et al. 2006

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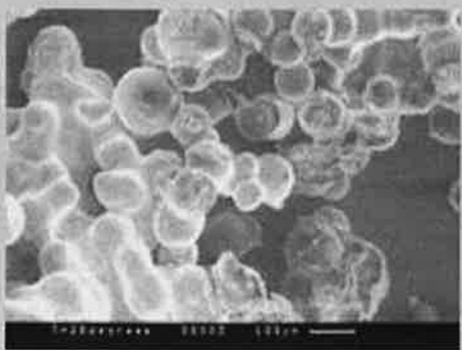
Effect of Viscosity

High viscosity



Low viscosity

Tan 2005

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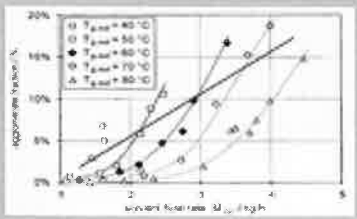
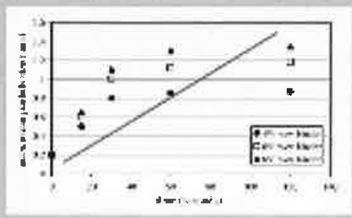
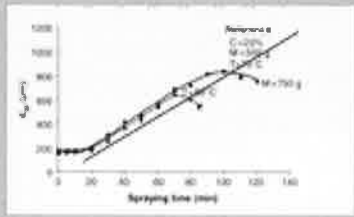
Formulation Variables
1- Effect of Binder Viscosity on Granule Size



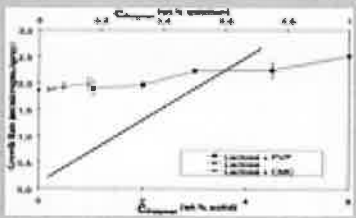
Becher et al 1998



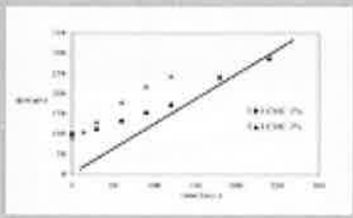
Zhai et al. 2009



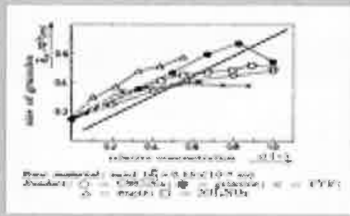
Jimenez' et al. 2006



Panda et al. 2000



Y. Chen et al 2008



Ormos et al 1979

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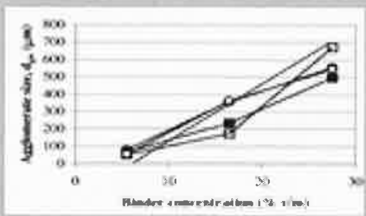
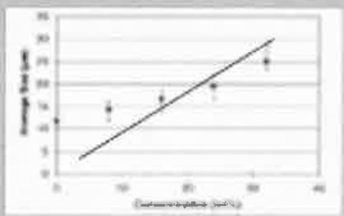
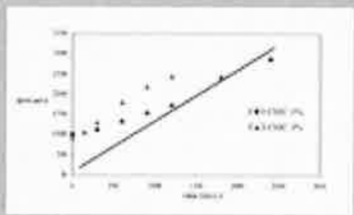
Effect of Binder Concentration on Granule Size



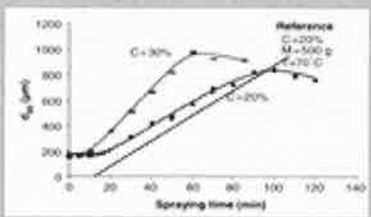
Seo et al. 2002



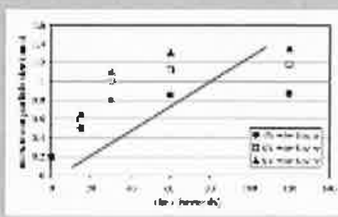
Y. Chen et al 2008



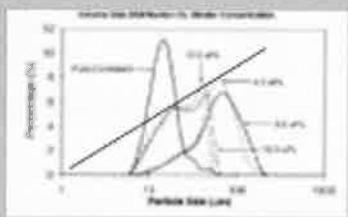
V. Pont et al. 2001



Jimenez' et al 2006



Zhai et al 2009



Y. Chan et al. 2009

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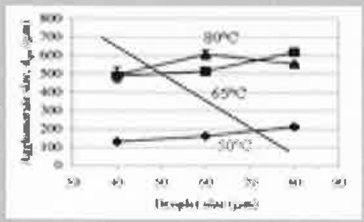
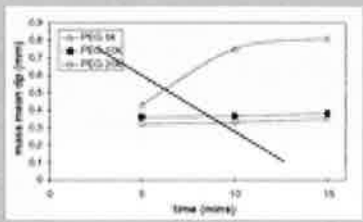
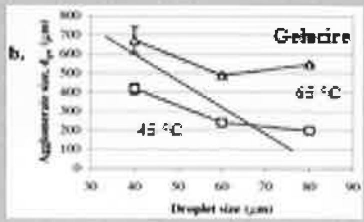
Effect of Viscosity (Fluidized Bed Melt Granulation)



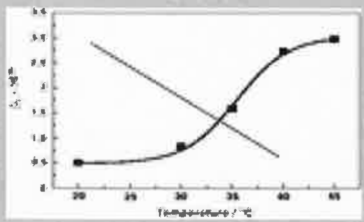
Seo et al. 2002



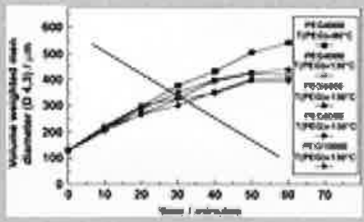
Walker et al. 2005



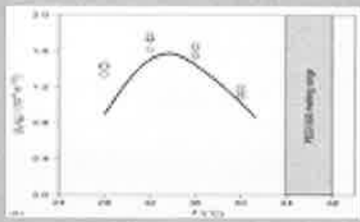
Seo et al. 2002



Boerefijn & Hounslow 2005



Boerefijn & Hounslow 2005



H.S. Tan et 2006

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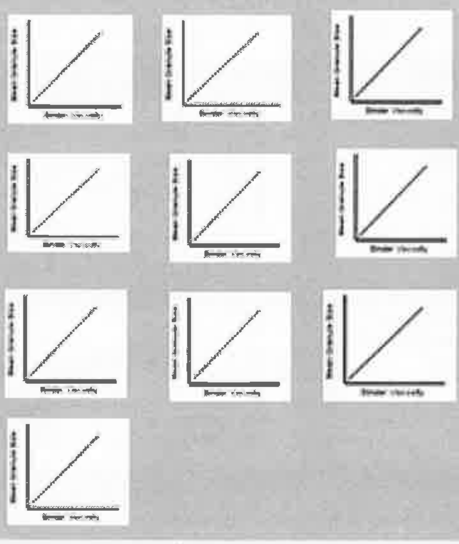
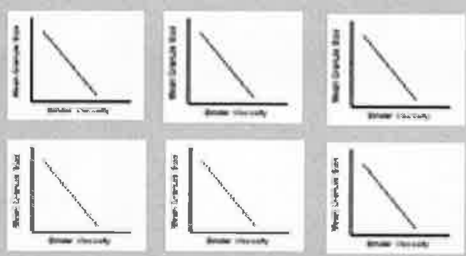
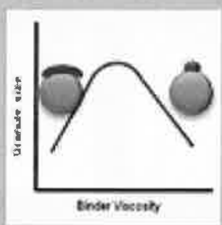
Effect of Binder Viscosity on Granule Size

Increasing the binder viscosity:
Increase the strength of bond between particles: increase
Decreasing the spreading of the droplet: decrease







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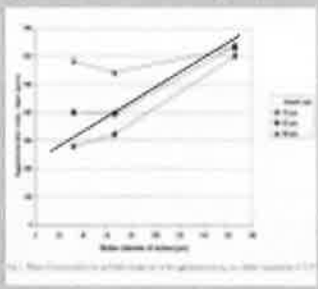
Formulation Variables
2- Effect of Primary Particle Size on Granule size

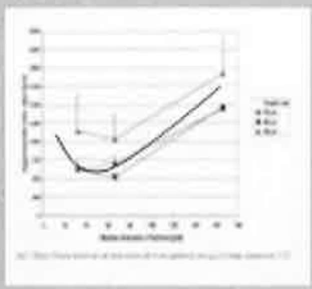
For strong binder: could hold big particle: increase in size
For weak binder: binder strength not enough to hold big particles; reduces size

Binder concentration 11.5%

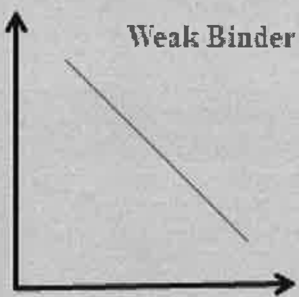


Abberger et al,2002

Binder concentration 22%



Abberger et al,2002



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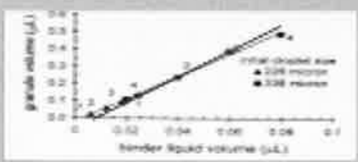
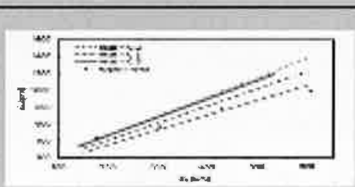
Effect of Droplet Size on Granule Size

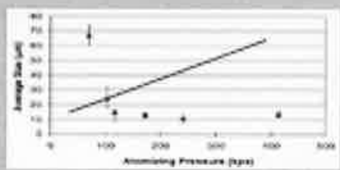
Small droplet; weak bond; may leave with air
Big droplet: stronger bounds between particles: decreasing droplet number



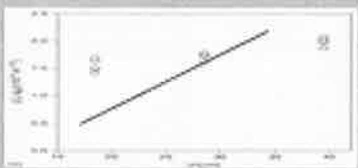
Schaafsma et al. 2000



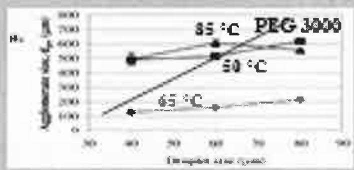
Ansari et al. 2006



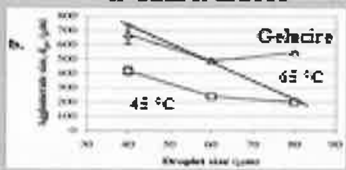
Y. Chen et al 2008



H.S Tan et al. 2006

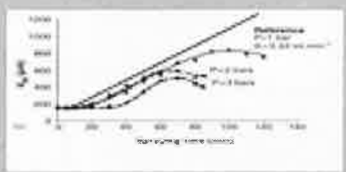


Seo et al. 2002

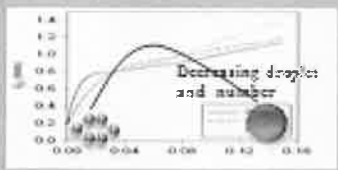


Seo et al. 2002

Y. Yan et al. 2009



Jemenez et al. 2006



L/S Tan 2006

The University Of Sheffield.

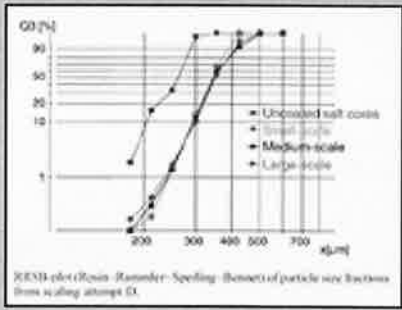
Scale-Up Fluidised Bed Granulation

Flux Number:

$$F_n = \log_{10}\left(\frac{\rho_p U_s}{\dot{q}_b}\right)$$

q_b Binder flow rate
ρ_p Particle density
U_s Velocity of solids

Flux Number: this is a dimensionless number indicating the balance between solid flux and spray flux that wets the solids in the spray zone

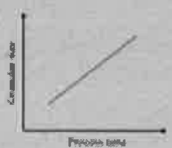


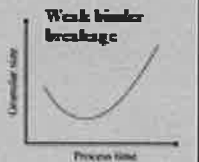
Hede et al, 2005

Process Variables

High Shear Mixer

Granulation time/ binder amount on Size



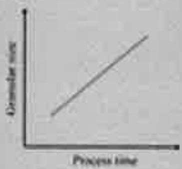


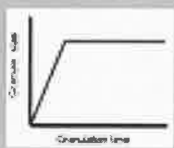
Granulation time/ binder amount on Porosity

Impeller speed on size

Impeller speed on Strength

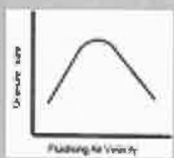
Fluidised bed





More binder
More growth

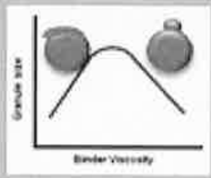
More liquid, increase the bond between particles: reducing porosity

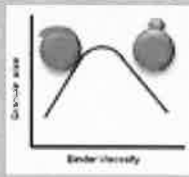


There is a critical air velocity; below which growth; after which breakage or droplet leaving the fluidised bed

High Shear Mixer | **Formulation Variables** | **Fluidised Bed**

Viscosity: Granule Size

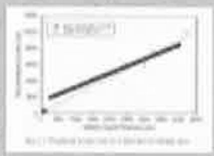




High viscosity; strong bound; less spreading; and less number of droplets

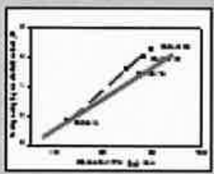
Viscosity: Strength Porosity

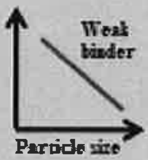
Droplet size: Granule size

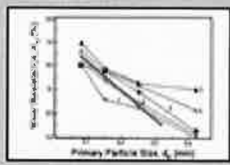


FBG: bound; less spreading; and less number of droplets

Primary particle size: Strength







The University Of Sheffield.

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Lecture 4. Continuous Processing in the Pharmaceutical Industry

Mr James Cartwright (GSK)

GlaxoSmithKline

Continuous Processing In the Pharmaceutical Industry

James Cartwright

GlaxoSmithKline

GlaxoSmithKline

Background and History

Background and History

There are many well known examples of continuous processes and some less well known ones;

- Car production (Henry Ford)

Background and History

Fermentation

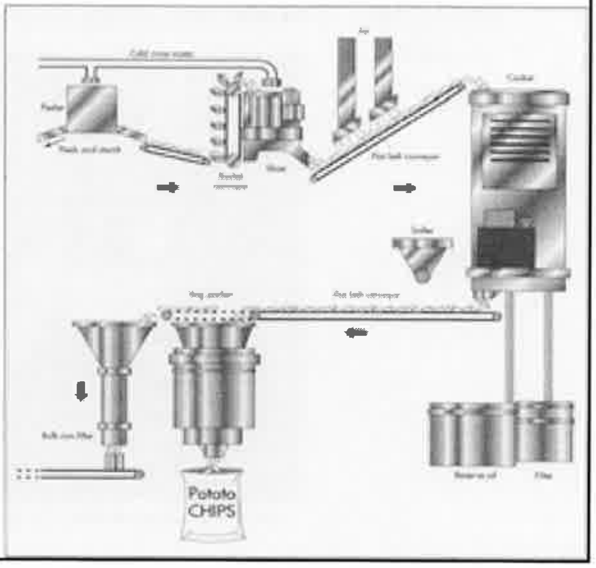
- 24 hours worth of production equals one batch of beer (we will come back to this point later)

Crisps (or Potato Chips) – Continuous Production

The origin of the humble potato crisp is somewhat disputed, however from those early days of batch production, there was a switch to continuous production.

This was no doubt fuelled by the popularity of the product.

Opposite is a process flow for a typical crisp production process



Crisps (or Potato Chips) – A Closer Look

Input Materials

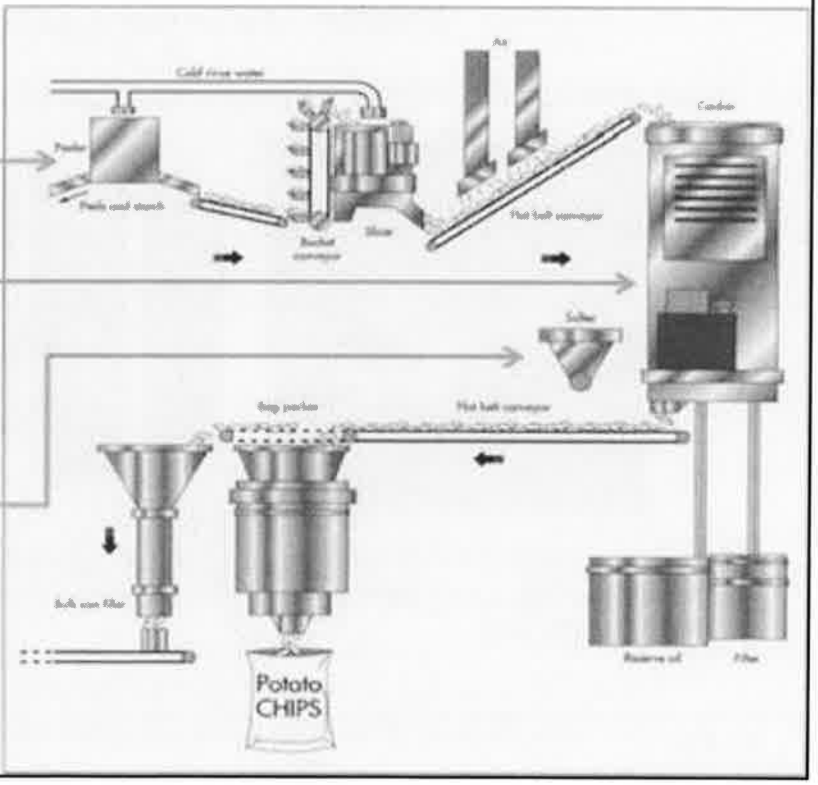
– Produce waste (peel and starch as well as any QC rejected potatoes upstream)

Cooking

– Requires energy

Flavour addition step

– This is added after the frying of the potato slice (added to the surface only)



Pringles – Continuous Production

Proctor & Gamble, Tennessee

Won the Governor's Award for Excellence for its outstanding achievements in reducing the environmental footprint of the plant through major recycling efforts and significant reductions in energy consumption, water usage, and solid waste. This plant produces Pringles for North America and 75 other countries.

[illegible]

Pringles – Continuous Innovation

Project undertaken to personalise the product for consumers

"An article of commerce comprising an edible substrate having an image disposed thereon, and a method for making edible substrates having a variety of different images."

Publication number: [illegible] Publication date: 2005-01-27 Inventor(s): WEN LUFANG [US]; ROMANACH BENITO ALBERTO [US]; PHILLIPS AMY DAWSON [US] [illegible]

GlaxoSmithKline

Continuous Processing within Pharma

The Business Arguments Make Sense

Allows a reduction in;

Development time (weeks instead of months)

API (230kg of API saved in 1 example)

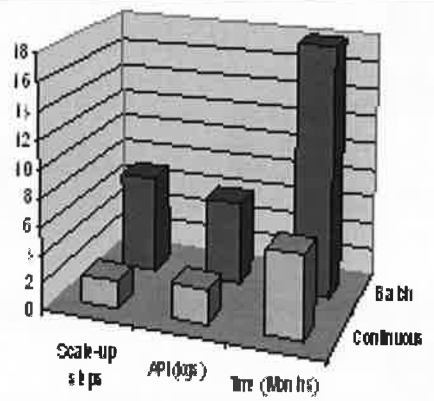
Waste (yield increased, wash waters reduced)

Designed with integrated PAT for real time control & assurance

Simplified site transfers

Reduced infrastructure (80% footprint reduction compared to batch)

No or very limited scale up



Examples of products using continuous unit operations

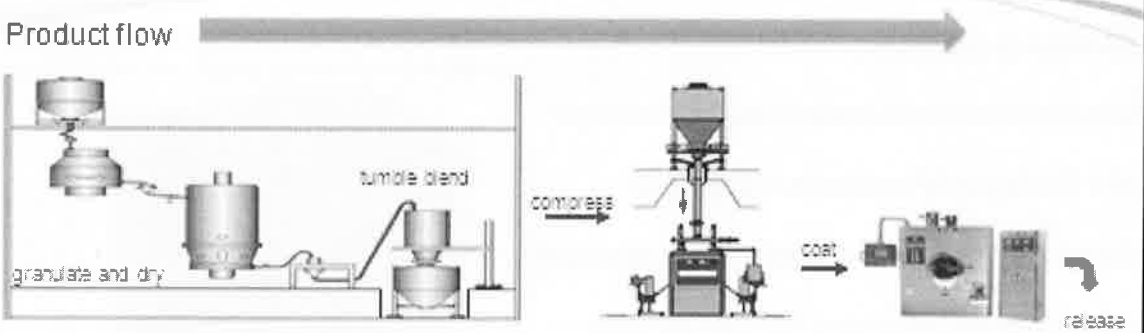
Absolutely anything that has been;

- Size reduced (milled, micronised ....)
- Roller Compacted
- Extruded
- Tabletted
- Check weighed
- Metal checked
- Filled into a capsule/sachet/bottle/blister

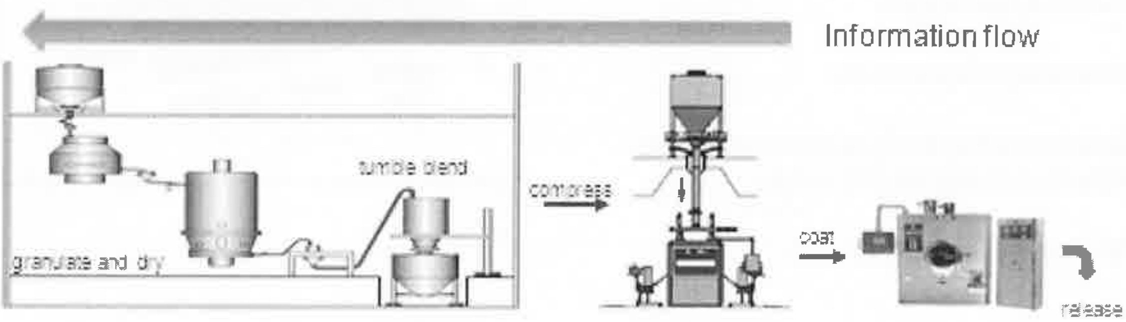
These are continuous processes by definition when considered in isolation, so what is the big deal?

Linking Unit Operations together

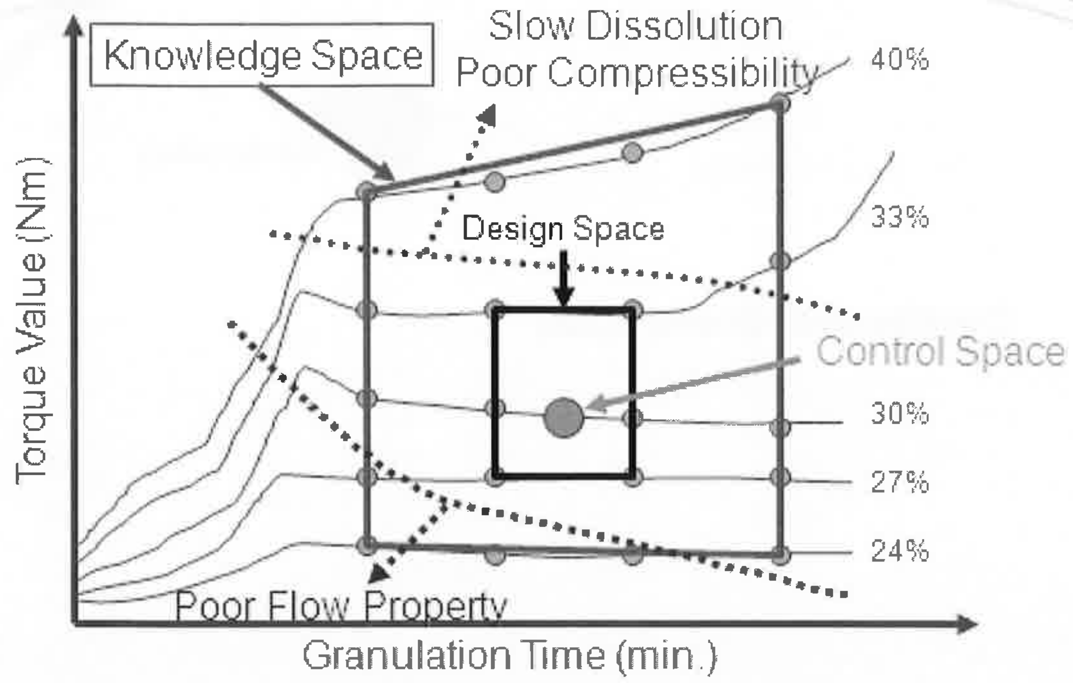
Product flow



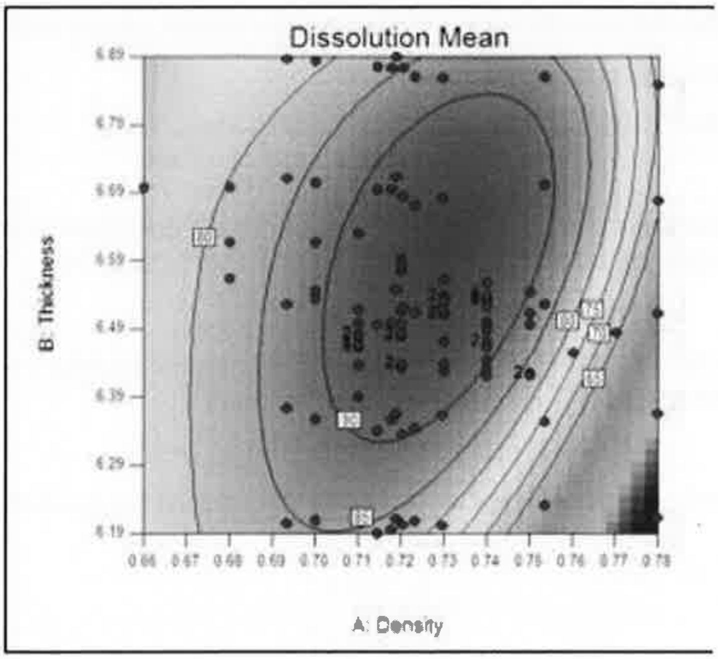
Information flow



Link via Quality by Design (QbD) principles



Response Surface of Mean Tablet Dissolution to Granule Tapped Density and Tablet Thickness



GlaxoSmithKline

Continuous Granulation

Some obstacles remain

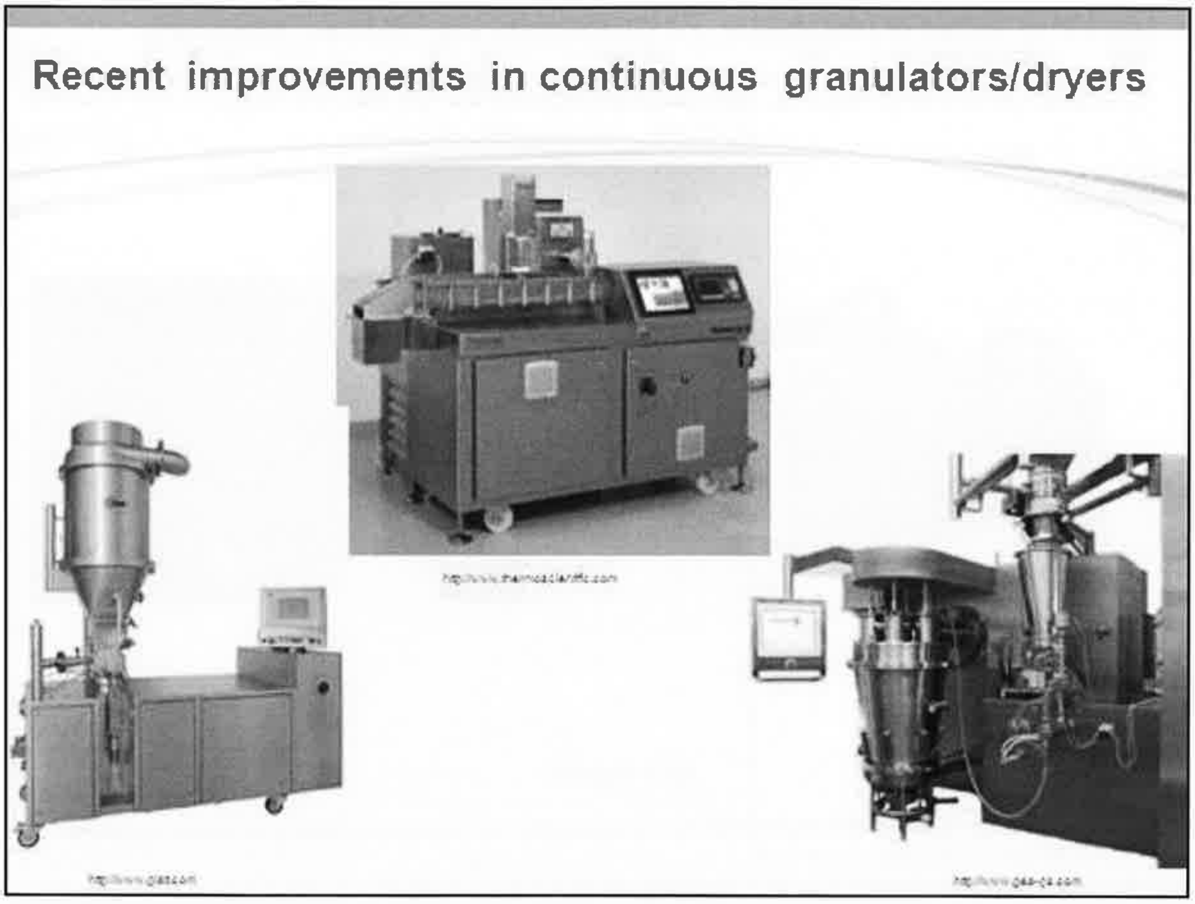
Although some unit operations are continuous by nature, others are not;

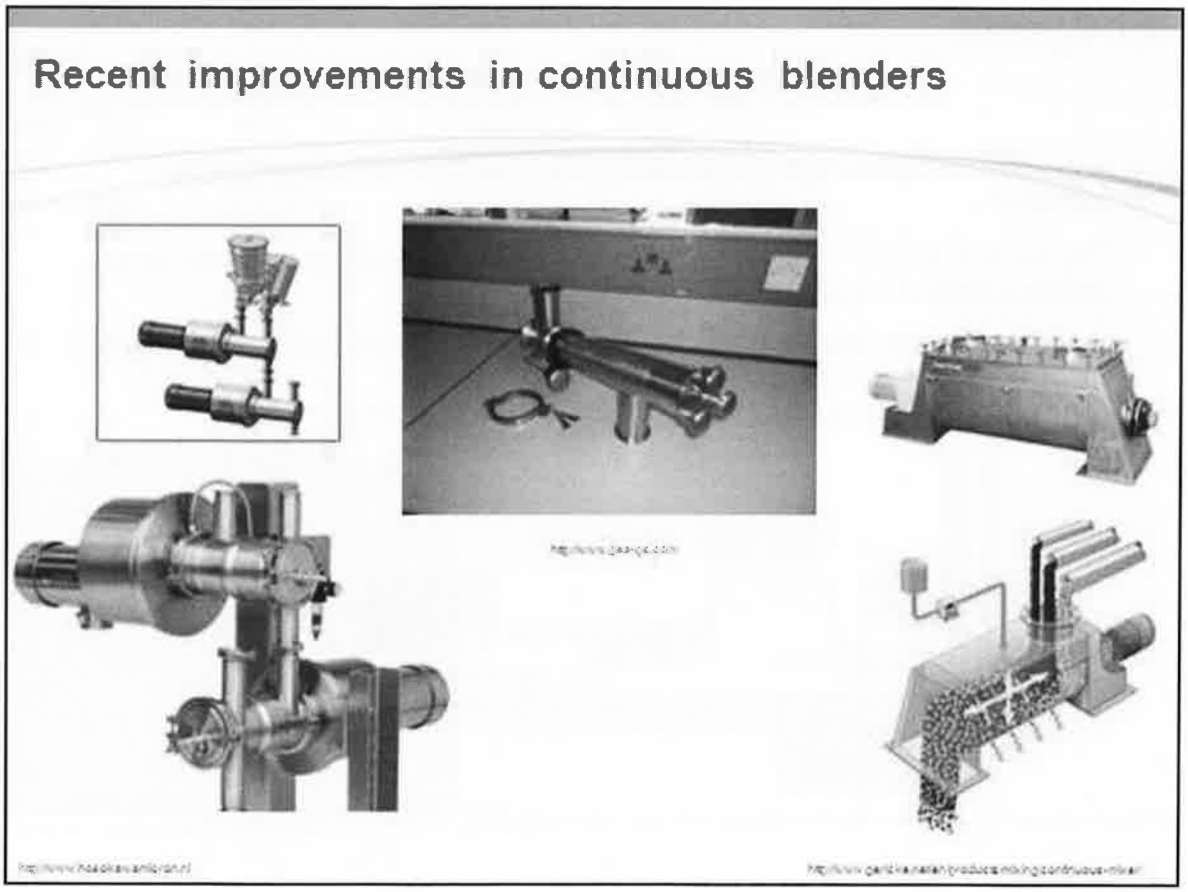
- High shear wet granulation (HSWG)
- Aqueous film coating of tablets

HSWG is by far the most common platform to address poor flow or poor compression properties of Active Pharmaceutical Ingredients (API)

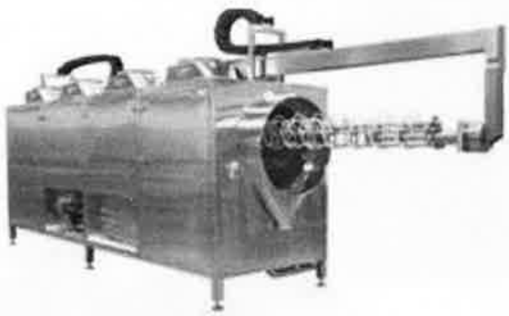
Until recently, pharmaceutically acceptable continuous granulators were not available "off the shelf"

The same can be said for development scale continuous fluid bed dryers


Recent improvements in continuous granulators/dryers
http://www.thermoscientific.com
http://www.glatt.com
http://www.gea-ps.com


Recent improvements in continuous blenders
http://www.gea-ps.com
http://www.hosokawamicron.nl
http://www.gericke.net/en/products/mixing/continuous-mixer

Recent improvements in continuous tablet coaters

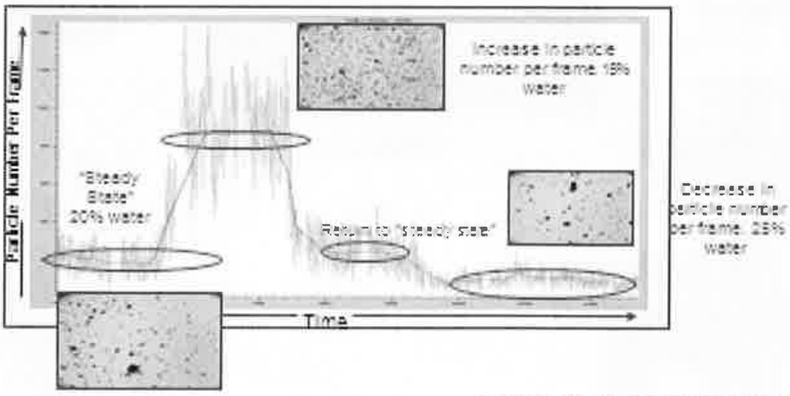


Endpoint

In the case of **batch** High Shear Wet Granulation, the outcome is typically variable*

This leads to extensive work to predict and measure a suitable endpoint across various scales of development and production.

Continuous granulation does not have an endpoint. It works under steady state conditions.



* (Bochon et al Chemical Engineering Journal 164 (2010) 268-281).

Other obstacles still remain

Historically we have always done batch manufacturing.

And these are just some of the '~~excuses~~ reasons' we use to justify that position

21 CFR 211.165(a) – Sampling

21 CFR 211.192 – Investigation

21 CFR 211.188 – Batch records

21 CFR 211.150(b) – Distribution

21 CFR 210.3(b)(2) – Batch definition

21 CFR 210.3(b)(10) – Lot definition

Food and Drug Administration Code of Federal Regulations (www.fda.gov)

Other obstacles also remain

Removal of obstacles

FDA - 1st Continuous Manufacturing Symposium

11th March 2010, Bethesda, MD

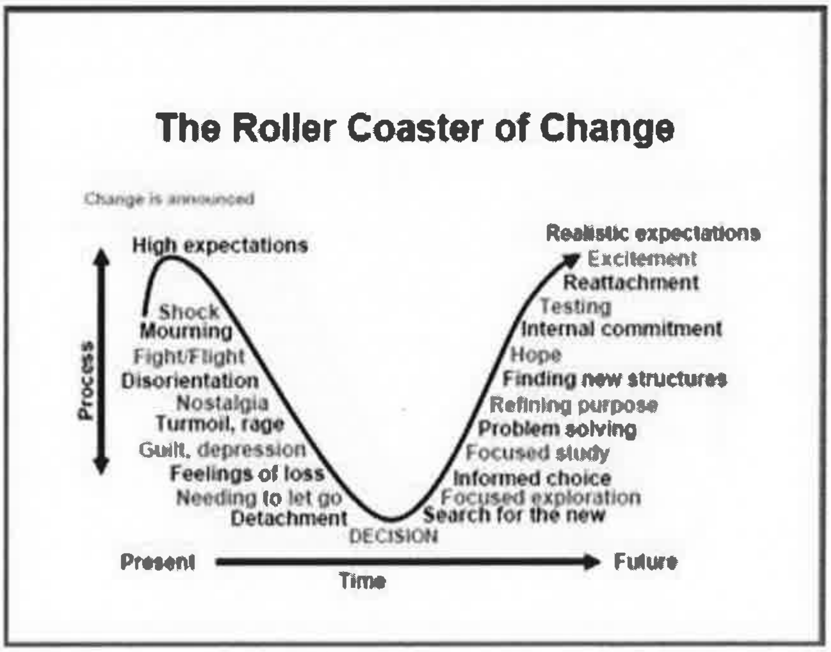
124 participants (1 from Pfizer, 1 from GSK and 1 from GEA)

All the others came from various internal FDA offices

The chairman's introductory presentation highlighted that in the view of the FDA, the use of continuous processing in pharmaceutical production will lead to an improvement in product quality.

Additionally the chairman stressed that the FDA encourages pharmaceutical companies to go that way and that the agency is very supportive of this.

Other obstacles also remain



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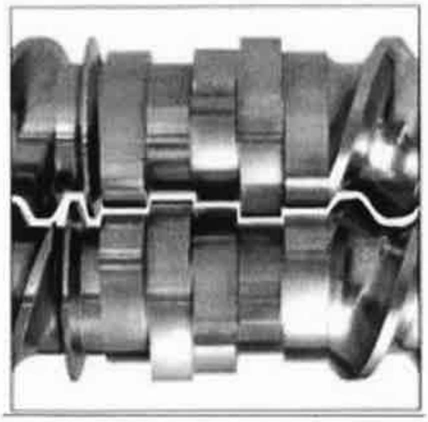
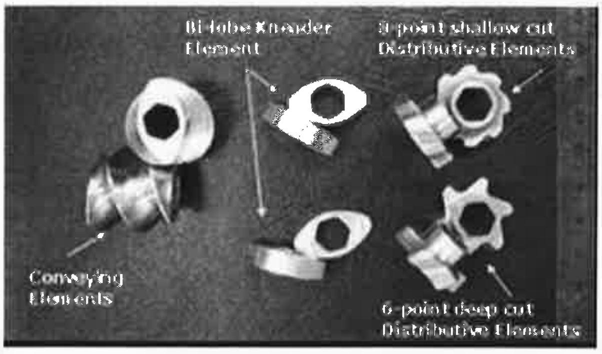
Continuous process flow in more detail

Twin Screw Granulation in more detail

- "Converted" extruders
- 2 co-rotating screws containing a combination of transport, distributive and/or granulating (kneader) elements.





- Elements are mounted on a hexagonal shaft – highly configurable to your products requirements

Twin Screw Granulation in more detail

Granulators are fed by loss in weight (LIW) feeders.

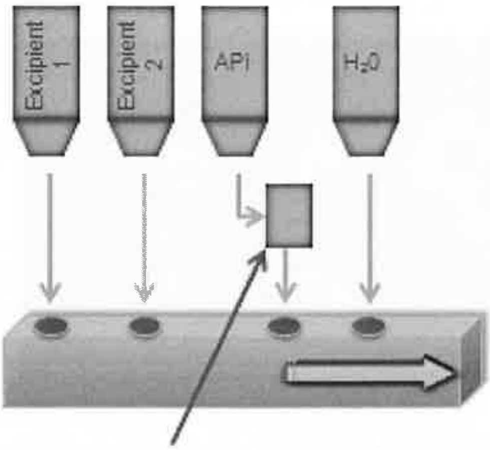
These are typically run under gravimetric control conditions. This is because pharmaceutical products tend to have poor powder flow characteristics (hence volumetric feeding is less accurate due to densification upon transport).

LIW feeders can be grouped into essentially 2 categories

- Rigid frame – used for free flowing powders (K-Tron Soder)
- Flexible frame – used for cohesive, sticky API's that easily bridge (Brabender, Schenk)

Twin Screw Granulation in more detail

Granulators are defined by a specific ratio L:D (Length : Diameter) of their barrel and their screw diameter.

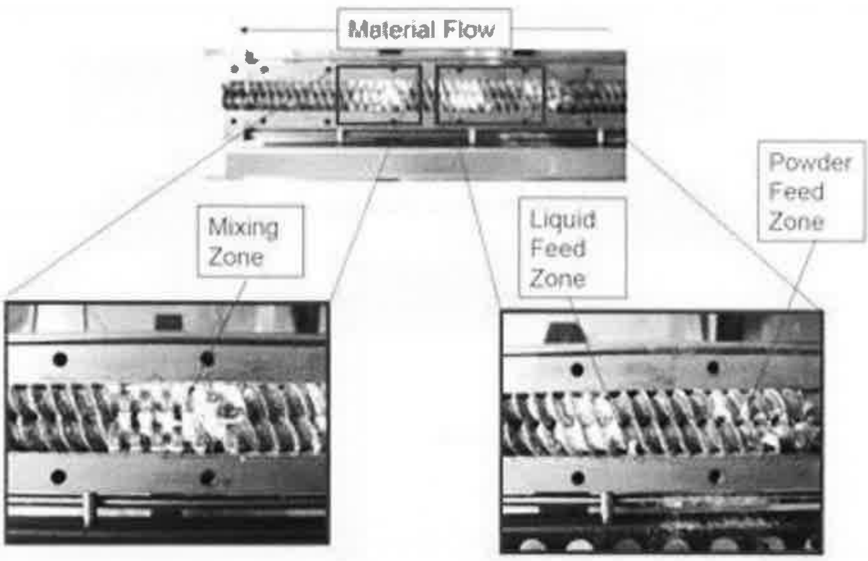


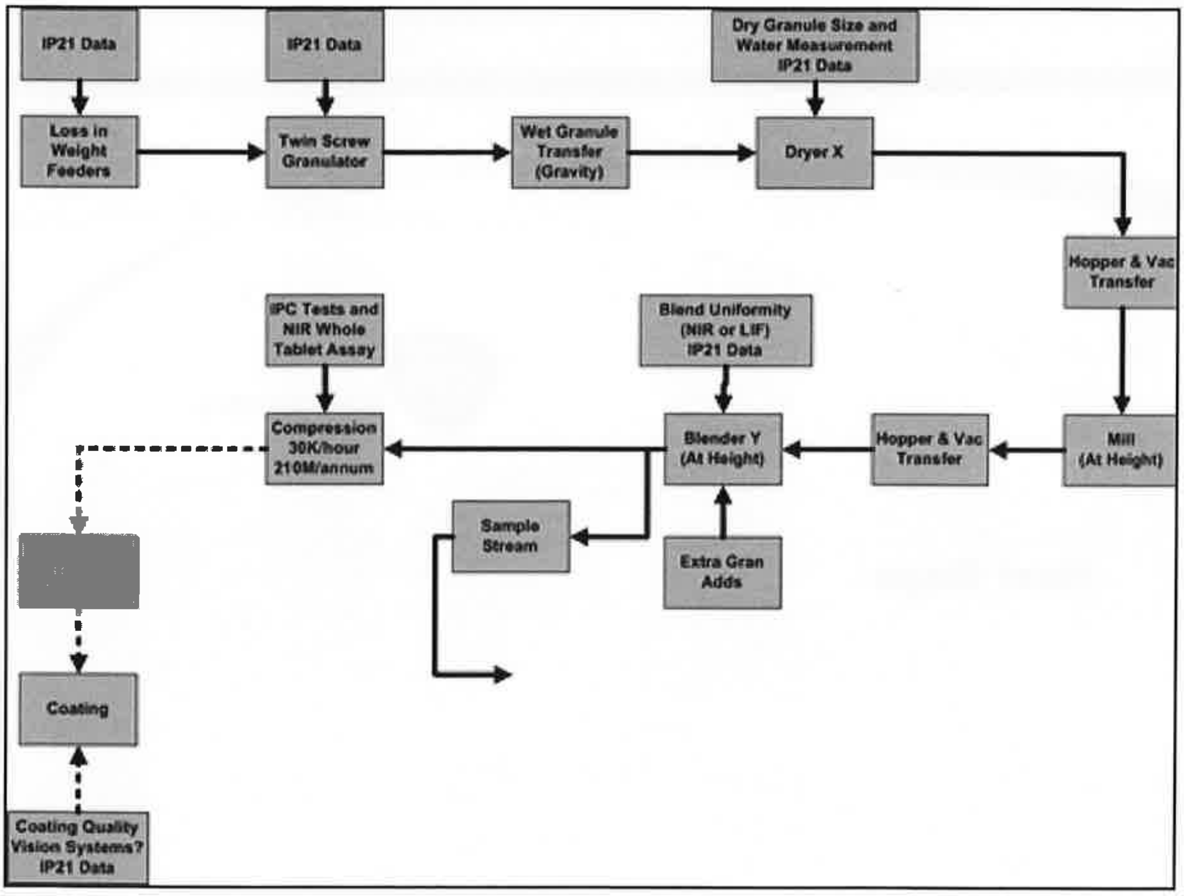
	Thermo Fisher	GEA	Leistritz
Barrel size (mm)	16mm 24mm 36mm	25mm	18mm 27mm 40mm 50mm
L : D	25:1 (16mm) 30:1 (24mm) 40:1 (both)	10:1 (module)	Variable up to 60:1

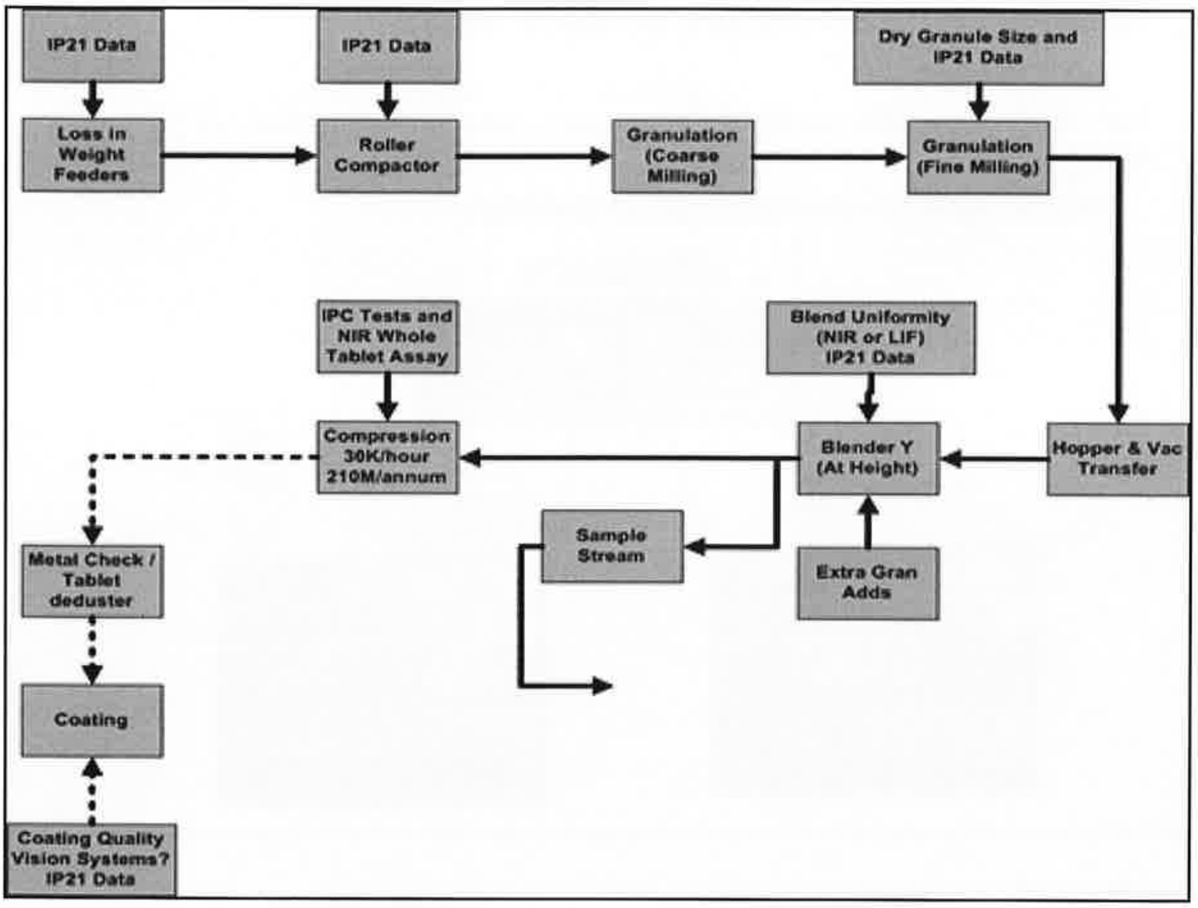
Twin Screw Granulation in more detail

Twin screw granulators are highly configurable and have a clam shell design typically.

- In development you can stop and look – frozen in time.






IP21 Data
Loss in Weight Feeders
IP21 Data
Roller Compactor
Granulation (Coarse Milling)
Dry Granule Size and IP21 Data
Granulation (Fine Milling)
IPC Tests and NIR Whole Tablet Assay
Compression 30K/hour 210M/annum
Blend Uniformity (NIR or LIF) IP21 Data
Blender Y (At Height)
Hopper & Vac Transfer
Sample Stream
Extra Gran Adds
Metal Check / Tablet deduster
Coating
Coating Quality Vision Systems? IP21 Data

Next Steps

Some Knowledge Gaps

Mechanistic understanding of the twin screw agglomeration process

Scale up rules between Lab and Commercial systems

- 16mm system sweet spot is say 1.5kg/hr
- 24mm system sweet spot is say 20kg/hr for the same poorly flowing product

"Binder" hydration rates

- They are in contact and mixed with water in a matter of seconds yet they require minutes to become effective. Why don't granules break up in the dryer.

Extended processing events

Residence time distribution – Plug flow is not realistic.

PAT Solutions

Lecture 5. Troubleshooting in Granulation Processes

Mr Nigel Somerville Roberts (Procter & Gamble)

Troubleshooting in Granulation Processes

Thoughts and observations from 20+ years of trying to work out what just went wrong - and why.

Nigel Somerville Roberts

(Procter and Gamble)

Troubleshooting in Granulation Processes

- Granulation processes are complex (recycles!) and often inherently unstable. Effective troubleshooting often means being able to separate effects from causes and disentangling complex chains of events into their constituent parts.
- The objective of this talk is to show how we can use basic granulation theory and mechanisms, as well as an understanding of agglomerate properties, to help understand what must be happening and hence extrapolate back to the root cause (why? why? why?).

Troubleshooting in Granulation Processes

Question – who can tell me what the problem is below?

Answer – the agglomerates are too big to fit in a box of washing powder.

Answer – a powder feeder momentarily blocked causing over-agglomeration and blockage of the mixer.

- Granulation – a natural system where simple interactions can give complex outcomes.
- All processes are a combination of
  - Material characteristics – esp mixture characteristics
    AND
  - Mixer design and operation
- When a process deviates from centreline, it has to be because something has changed one of the above factors. Changes in one will very often cause changes in the other. Processes do not vary randomly – even though it may seem like it.
- If you cannot correlate defects to any variable, it probably just means that you are not measuring, or are aware of, the critical variable(s).

Troubleshooting in granulation processes

- Need to have a quick re-cap through some basic granulation mechanisms (with particular thanks to Karen Hapgood) to understand how material characteristics and mixer operation can interact.

Nucleation & Liquid Distribution

Karen Hapgood

- Nucleation processes is starting point for entire granulation process
- Poorly distributed liquid will form coarse, wet granules in granulator
  - Affects PSD and downstream properties
  - Harder to control, less reproducible
  - Why powder wettability is important
- Can use agglomeration regime map to understand what happens next.

Granulation mechanisms

Source: Iveson, Hapgood, Litster, Powder Tech, 2001

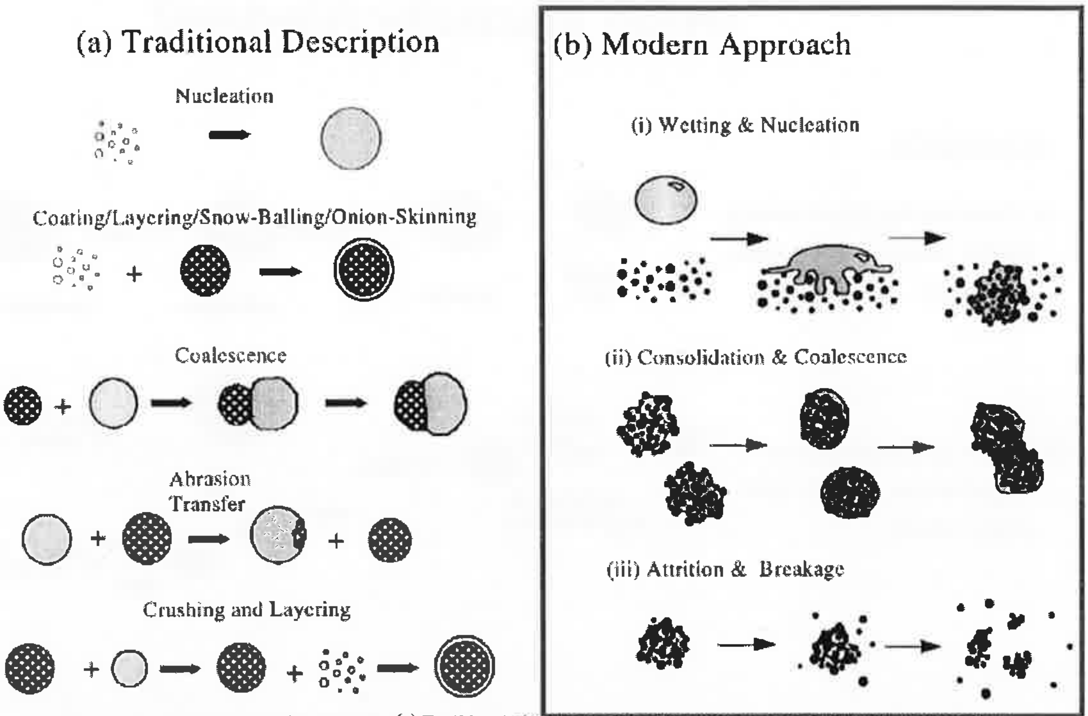
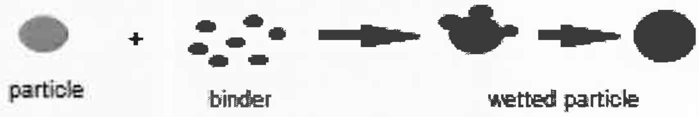


Fig. 1. Schematic of granulation processes (a) Traditional view (after Sastry and Fuerstenau [26]); (b) Modern approach [1].

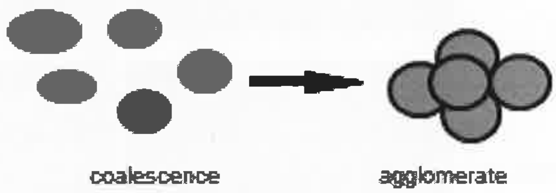
Agglomeration Mechanisms – Distribution (Low Viscosity binders)

DISTRIBUTION

a) Binder dispersion by particle wetting



b) Agglomeration by coalescence of wetted particles.

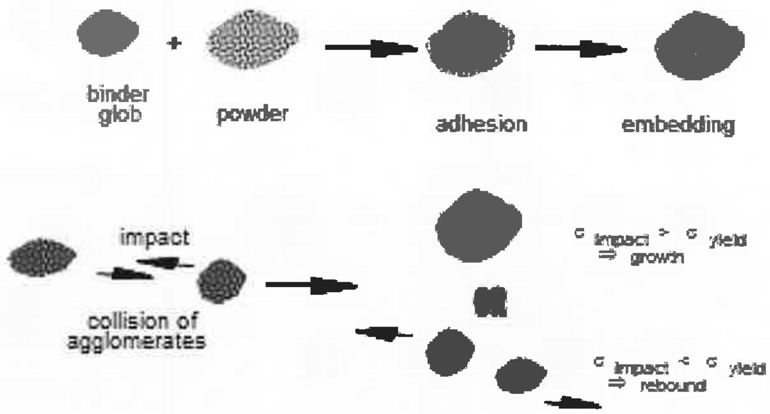


Agglomeration Mechanisms - Immersion. (High Viscosity binders)

IMMERSION

a) Dispersion by globule cutting, powder adhesion and powder embedding;

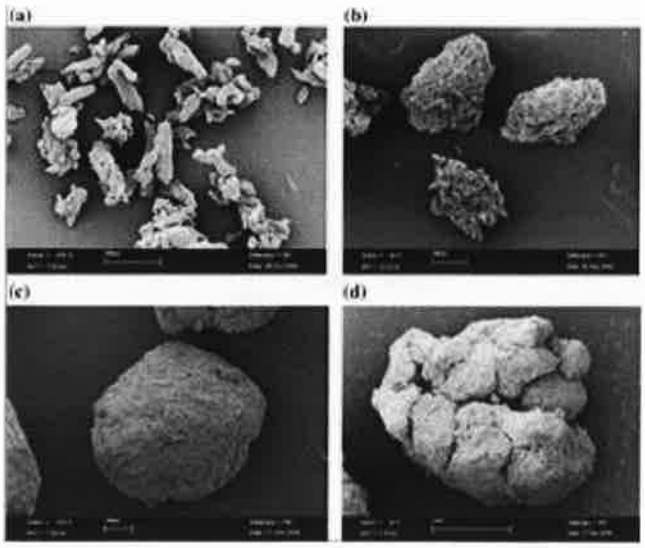
b) Growth by coalescence of agglomerates – plastic yield stress criteria.



Agglomeration Stages

NUCLEI

COALESCENCE

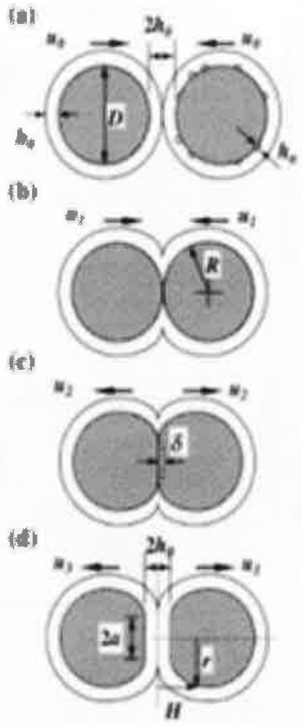


CONSOLIDATION

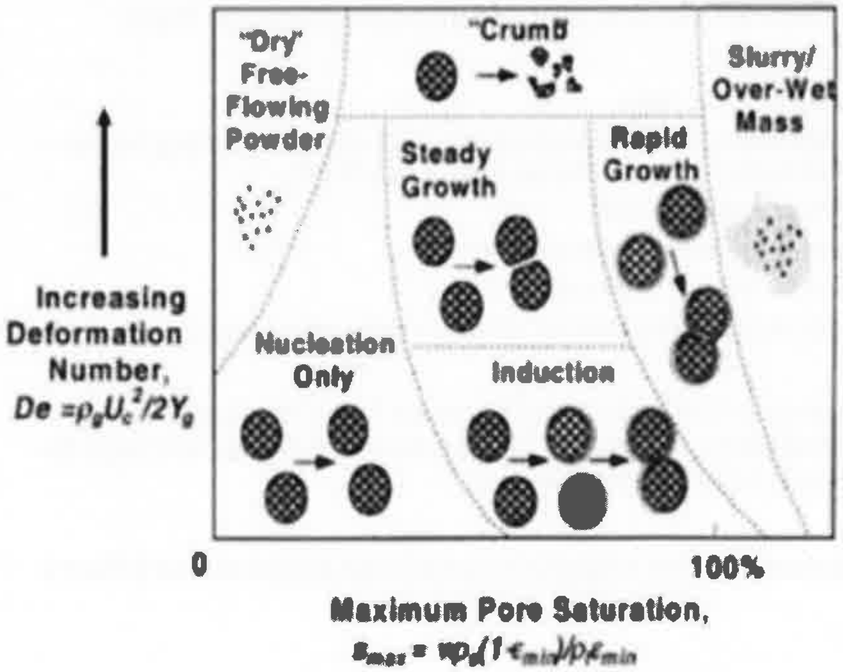
OVER GROWTH, SATURATION

Consolidation and Coalescence

- Particles need to collide to coalesce.
- Assumption is that particles can coalesce if the kinetic energy of impact can be dissipated by *viscous dissipation* – the energy taken up by deforming the particle.
  - The more deformable the particle is, the easier it can absorb the energy of impact.
- Likelihood of coalescence is greater if additional fresh binder will be forced to the surface by the impact (hence importance of saturation of pores with binder).
- Else the particles will bounce apart after consolidating the particles.

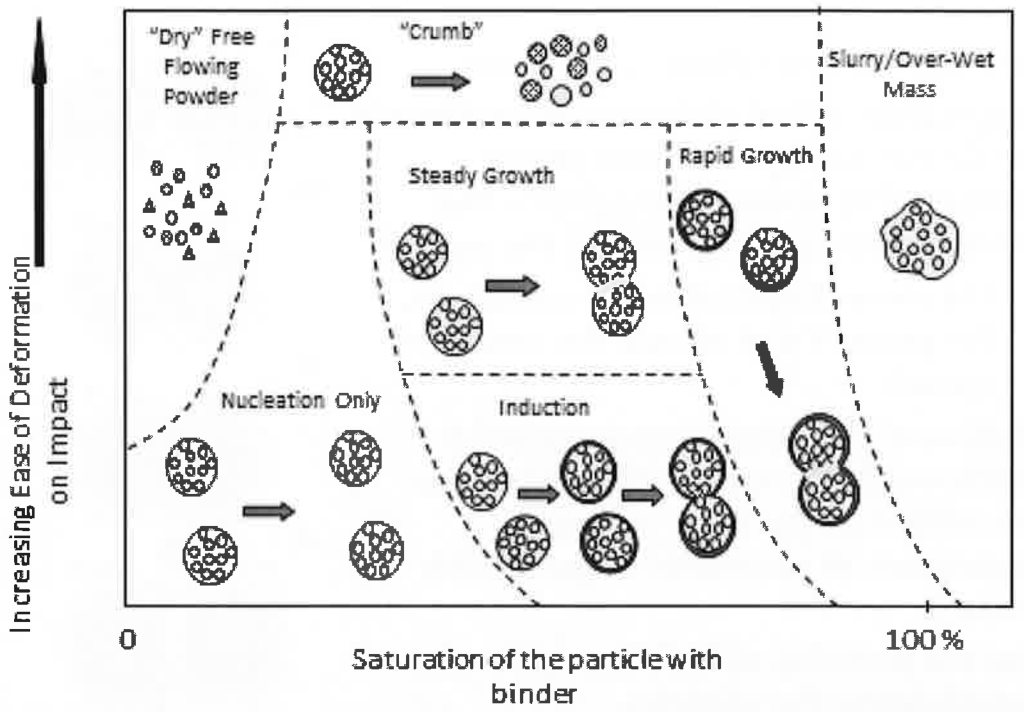


How to relate these to our processes ?



Consolidation of granules is brought about by the motion of the material in the mixer –

Compressive and shear forces produced by particle impacts and impacts between the mixer tools and walls.



Troubleshooting in granulation processes

- Anything which can change the "% Saturation of the Particle with Binder" or the "Ease of Particle Deformation" will move the process around the map. This can put the process into an undesired state.
  - Changing the Liquid/Solid ratio
  - Increased consolidation by increased mechanical energy input (eg higher mixer speed, wall make-up, tool design, residence time)
  - Increased material temperatures
  - Less absorbent or more absorbent powders
  - Liquids being harder/easier to disperse
  - Viscosity changes due to temperature effects or chemical reaction.

REMEMBER – changes may only need to occur for a few seconds to cause major problems. A short deviation due to hold-up in a loss-in-weight feeder can easily block a mixer.

Will run through some of the situations which can cause these effects.

- Liquid/Solid Ratio Variability
  typically arising due to feeder variability in continuous systems, causing process fluctuations, mixer make-up. Improve feeder operation, eg air pads, vibrators etc.

- Increased particle consolidation
  leading to increased granulation. Typically arising due to mixer make-up or running the mixer too fast. Often linked to feeder variability as the root cause.

- Increased material temperature
  leading to increased granulation. Can happen due to ambient weather conditions, mixer make-up causing friction and high power use, recycling hot material over time, fresh deliveries of (hot) raw materials.

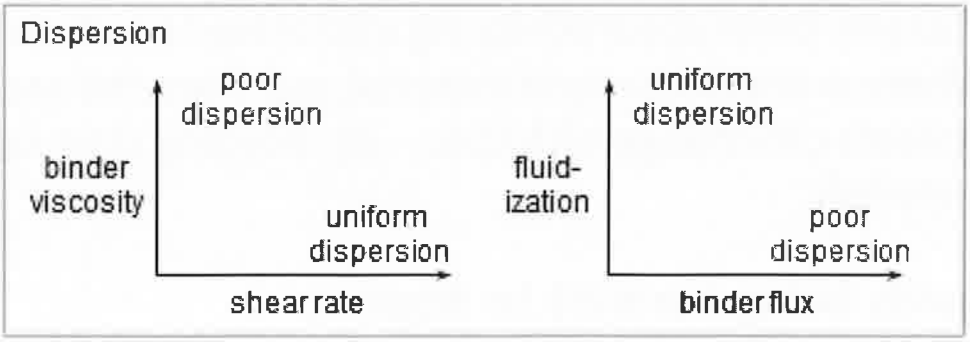
- Less absorbent/more absorbent RM powders
  typically arising due to raw material changes – either fresh batches with different properties or RMs stored too long/incorrectly and caked/hydrated together to increase PSD and lower absorptivity (eg micronised powders). Where processes recycle material, esp fines, the recycle streams can change with time – eg recycling start-up materials.

- Liquids being hard(er) to disperse
  Can arise due to viscosity, visco-elasticity or wettability.

Binders Dispersion and Viscosity

- Dispersion of a binder into a powder depends both on the binder viscosity and the applied shear rate of the process. A combination of high shear and low viscosity will disperse the binder evenly throughout the powder mass
- Using a viscous binder with insufficient shear results in a heterogeneous mixture of over-wet globules and dry powder. Increase the mixer speed.
- Increasing the viscosity of the binder, eg by reducing the temperature, can give less wall make up. With some binders, this change in temperature / viscosity reduces the 'stickiness' of the material which modifies the growth rate.
- When fine solids are used (eg zeolites, ground powders), it can also give a more controlled consolidation stage and slower initial size enlargement.

Dispersion Influence



A current example of dispersion

The P&G plant in Worms, Germany, has been experiencing high pressures in the fluid bed dryer filters when making a new version of a perfume agglomerate.

No apparent change in the process conditions, such as recycle levels.

What is going on?

The new formulation has a more viscous, harder to disperse binder. Running the mixer at the same conditions meant that the binder was just not being dispersed well enough.

Unagglomerated fine raw material powder was being elutriated into the filters and coating the filters, causing high pressures.

Elutriation rate had not changed – but the nature of the material had.

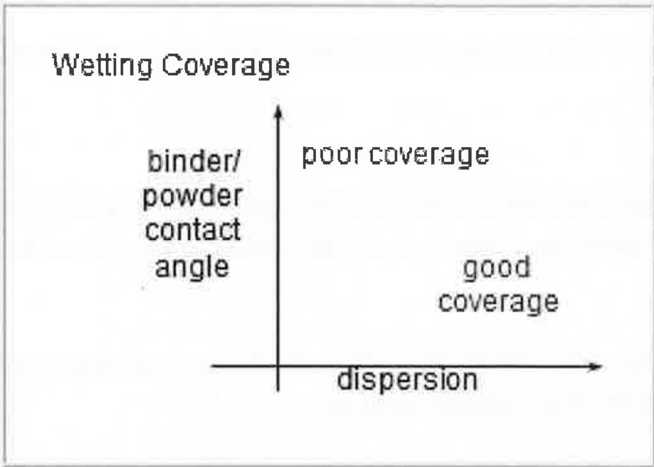
The increased overs rate was not detected due to a mistake in the installation of the oversize recycle screen.

Wetting With Low Viscosity Binders

- Wetting depends on how well the binder disperses into the bulk of the powders.
- Wetting is also successful when the binder solution / melt and the solids are compatible materials, e.g. the contact angle is low and the binder spreads readily over the solid.

- If the particles are wetted poorly by the liquid, it may be difficult to form good granules.

Wetting Coverage

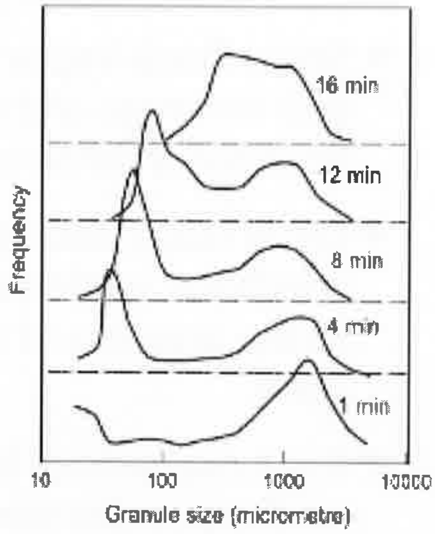


Wetting Of Powders

- Poor wetting leads to poor nucleation, and hence broad granule size distributions, leading to high recycle rates.
- In mixer granulation, increasing the mechanical energy (speed) can be used to force the binder liquid and solid to mix.
- However, it is easier to control the size and size distribution of drops from a spray nozzle than it is to mechanically disperse the liquid through the bed.
- The poorly wetted granules may also be weak and may break up during drying / cooling.
- The strength of the dry / cool granules depends on how good the adhesion is between the solidified binder and the solid, which is also determined by the initial wetting.
- However, it may be possible to form good granules if the binder viscosity is high due to formation by immersion.

Binder Distribution with Time

- Liquids added as streams -> large droplets from cutting action of mixer.
- Not homogeneous mix. Wetted powder surrounded by unwetted powder.
- Bimodal psd. Move to monomodal with mixing time increase.
- Due to breakage of coarse granules, transfer of liquid from coarse to drier granules, and coalescence of dry fine with coarse wet granules.



Coarse = high active
Fine = low active
Dispersion Index = <u><1180</u>
>250

Knight, Instone, Pearson, Hounslow (1998). Powder Technology 97: 246-257.

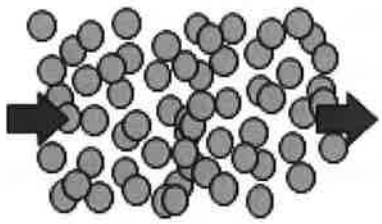
Effect Of Mixer Speed

- High impeller and chopper speeds are advantageous in distributing high viscosity binders.
- High impeller speeds may be advantageous in consolidating the particles.
- However, too much speed may increase risk of make up and over-agglomeration.
- Mixers with no chopper blade and or low impeller speed may give 'balling'. High impeller speeds can prevent this – unless wall make up is formed.
- Under favourable conditions, a high speed can produce a narrow size distribution and smooth, spherical granules.
- With weak granules, (large size, low viscosity binder) high speeds may produce a wet mass which adheres to the wall of the mixer.

SPRAY ZONES IN PADDLE GRANULATORS AND FLUID BEDS

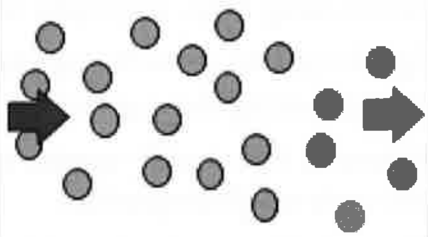
- Spray flux is important in granulators. Need to get god coverage and avoid droplet overlapping and poor spray patterns.
- Spray flux is defined as the ratio of the rate at which the wetted area is covered by the droplets to the area flux of the powder through the spray zone.
- It is a measure of the density of the drops falling on the powder surface. High values will mean droplet overlap, hence bad distribution and localised saturation and over-agglomeration.

Dimensionless Spray Flux Ψ_a



High Ψ_a

- high sprayrate or slow powder velocity
- high spray density
- significant drop overlap

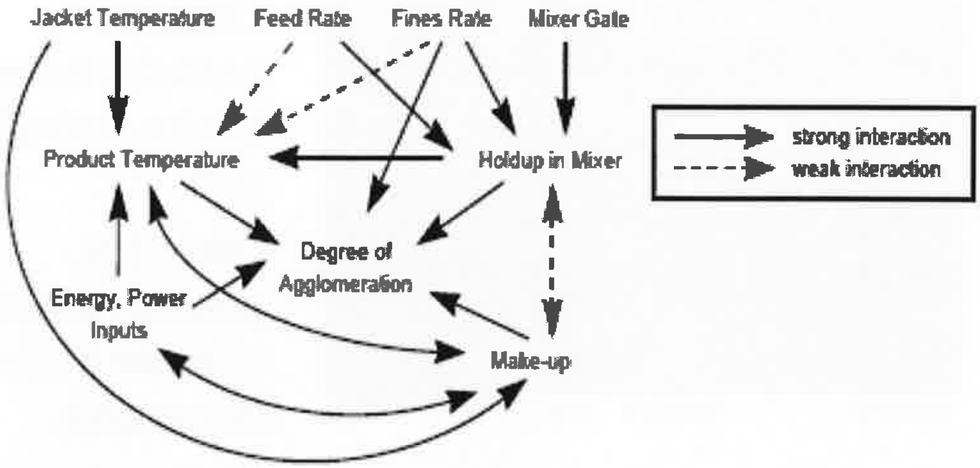


Low Ψ_a

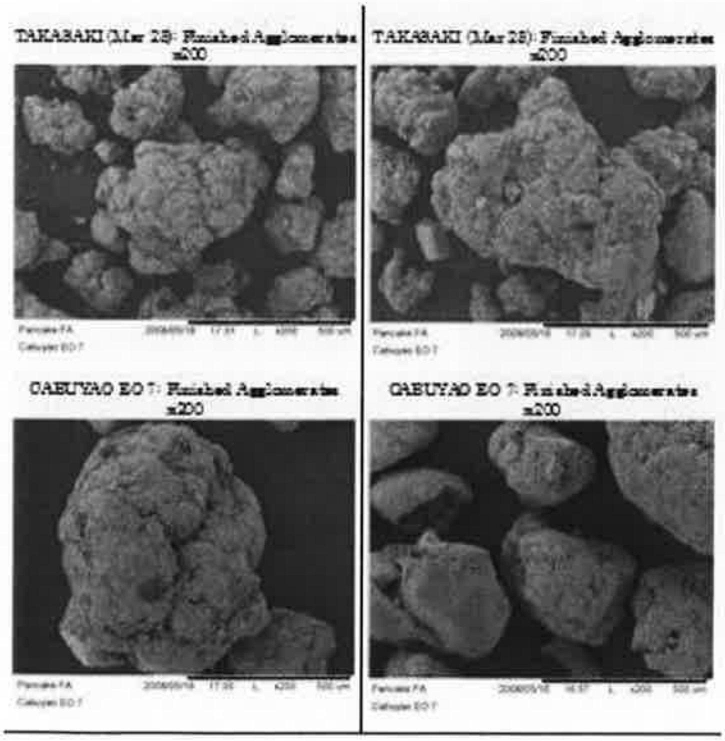
- low sprayrate or fast powder velocity
- low spray density
- minimal drop overlap

Litster, et al. (2001) Powder Technology 114(1-3): 32-39.

Operating Variables – Some Possible Interactions

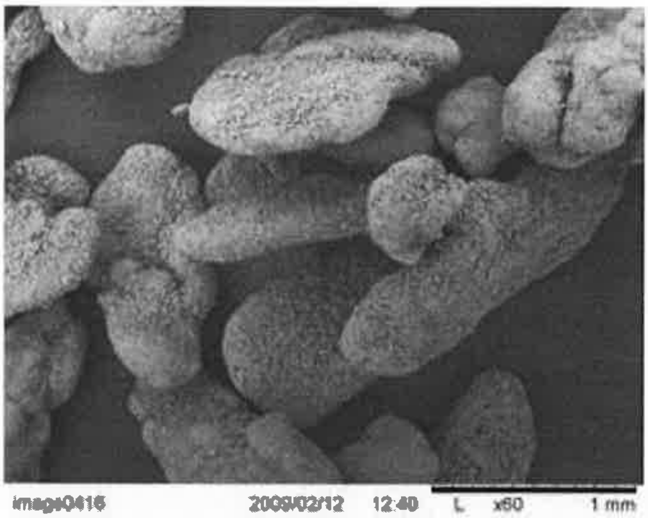


Looking at granule shapes



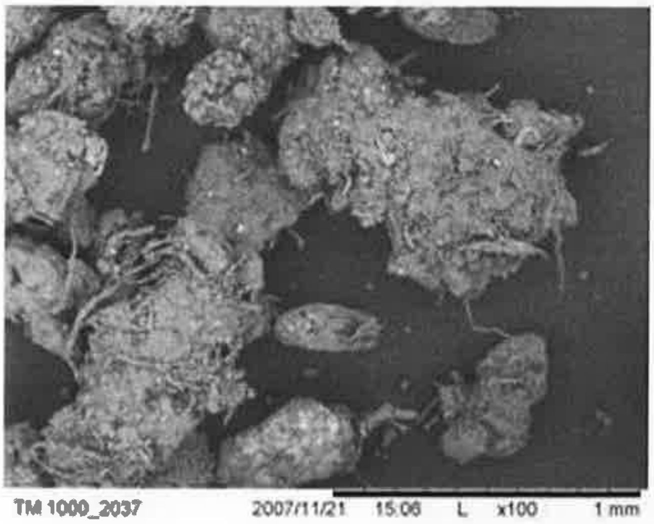
Agglomerate at the top is more irregular than the one at the bottom, despite identical compositions. Differences are due to how the powders were milled. The top agglomerate is more prone to break-up and fines generation than the rounder, bottom agglomerate.

Polymer Agglomerate



- Irregular shapes
- Elongated particles from binder 'stringing out'
- Dilute the polymer solution to make it more dispersible.

Perfume Agglomerate



- Poorly formed particles with very rough surfaces.
- Very poor handling properties.

Lecture 6. Mathematical Modeling of Granulation Processes

Prof. Jim Litster (Purdue University)

Mathematical modeling of granulation processes

Jim Litster

Purdue University

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Outline

- Types of design and scaling models
- Population balance framework
- Modeling granulation rate processes using the population balance
- Examples and case studies

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Quantitative Engineering Approaches

What do we know?	How do we design experiments and scale ?	Implications
Nothing except parameters we can vary →	Statistical Experimental Design →	Lots of experiments at all scales
Controlling mechanisms →	• Careful formulation and process characterization • Designing experiments based on **dimensionless groups and regime maps** →	• Reduced experiments at all scales • Use dimensionless groups to scale up
Fully predictive model →	• Careful formulation and process characterization • Design min. number of experiments to validate and fine tune the model →	• Least number of experiments • Pilot/full scale model validation and parameter estimation

Defining Design Space
Regime Map Approach

Measure Formulation Properties: d_p, $\gamma \cos\theta$, μ, Y…

Estimate Process Parameters at different conditions: U_c, $R\omega$…

↓

Calculate important dimensionless groups: Ψ_a, t_p, St_{def}, S…

↓

Locate the regime of operation on nucleation and growth regime maps that are functions of dimensionless groups

↓

Design and perform laboratory scale experiments regarding to regime maps

↓

Determine the exact borders of different regimes on the regime map for the given formulation and determine optimum design space

↓

Scale-up by keeping the dimensionless numbers constant

4

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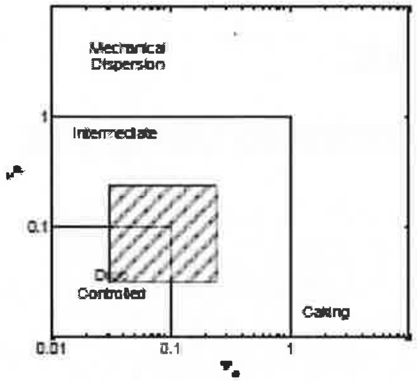
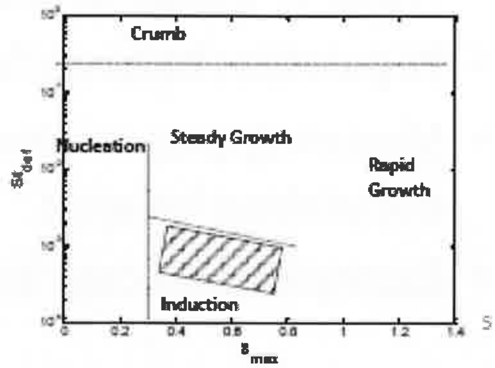
Regime Map Approach





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Problems with this approach

- Large numbers of experiments at various scales required
- Relationships do not easily transfer across different types of equipment
- Very simplistic approach to powder flow and granule mechanics
- Distribution of granule attributes is not predicted directly
- Impossible to scale keeping all granule attributes constant

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Outline

- Types of design and scaling models
- Population balance framework
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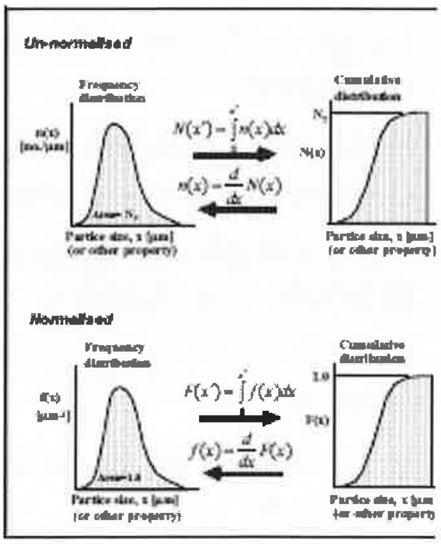
Particles have property *distributions*

- Frequency *f(x)* or cumulative *F(x)*
- *F(x)* is the number fraction of particles less than size *x*
- *f(x)dx* is the number fraction of particles in the range *x* to *x+dx*
- Normalised *F(x), f(x)* Un-normalised *N(x),n(x)*



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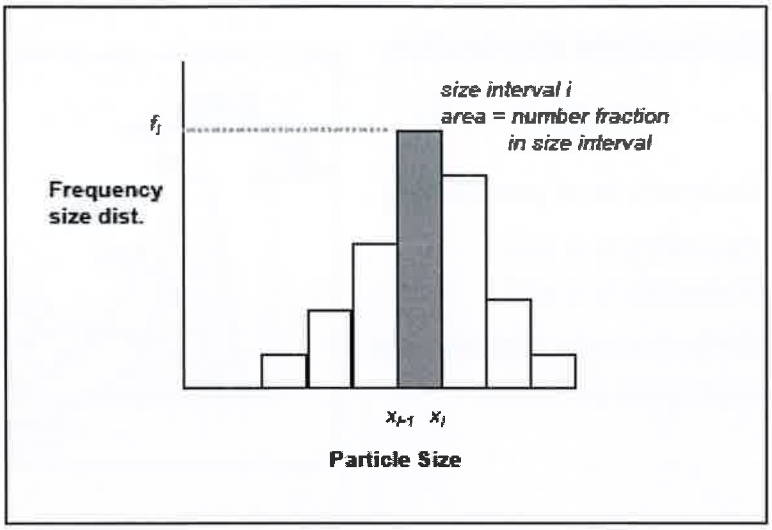
Discrete size distributions



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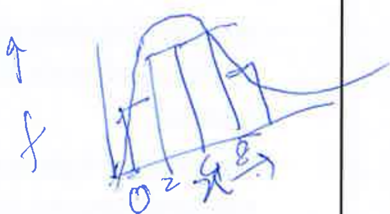
Example

- Sketch the cumulative distribution and frequency histogram for this data:

Range (μm)	No. of particles
0-2	5
2-4	10
4-8	10
8-16	5



$f(x)/n(x)$ $n(x)/N_T$

$f(x)$

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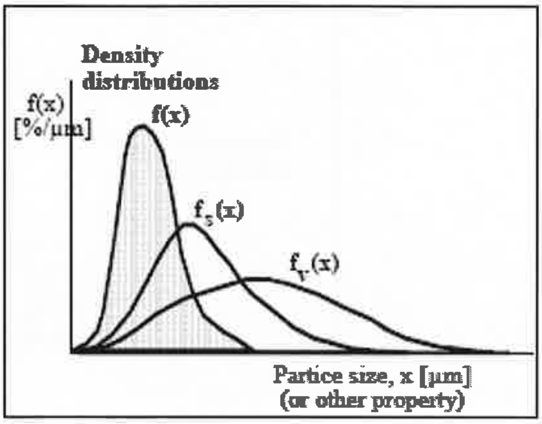
Different forms of size distribution

- Generalised distribution

$$f_\alpha(\xi)$$

- Quantity α of property ξ
- Quantity is y axis
  Property is x axis
- Different representations look *very* different



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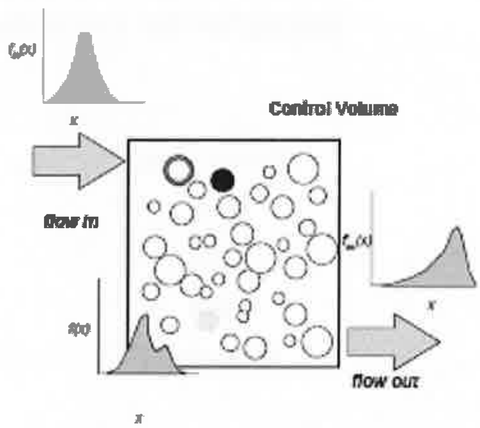
Deriving the PB

- Chemical reactor
  - mass, energy balances
  - reaction kinetics
  - mixing
- Particle generator
  - property distribution replaces chemical species
  - population balance replaces species balance



Particle Generator (Granulator)

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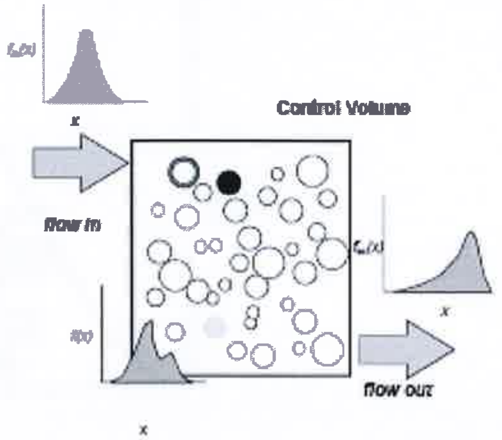
Deriving the PB

- Balance eqn.
  IN - OUT = ACCUM.
- What processes need to be accounted for?

AGG
BREAK
NUCLE

ATTRITION
DISS^n
LAYERING
COATING



Particle Generator (Granulator)

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Derivation of the PB

- Accounting of number of particles in size range x to $x+dx$

  Accum. =Flow in -Flow out +growth +birth -death

$$\frac{\partial Vn(x,t)}{\partial t} = \dot{Q}_{in}\, n_{in}(x) - \dot{Q}_{ex}\, n_{ex}(x) - V\frac{\partial Gn(x,t)}{\partial x} + V\,\dot{b}(x) - V\,\dot{d}(x)$$

- This is the macroscopic, one dimensional population balance for a well mixed control volume

LAYN
ATT

$$\frac{\partial Vn(v,t)}{\partial t} = \dot{Q}_{in} n_{in}(v) - \dot{Q}_{ex} n_{ex}(v) - V\frac{\partial (G^{*} - A^{*}) n(v,t)}{\partial v}$$
$$+ V(\dot{b}(v)_{nuc} + \dot{b}(v)_{coal} + \dot{b}(v)_{br} - \dot{d}(v)_{coal} - \dot{d}(v)_{br})$$

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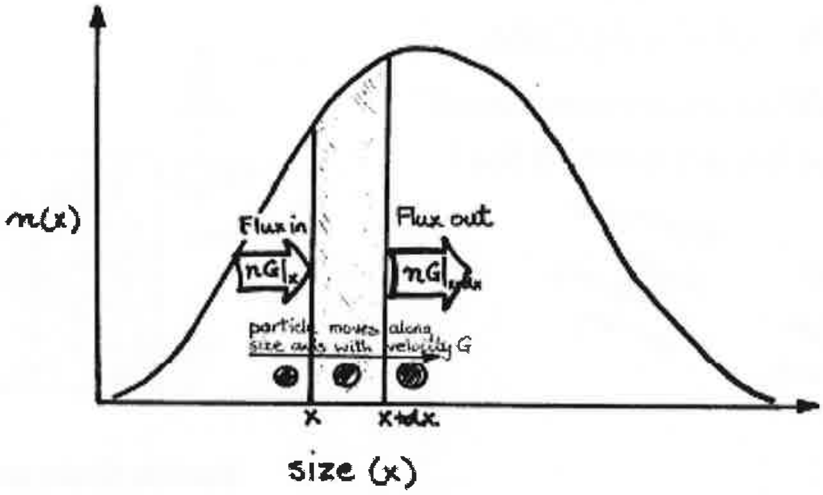
Layered growth as a "flux"



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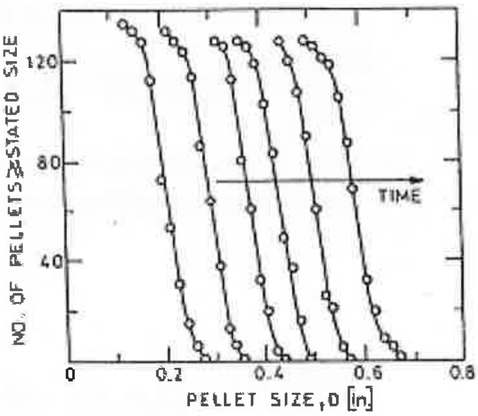
Layered Growth on Seed Granules

- Layered growth:
  - Growth rate controlled by mass balance
  - If ***all*** new feed goes to layering, then

    $$\dot{V}_{feed} = (1-\varepsilon)\int_0^\infty G^*(v)n(v)dv$$

  - If linear growth rate is size independent:

    $$G^*(v) \propto v^{2/3} \propto x^2$$



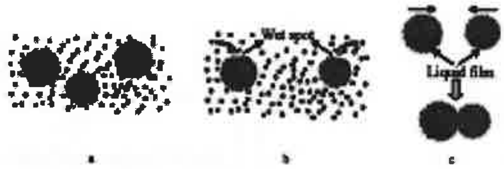
Modelling consolidation and layering

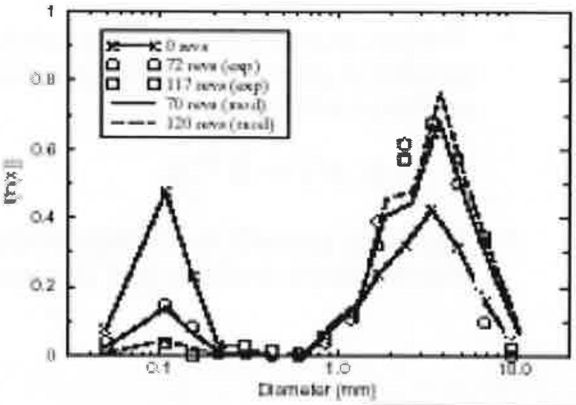
- Consolidating granules pick up fines (layering) as liquid is squeezed to the surface
- When fines are used up, coalescence may start

$$G(v) = -k_{con} v \frac{\varepsilon - \varepsilon_{\min}}{\varepsilon}$$

$$k_{con} = f(St_{def})$$

- Predict induction time in batch systems





Wildeboer, 2002

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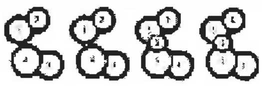
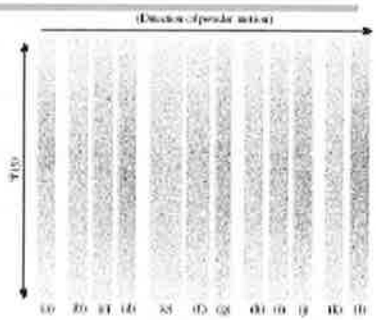
Modelling Nucleation

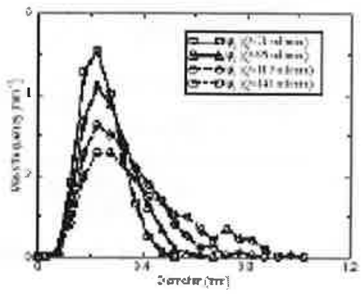
- Purely drop controlled:

$$\dot{b}(v)_{nuc} = Sn_s(s\varepsilon v)$$

- Extension to allow for non-uniform (real) sprays and some drop overlap using Monte Carlo simulation







Wildeboer, 2002

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Modeling coalescence

- Birth and death terms for coalescence

$$\left[\frac{dn(v)}{dt}\right]_{agg} = \dot{b}_{agg}(v) - \dot{d}_{agg}(v)$$

$$= \frac{1}{2}\int_0^v \beta n(v')n(v-v')dv' - \int_0^\infty \beta n(v)n(v')dv'$$

- The key parameter is the coalescence kernel which is difficult to predict *a priori* and is the product of the collision frequency and collision efficiency

$$\beta(u,v) = k * \eta$$

- Typically, growth by coalescence gives broad granule size distributions and the gsd depends on the functional form of β

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The coalescence kernel

- Many different forms

Kernel	Reference and comments
$\beta = \beta_o$	Kapur & Fuerstenau [*I&EC Proc. Des. & Dev.*, 8(1), 56 (1969)]. Size independent kernel.
$\beta = \beta_o \dfrac{(u+v)^a}{(uv)^b}$	Kapur [*Chem. Eng. Sci.*, 27, 1863 (1972)]. Preferential coalescence of limestone.
$\beta = \beta_o \dfrac{(u^{2/3}+v^{2/3})}{1/u + 1/v}$	Sastry [*Int. J. Min. Proc.*, 2, 187 (1975)] Preferential balling of iron ore and limestone.
$\beta(u,v) = \begin{cases} k, w < w^* \\ 0, w > w^* \end{cases} \quad w = \dfrac{(uv)^a}{(u+v)^b}$	Adetayo & Ennis [*A.I.Ch.E. J.*, (1996)]. Based on granulation regime analysis.

$$w^* = \frac{\pi}{6}\left(\frac{9\mu}{4\rho_a U_c} St^*\right)^3$$

- Kernel functional form effects the shape of the granule size distribution

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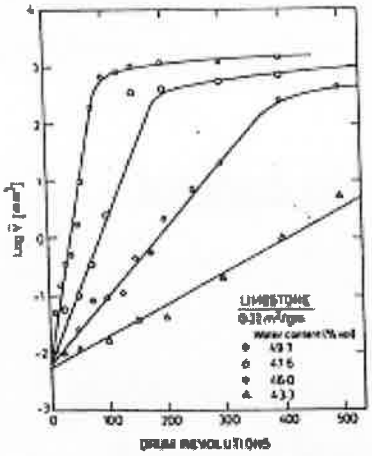
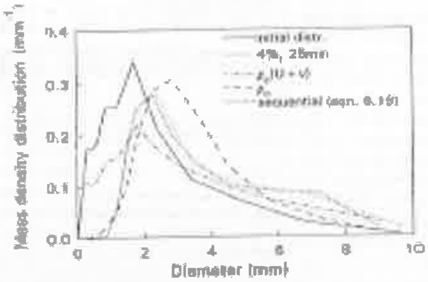
The coalescence kernel





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Modeling breakage

$$\dot{d}_{br} = S_{br}(v)n(v,t)$$

$$\dot{b}_{br} = \int \varphi(v',v)S_{br}(v')n(v')dv'$$

- Two parameters are breakage rate S_{br} and the fragment distribution ϕ
- Breakage rate is a function of St_{def}

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Using the population balance for granulation

- Critical analysis of lab and plant data
- design
- sensitivity analysis
- optimisation and process control

- CAUTIONARY NOTES
  - only as good as the kinetic parameters
  - usually requires numerical solutions

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Outline

- Types of design and scaling models
- Population balance framework
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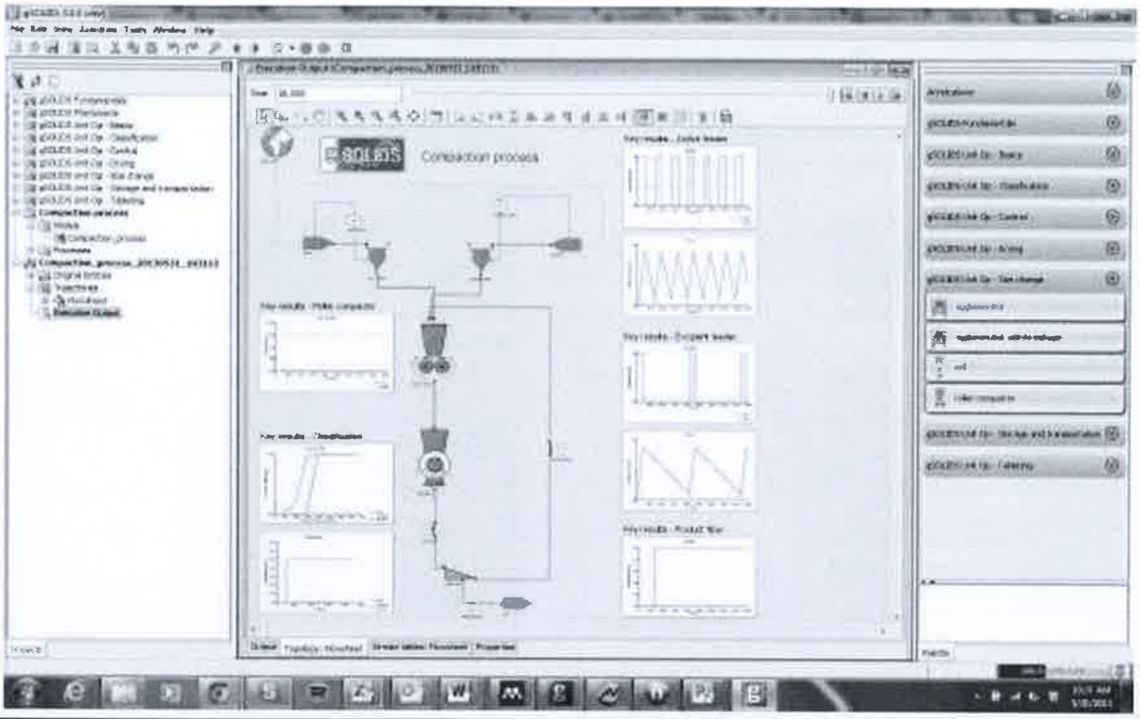
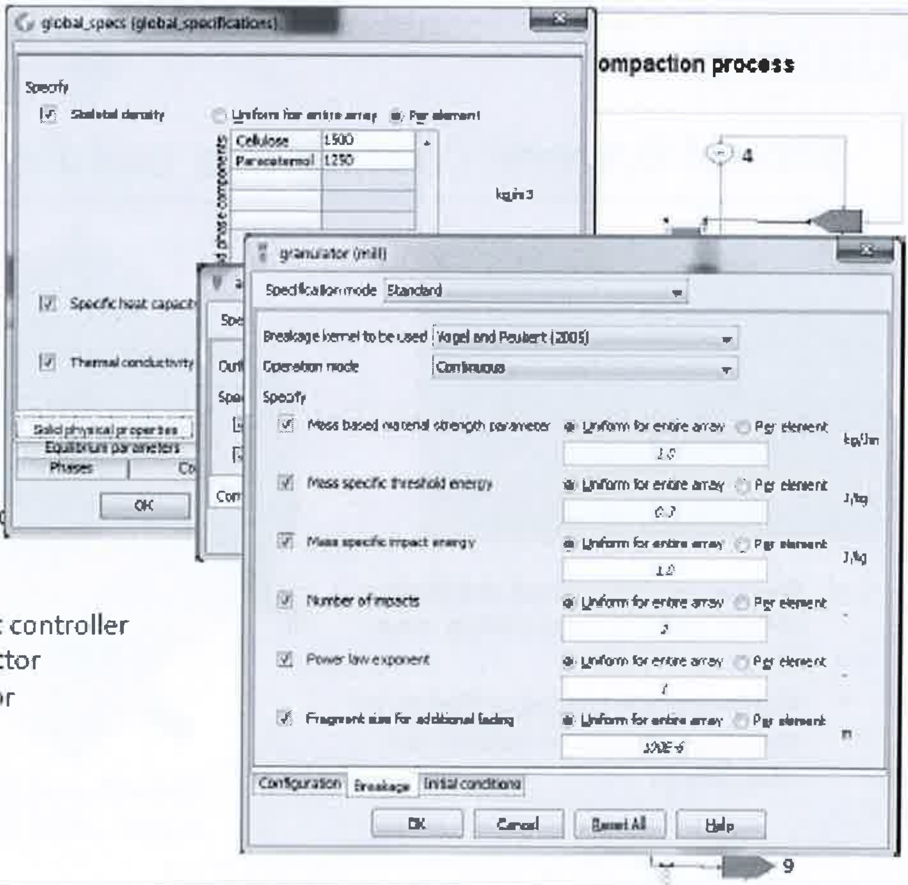
- Examples and case studies

Modeling a Roll Compaction Process in gSOLIDS





1: global specific
2: source
3: feeder
4: loss in weight controller
5: roller compactor
6: mill granulator
7: PSD sensor
8: screen
9: sink

gSolid and SolidSim from ASPEN

Simulation Results

Key results for the mill_sensor unit

Average particle sizes

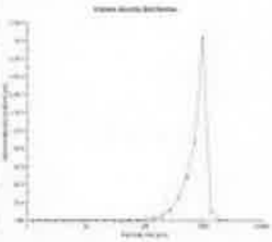
Property	Value at time 18000.0	Units
Number average mean D[1,0]("Solid")	346.339	µm
Sauter mean D[3,2]("Solid")	796.594	µm
Volume mean D[4,3]("Solid")	876.552	µm

Key Quantiles

Property	Value at time 18000.0	Units
D0.1("Solid")	546.758	µm
D0.5("Solid")	906.328	µm
D0.9("Solid")	1167.80	µm

All Quantiles

Property	Value at time 18000.0	Units
D0.05("Solid")	479.516	µm
D0.1("Solid")	546.758	µm
D0.16("Solid")	634.740	µm
D0.25("Solid")	738.934	µm
D0.5("Solid")	906.328	µm
D0.75("Solid")	1040.09	µm
D0.84("Solid")	1106.67	µm
D0.9("Solid")	1167.80	µm
D0.95("Solid")	1245.71	µm



Key results for the recycle_sensor unit

Average particle sizes

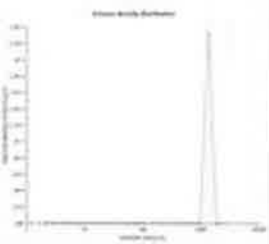
Property	Value at time 18000.0	Units
Number average mean D[1,0]("Solid")	1347.15	µm
Sauter mean D[3,2]("Solid")	1347.17	µm
Volume mean D[4,3]("Solid")	1347.18	µm

Key Quantiles

Property	Value at time 18000.0	Units
D0.1("Solid")	1128.57	µm
D0.5("Solid")	1347.15	µm
D0.9("Solid")	1608.12	µm

All Quantiles

Property	Value at time 18000.0	Units
D0.05("Solid")	1082.20	µm
D0.1("Solid")	1128.57	µm
D0.16("Solid")	1172.21	µm
D0.25("Solid")	1226.53	µm
D0.5("Solid")	1347.15	µm
D0.75("Solid")	1479.66	µm
D0.84("Solid")	1548.23	µm
D0.9("Solid")	1608.12	µm
D0.95("Solid")	1677.05	µm



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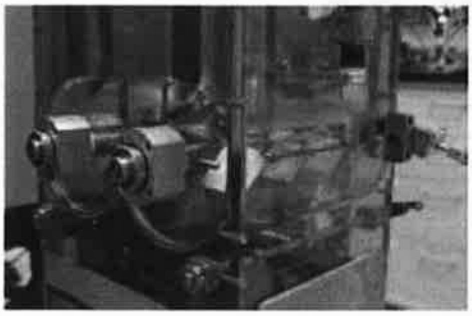
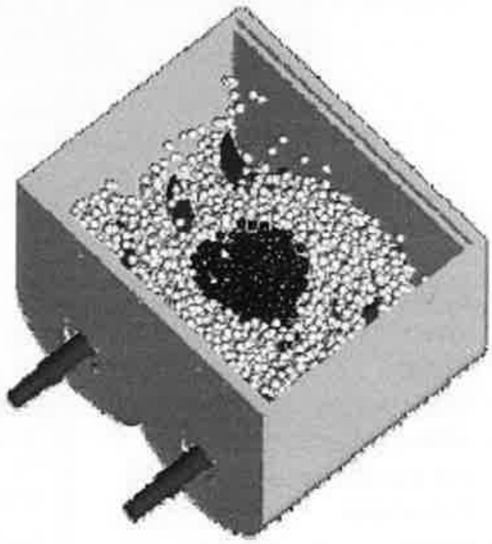
Model System: coating in a paddle mixer





- Develop models to track distribution of inter-particle spray coating over time
- Aim to improve coating uniformity by optimizing process conditions and mixer design

Freireich *et al.*, *Chem Eng Sci* (2011)
Li *et al.*, *AIChE J* (2011)

Ben Freireich, Jianfeng Li, Carl Wassgren, Jim Litster

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Population Balance Model

- Particle 2-D volume distribution $n(v_a, v_l, t)$
  - Seed volume v_a, coating volume v_l
  - Initial log normal seed distribution
- Volume based growth rate $G_{v,l} = \dfrac{dv_l}{dt} = k(v_a + v_l)^r$
- Model equations

spray compartment
$$\frac{\partial n_S}{\partial t} + \frac{\partial}{\partial v_l} \cdot (G_v n_S) = \frac{1}{(1-\lambda_S)T_S}\left(\sum_j (n_j f_{j,S}) - n_S\right) \qquad (*)$$

N bed compartments
$$\frac{\partial n_{Bi}}{\partial t} = \frac{1}{(1-\lambda_B)(1+R)T_B}\left(\sum_j (n_j f_{j,Bi}) - n_{Bi}\right), \text{for } i = 1 \text{ to } N$$

mass balance
$$\int_{v_a}\int_{v_l} G_{v,l} V_s n_s \, dv_l v_a = \eta_l \dot{Y}_l$$

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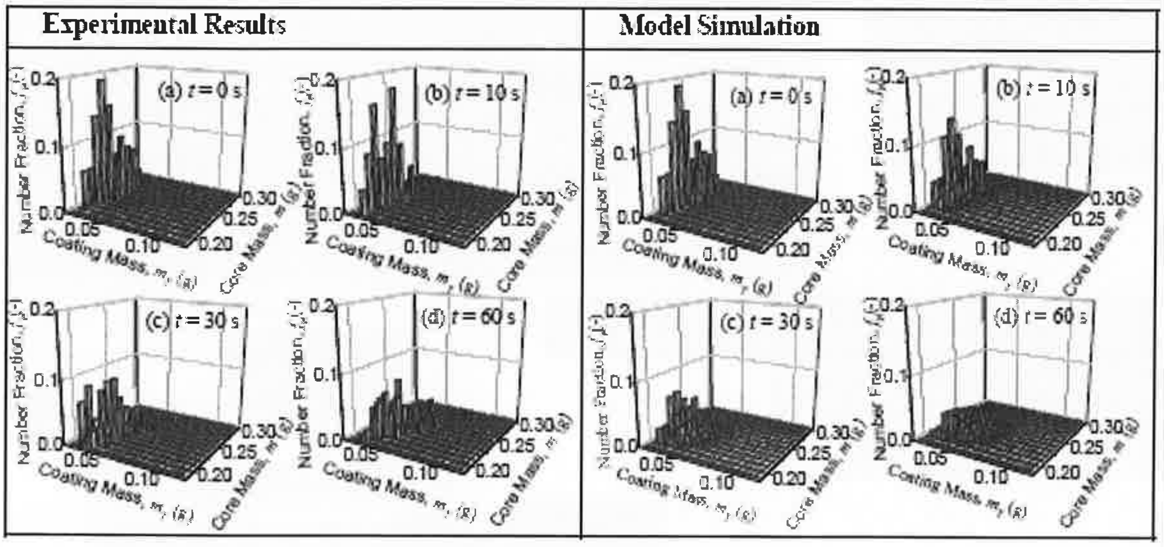
Do the predictions match experiment?



Li *et al.*, paper 15

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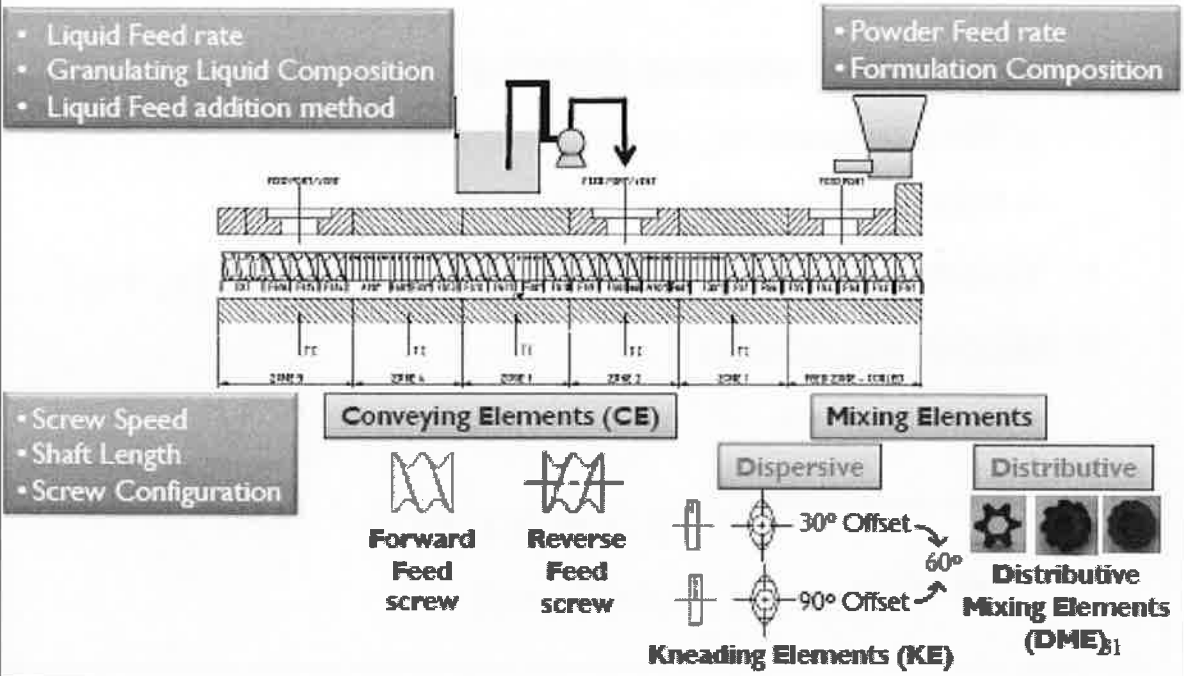
CP3

Twin Screw Case Study



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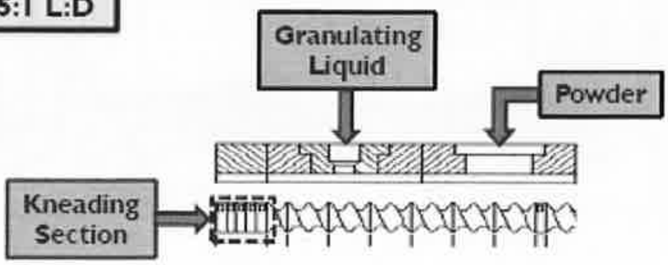
Experimental Setup

Formulation	
Lactose	73.5%
Avicel PH101	20%
Hypromellose	5%
Ac-Di-Sol	1.5%

Screw Type	Number	Advance Angle	Angle Direction
Conveying	--	--	--
Kneading Elements	3, 5 and 7	30°	Forward
		60°	Reverse
	3, 5 and 7	30°	Forward
		60°	Reverse
	3, 5 and 7	90°	--

Equipment: EuroLab 16 mm TSG 25:1 L:D

Fixed Process Parameters
- Powder feed rate: 4 kg/h
- Screw speed: 400 rpm



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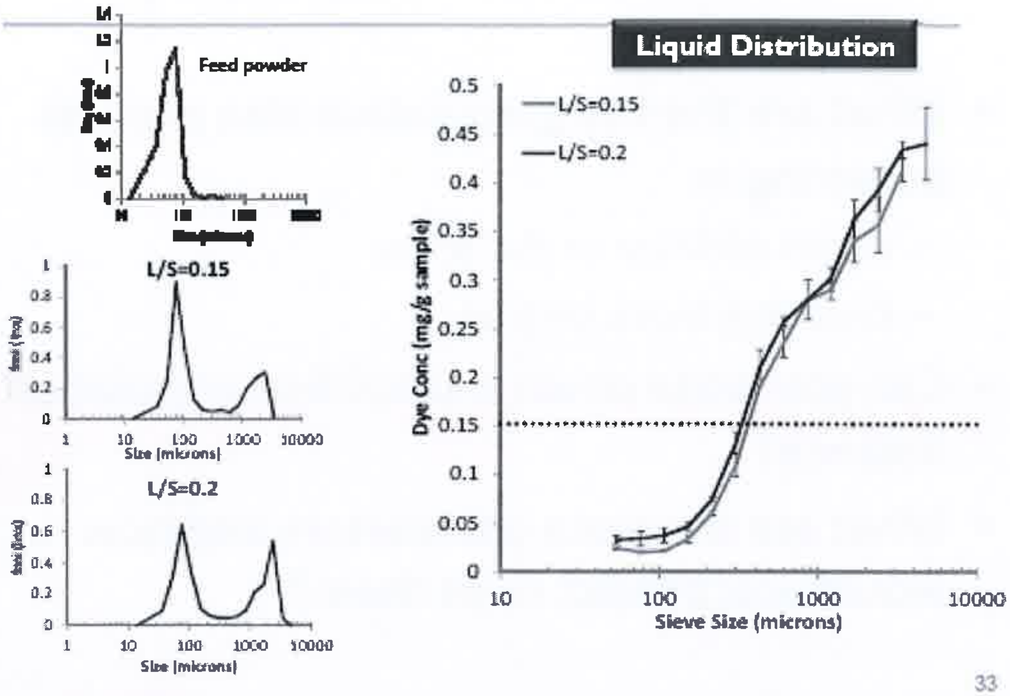
Granulation in Conveying Elements

Liquid Distribution



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X Jurgen

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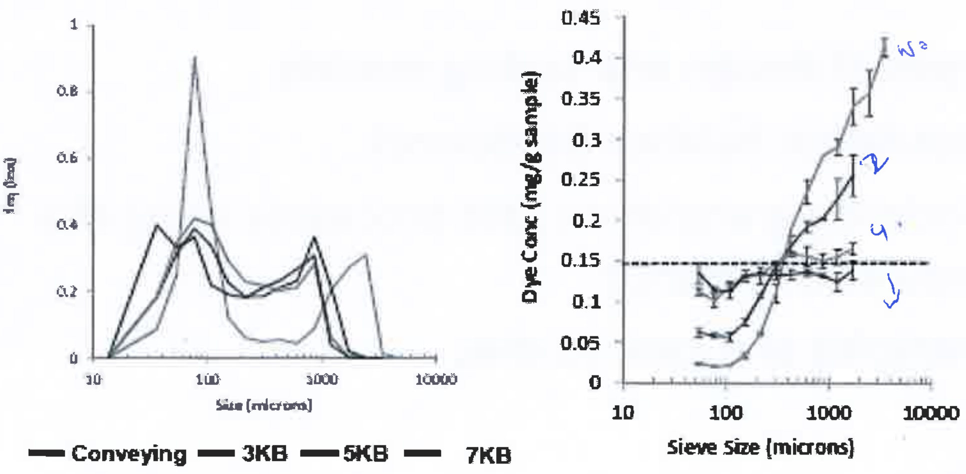
Impact of the kneading elements



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Twin screw case study

- What are the key granulation rate process occurring in
  - Liquid addition to the screw
  - Kneading block section
- Can you write down a simplified population balance?
- What are the main parameters and how would you predict or fit them?

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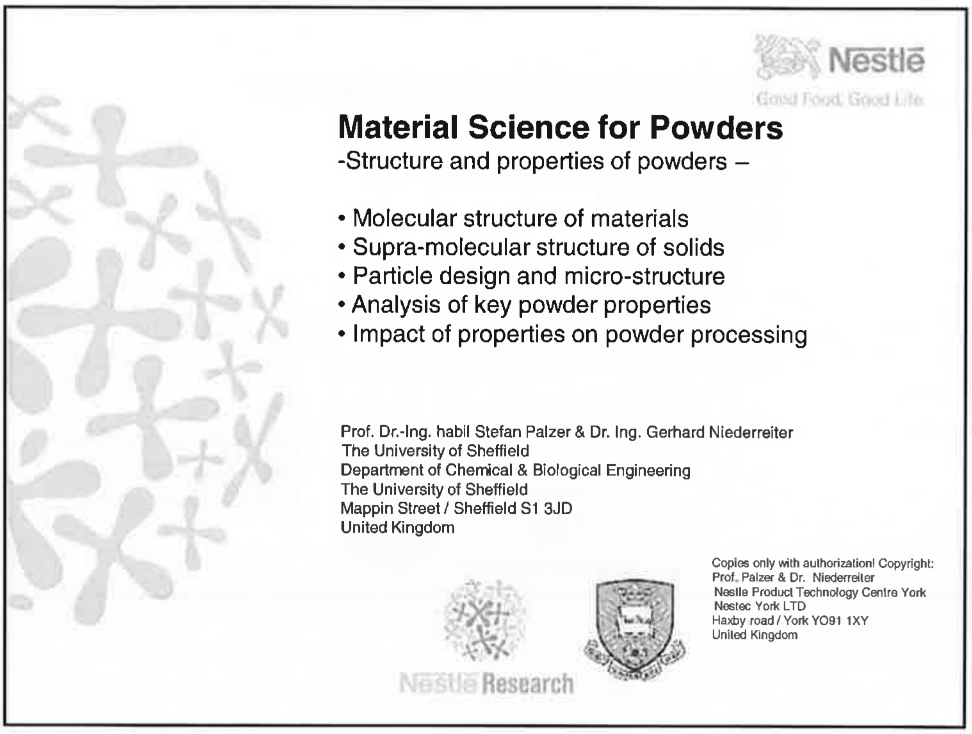
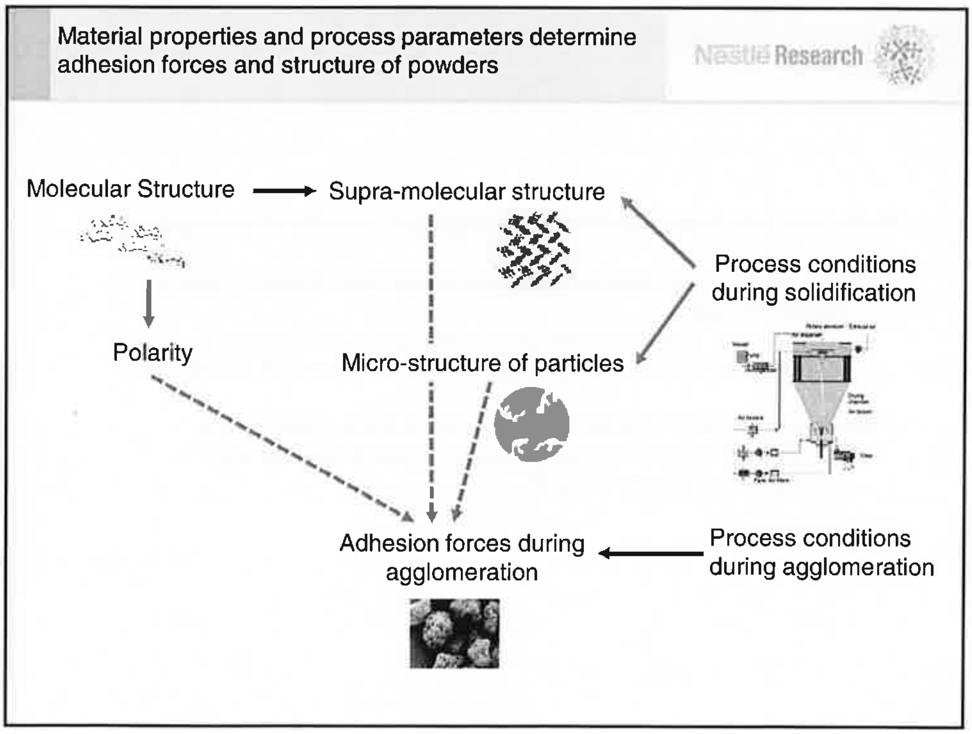
Outline

- Types of design and scaling models
- Population balance framework
- Modeling granulation rate processes using the population balance
- Examples and case studies

Lecture 7. Powder Characterisation

Prof. Stefan Palzer (Nestlé)





Molecular structures of solid materials

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Relevance of molecular structure for material properties

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Molecular structure determines polarity and mobility of molecules

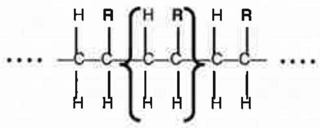
- Long and branched molecules are less mobile than shorter molecules
  → Higher viscosity
  → Formation of amorphous structures favored; lower degree of cristallinity (physical properties depending on degree of crystallinity)

- Solid matrices build of polar molecules interact with polar liquids
  - Migration of liquid into solid matrix → plastification of solid
  - Dissolution of solid in liquid

Molecular structure and Polarity of solids

Atoms:	Neutrally charged
Molecules:	Neutrally charged; composed of several atoms
Ions:	Positively or negatively charged; 1 or several atoms

- Monomers: Building block molecules for oligo- or polymers
- Oligomers: Build of a few monomer units
- Polymers: Build of a larger number of monomer units



Polarity:
Homogeneity of charge distribution along molecular structure
→ interaction with polar or aploar solvents (e.g. hydrophobic or hydrophilic)

Structure of polymers and their impact on supra-molecular structure

- Polymers can be linear, branched or they can be a network (crosslinked)

Branching influences molecular mobility and thus viscosity

- Polymers can have an amorphous (no order), semi-crystalline or crystalline (highly ordered) supra-molecular structure

random coil crystalline region

Branching and tacticity (distribution of side chains) influence molecular mobility and thus degree of crystallinity produced during e.g. drying processes

Atactic (randomly) polymers are mostly amorphous

Molecular modifications performed to change physical properties or biological effect of solids

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Examples for important molecular modifications:

- Isomerisation ≡ change in arrangement of atoms in molecules or ions → change in physical properties
- Polymerization ≡ covalent bonding of monomer units (by e.g. condensation) → creation of new materials
- Addition of functional groups (e.g. Methylation, Carboxylation) → modify solubility and interaction between molecules
- Depolymerization ≡ decomposition of polymers into monomers (acid hydrolysed, enzymatically hydrolysed) → generation of new substances, new mechanical properties
- Cross linking of macro-molecules (e.g. disulfide bridges) → generate different mechanical properties

Molecular modifications
Example: De-polymerization

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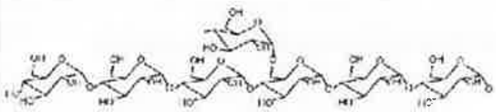
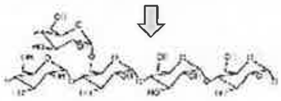


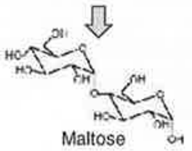
Starch: Amylose & Amylopectin

⇩



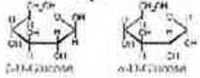
Maltodextrine (DE 6-20)
Dextrose syrup DE > 21

⇩



Maltose

⇩



Glucose

DE:= dextrose equivalent/reducing potential

No sweetness
Slower digestibility/lower GI
Limited solubility
Gel forming High viscosity
Physically stable

⇩

Sweetness depending on DE
Medium GI
Good solubility
Medium viscosity
Limited physical stability

⇩

Sweet taste
High GI
High solubility
Low viscosity
Physical unstable at high temperature/moisture content

Methods for analysing the molecular structure of solids

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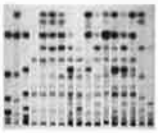
- Gas chromatography (GC) e.g. with Flame Ionisation Detector (FID)
- High pressure liquid chromatography (HPLC)
- Thin film liquid chromatography (TLC)
- Size exclusion chromatograhie
- Mass spectroscopy (MS)
- Time of flight detector (e.g. LC QToF MS)

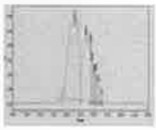
Principle: Interaction of molecules with static and mobile phase

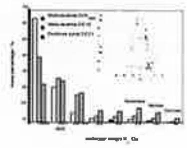
Principle: Molecular size/mobility

Principle: Mass of different molecular fragments

Principle: Flight time of fragments







Supra-molecular structure of solid materials

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