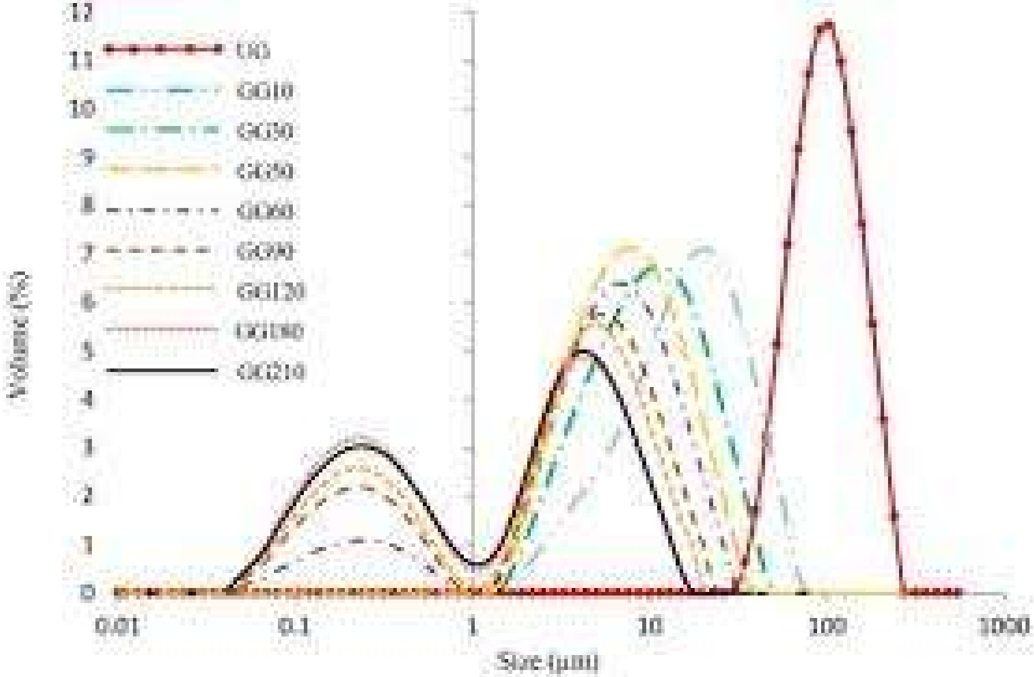
Mechanical milling and Jet Milling

Mostafa Nakach

mostafa.nakach@sanofi.com



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Objectives

- *Description of the methodology related to development and industrialization of mechanical and jet milling technologies*
- *Description of different steps of mechanical and jet milling studies and their specificities: HSE, analytical characterization*

Methodology of milling or jet milling study

Terminology

Objectives

- Particle size reduction
- Milling
  - Mechanical milling
  - Jet milling or micronization
  - Nanomilling or nanonization
- Grinding
- Comminution

Methodology of milling or jet milling study

Why reducing the particle size?

Requirements specifications

- **Why reducing the particles size ?**
  - *Enhancing of bioavailability by increasing the dissolution rate of API*
    - **Noyes-Whitney equation**

$$\frac{dc}{dt} = \frac{K * SSA}{h}(C_s - C)$$

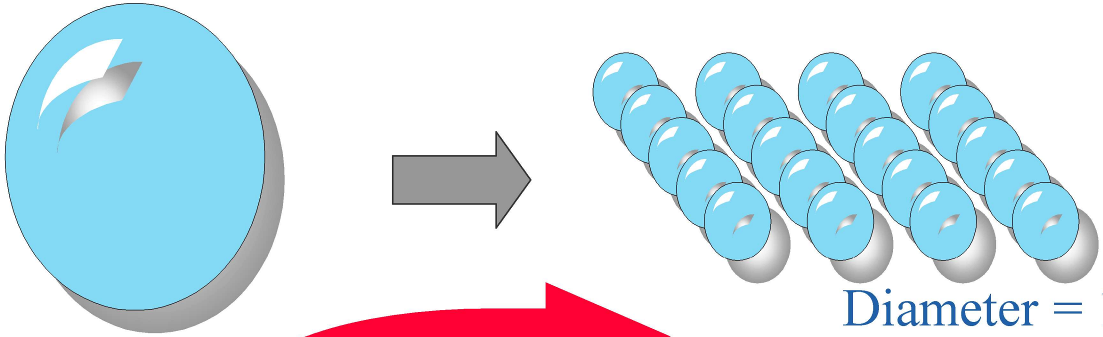
SSA: specific surface area ↑ when d_{50} ↓

h: diffusionnal distance ↓ when d_{50} ↓

C_s : Saturation solubility ↑ when $d_{50} < 100$ nm

C: bulk concentration

Relationship SSA-d_{50}



Diameter = 10 µm

1000 spheres

Surface = 314000 µm²

Factor = 10

Diameter = 100 µm

1 sphere

Surface = 31400 µm²

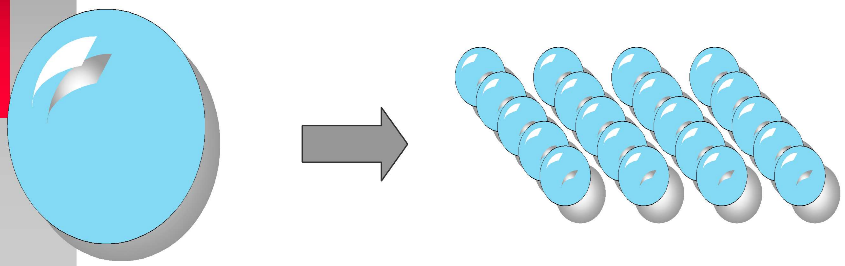
Diameter = 0.2 µm

125 10^6 spheres

Surface = 15,7 10^6 µm²

Factor = 500

Relation SSA-d50



$V = \pi d^3/6 \rightarrow m = \rho * \pi d^3/6$

$S = \pi d^2$

$SSA = S/m = 6/\rho * d \sim 6/d_{50}$

- $SSA_{(created)} = SSA_{(milled)} - SSA_{(unmilled)}$
- $SSA_{(created)} = 6/d_{50\,(milled)} - 6/d_{50\,(unmilled)}$

Requirements specifications :

Increasing the dissolution rate of API

Digoxin drug

Table 1. Particle size, disintegration time and dissolution rate of three varieties of digoxin tablets

Tablet	Particle size, mean diameter μ (90% confidence limits)	Disintegration time, min	Dissolution rate, percentage in solution at 15 min	30 min	60 min
A	13 (5 - 30)	5.5	58	59	71
B	102 (80 - 150)	4.5	12	18	18
C	7 (3 - 10)	5.5	49	55	62

Effect of particle size on bioavailability
Jounela et.al

Requirements specifications :

Increasing the dissolution rate of API

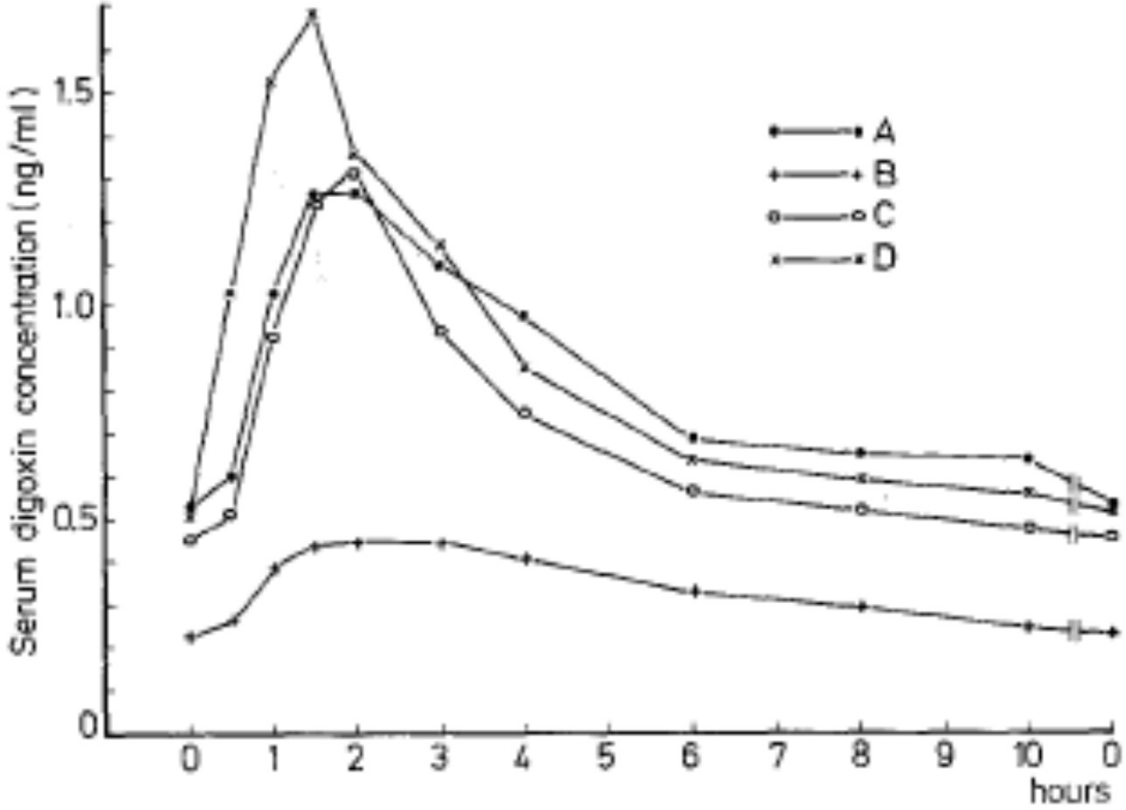


Fig. 1. Steady state serum digoxin concentration after administration of 0.25 mg of four varieties of digoxin products; mean values from 7 subjects.

Digoxin drug 0.25 mg tablet administred with 100 ml of water

Effect of particle size on bioavailability
Jounela et.al

Requirements specifications :

Increasing the dissolution rate of API

Digoxin drug

Preparation[a]	AUC[c] (ng.hr.ml^{-1}), mean ± SE)	% of D
A	16.52 ± 1.51	96
B	6.49 ± 0.41	37
C	13.50 ± 1.58	78
D (alcoholic solution)	17.30 ± 1.41	100

Effect of particle size on bioavailability
Jounela et.al

Requirements specifications :

Increasing the dissolution rate of API

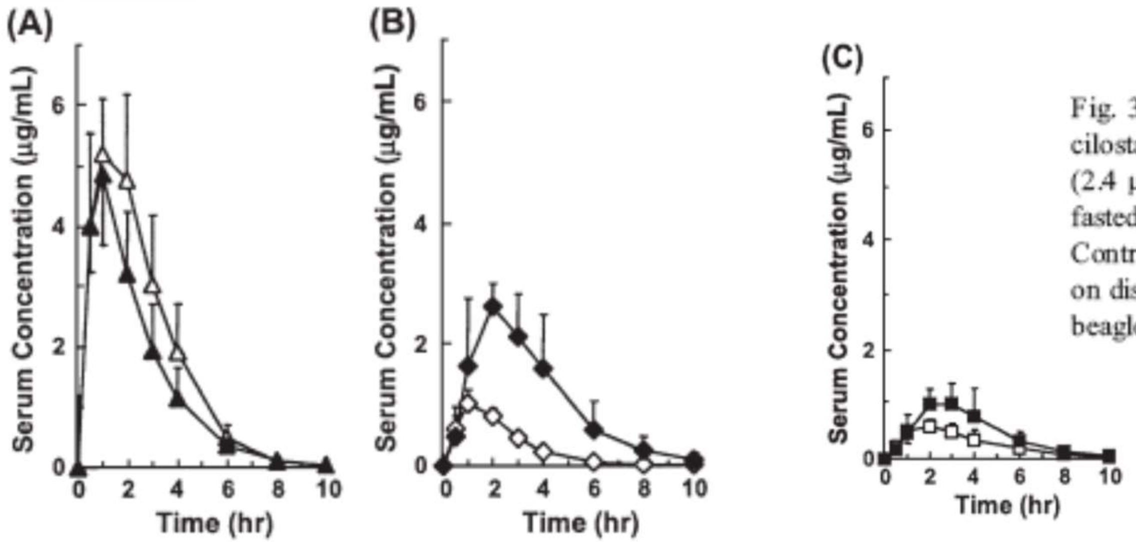


Fig. 3. Effect of food on bioavailability of nanosized and micronized API for cilostazol. (A) Nanocrystal suspension (220 nm); (B) jet-milled suspension (2.4 µm); (C) hammer-milled suspension (13.4 µm). Open symbols represent fasted state, filled symbols represent fed state (reprinted from Journal of Controlled Release, 111 (1–2), Jinno, J., et al., Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs, 56–64, Copyright (2006), with permission from Elsevier).

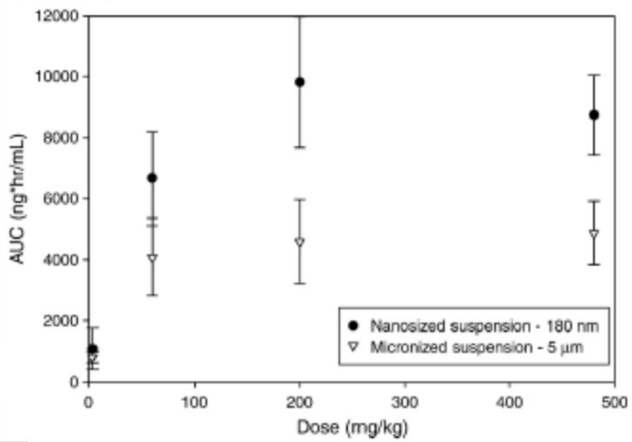
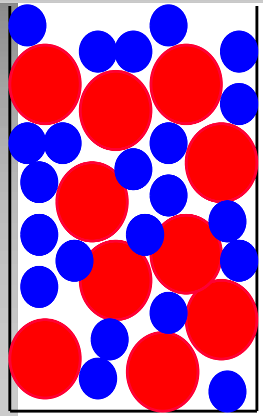


Fig. 1. Comparison of nanosized (180 nm) and micronized (5 µm) API for a development candidate in a dose proportionality study. Compound exhibits poor solubility (<0.1 µg/mL) across the physiological pH range. Increased dissolution rate for the nanoformulation results in a significantly higher bioavailability for the nanosized API over a wide concentration range (Merck data on file).

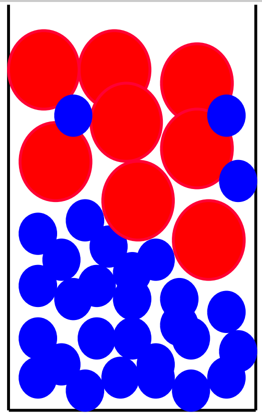
F. Kesisoglou et al. / Advanced Drug Delivery Reviews 59 (2007) 631–644

Requirements specifications :

Enhancing blend homogeneity

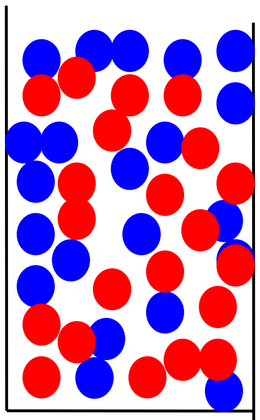


Settling after mixing

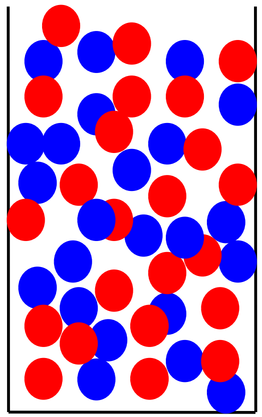


Differences in size, density and shape of constituent particles of a mixture may give rise to segregation

Even if particles are originally mixed by some means, they will tend to unmix on handling (moving, pouring, conveying, processing) or during storage



No Settling after mixing



Requirements specifications :

Inhalation therapy

- **Get access to inhalation therapy**
- *Systemic toxicity reduction*
- *rapid availability of API at the target*
- *High concentration within the lung*

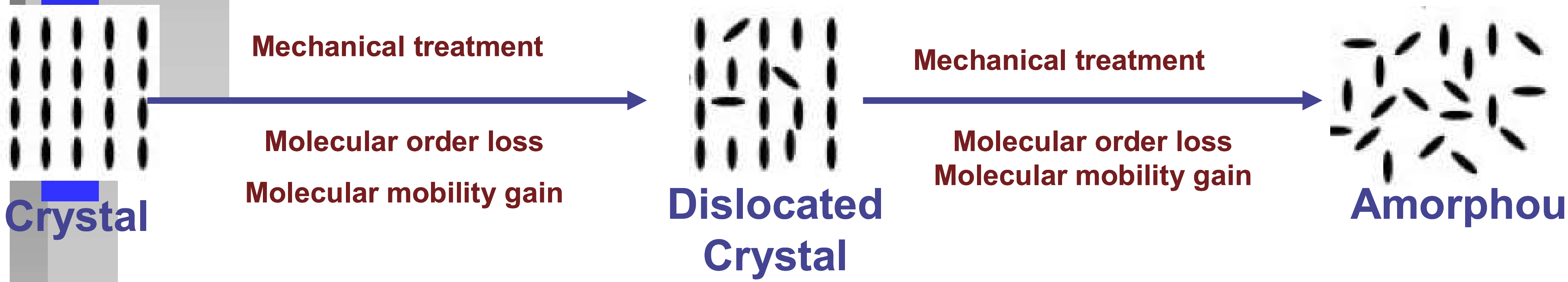
- *MMAD: Median massic aerodynamic diameter*
  - ***MMAD <1µm: exalted***
  - ***MMAD 1~5µm: target***
  - ***MMAD >5µm: Deposit within the throat (Vehicle case)***

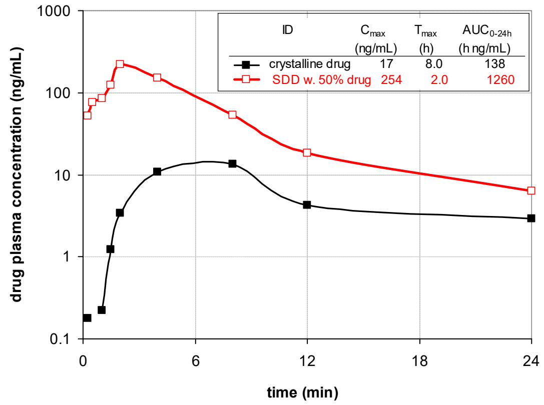
➢ *Strict control of MMAD will ensure reproducibility of aerosol deposit and retention.*

Requirements specifications :

amorphization

- ***increasing the dissolution rate of API by crystal structure modification: Amorphous solution or dispersion***
  - *Progressive perturbation of crystal structure and increasing of his free energy up to amorphization.*



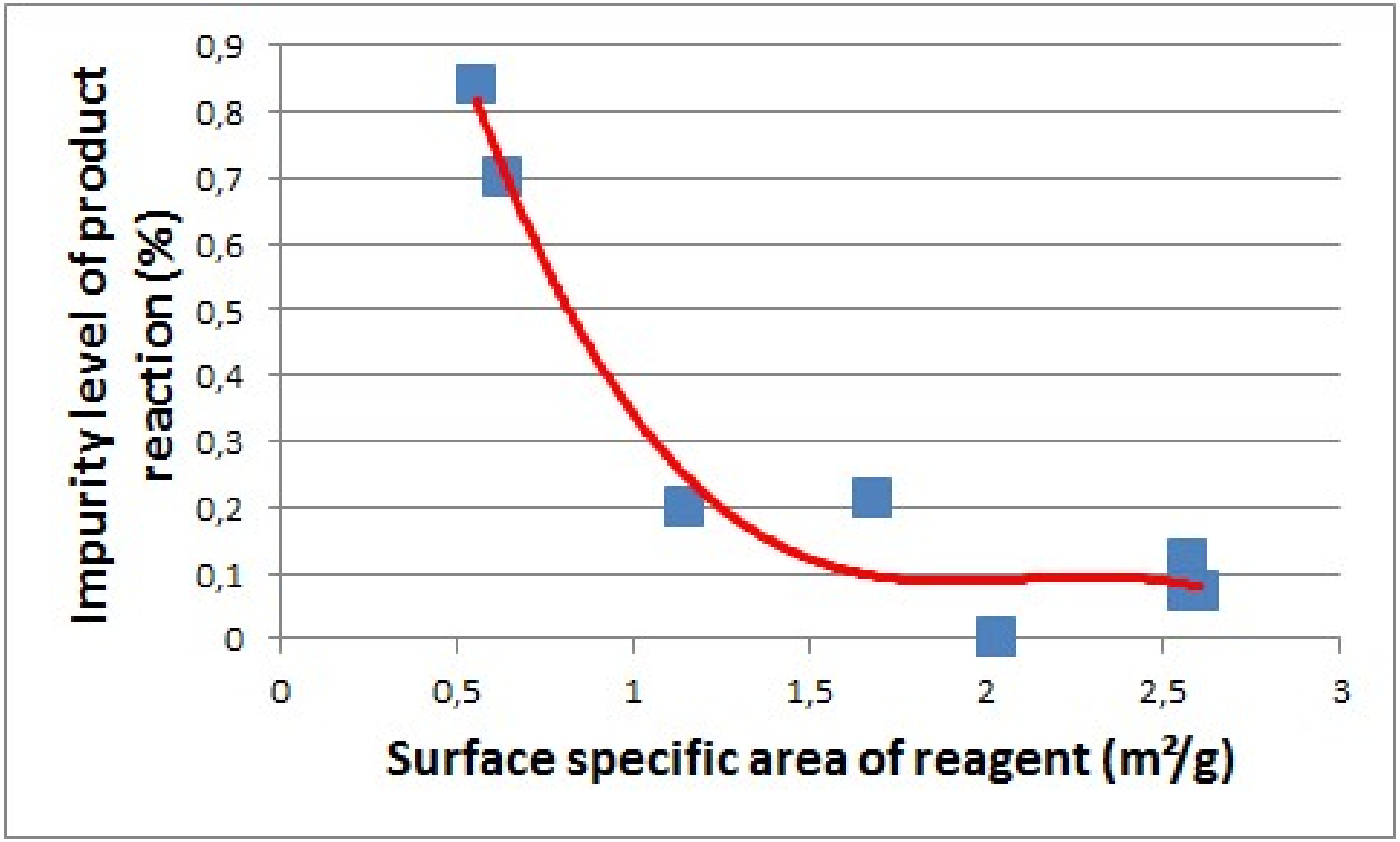


- ***Significant increasing of the bio-exposition***
- ***Enhancing of the therapeutic value***

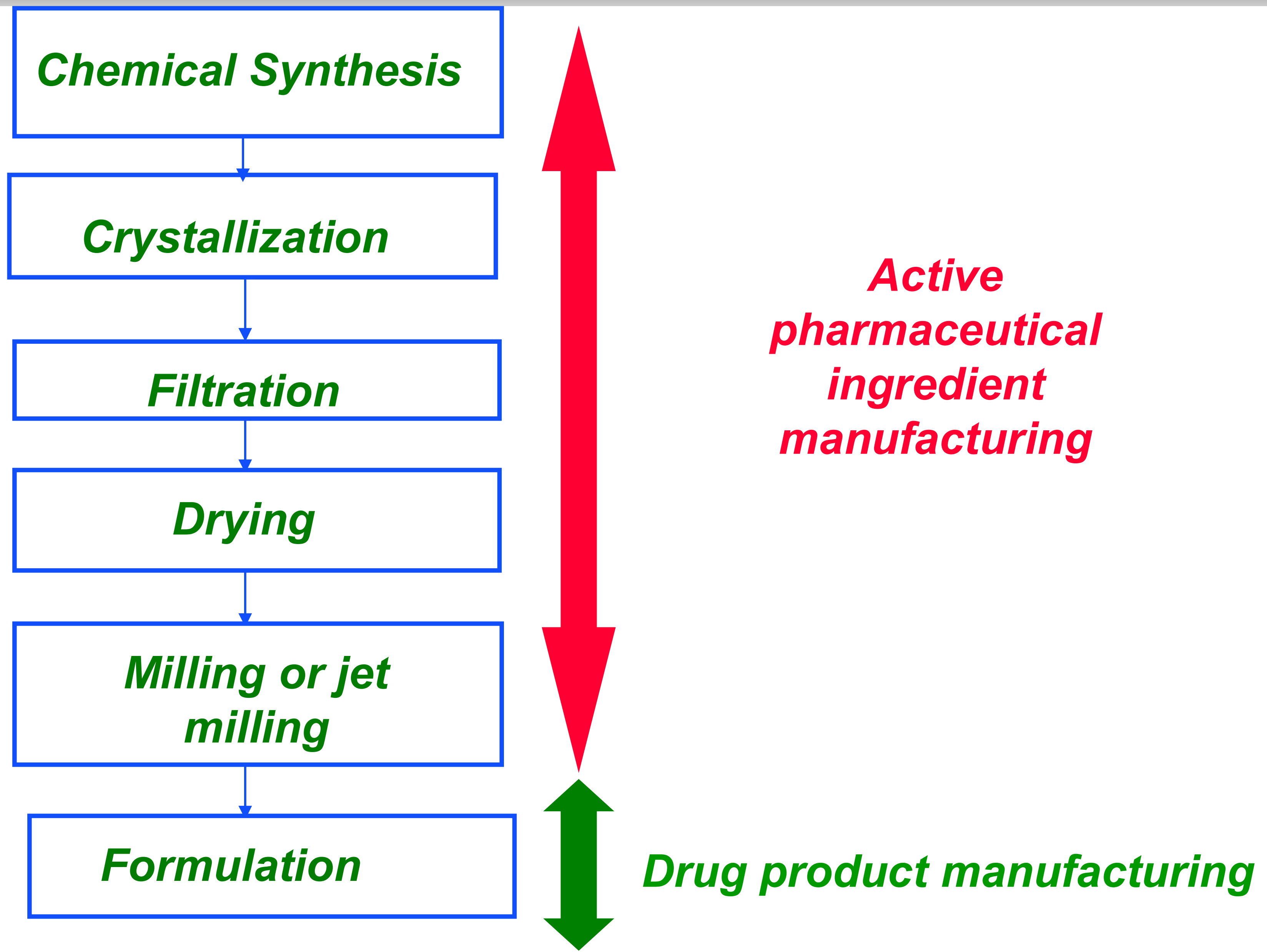
Requirements specifications :

Chemical reaction

- *It may be used to create particles of a certain size and shape, to increase surface area available for chemical reaction*



Process flow chart



Methodology of milling or jet milling study

Energy requirement

Particles size reduction:

Energy Requirement and Product Size Distribution

- There are three well-known postulates predicting energy requirements for particle size reductions
  - Rittinger (1867) proposed that the energy required for particle size reduction is directly proportional to the area of new surface created
    - If initial and final particle sizes are x_1 and x_2 respectively, then,

$$E = C_R \times \left(\frac{1}{X_2} - \frac{1}{X_1}\right)$$

    - If this is the integral form, then in differential form, Rittinger's postulate becomes

$$\frac{dE}{dX} = -C_R \times \left(\frac{1}{X^2}\right)$$

Particles size reduction:

Energy Requirement and Product Size Distribution

- *On the basis of stress analysis theory for plastic deformation, Kick (1885) proposed that the energy required in any comminution process was directly proportional to the ratio of the volume of the feed particle to the product particle*

$$E = C_K \times ln(\frac{X_1}{X_2})$$

  - ***If this is the integral form, then in differential form can be expressed as***

$$\frac{dE}{dX} = C_K \times (\frac{1}{X})$$

Particles size reduction:

Energy Requirement and Product Size Distribution

- Bond (1952) suggested a more useful formula:

$$E = C_B \times \left(\frac{1}{\sqrt{X_2}} - \frac{1}{\sqrt{X_1}}\right)$$

  - However, Bond's law is usually presented in the form shown below:

$$E_B = W_l \times \left(\frac{10}{\sqrt{X_2}} - \frac{10}{\sqrt{X_1}}\right)$$

  - Where E_B is the energy required to reduce the top particle size of the material from x_1 to x_2 and W_I is the Bond work index
  - In differential form Bond's formula becomes:

$$\frac{dE}{dX} = C_B \times \left(\frac{1}{X^{\frac{3}{2}}}\right)$$

Particles size reduction:

Energy Requirement and Product Size Distribution

- *In differential form Bond's formula becomes:*

$$\frac{dE}{dX} = -C \times \left(\frac{1}{X^n}\right)$$

N= 2, C= C_R for Rittinger

N= 1, C= C_K for Kick

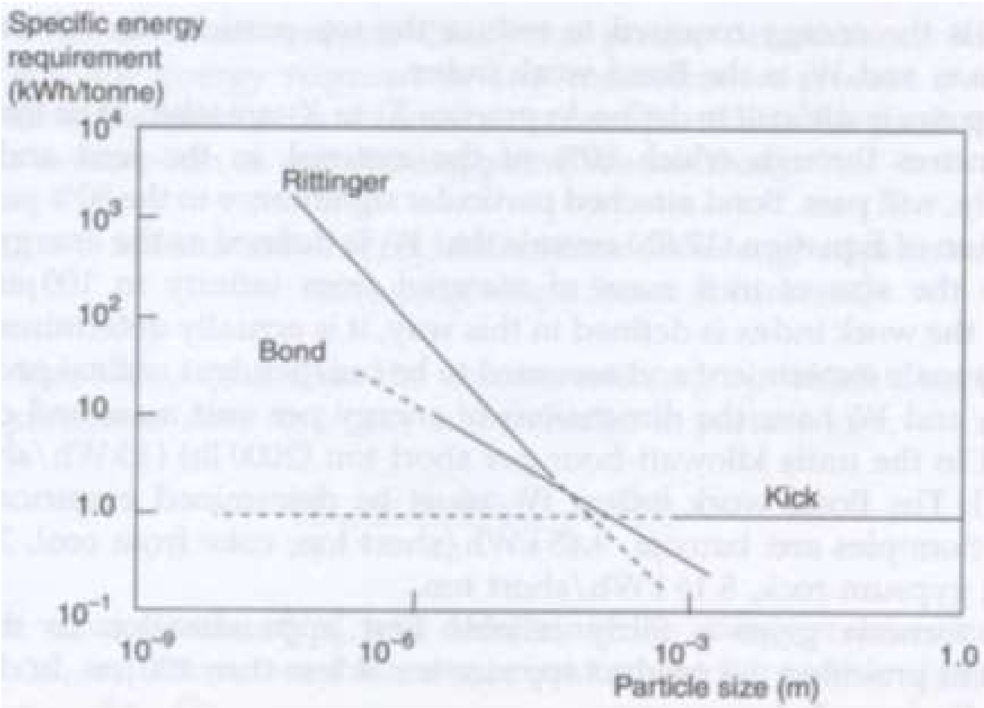
N= 1.5, C= C_B for Bond

Particles size reduction:

Energy Requirement and Product Size Distribution

- The three approaches to prediction of energy requirements are each more applicable in certain areas of product size

Rittinger's formula for very small particle size (ultra-fine grinding)



Kick's proposal is applicable for large particle size

Bond's formula is suitable for intermediate particle size,

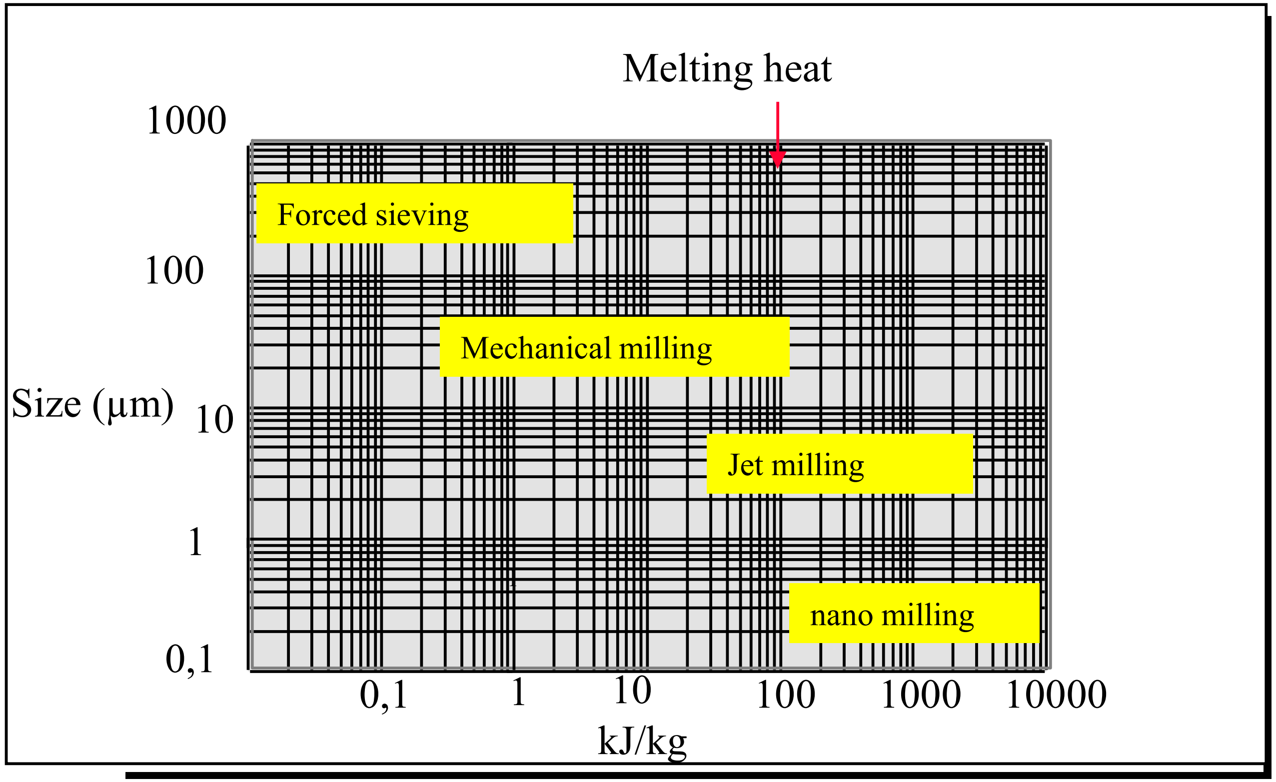
Methodology of milling or jet milling study

Technology selection according the desired particle size

Particles size reduction:

Energy Requirement depending on technology to be used

- The desired particles size will orient the technology selection



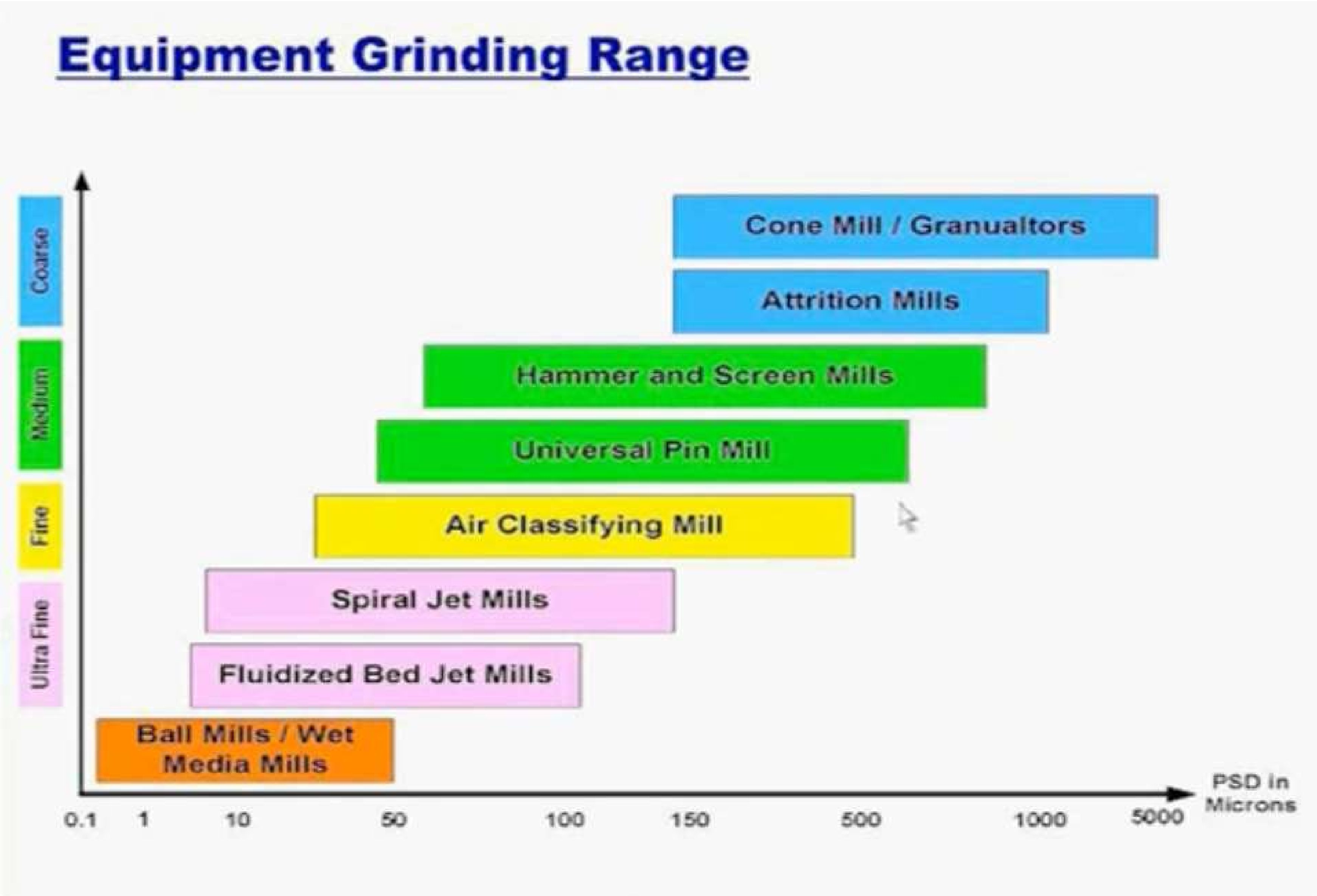
Particles size reduction:

Technology selection according the desired particle size

- **Forced sieving**
  - Delumping
    - **Bar mill (« Frewitt »)**
    - **Cone mill (« Quadrocomill », («CMA »)**
      - Used as preliminary step before ultra-fine milling.
      - Make uniform the PSD of drug product bulk before granulation
- **Coarse to fine milling : target from 10 to 80 µm**
  - Technologies: Mechanical mill, loop jet mill
  - Make uniform the PSD, enhancing the processability of drug product, enhancing of the dissolution profile…
- **Ultra-fine milling : target < 10 µm**
  - Technologies: Pancake jet mill, fluid bed jet mill
  - Used when the dissolution is critical, API for inhalation,
- **Nanomilling: Target < 1 µm**
  - Bead milling
  - High pressure homogenization

Particles size reduction:

Technology selection according the desired particle size



Methodology of milling or jet milling study

Coarse milling/ forced sieving

Particle size reduction by forced sieving

Drying → Forced sieving → Jet milling

- Delumping to avoid jet milling blockage

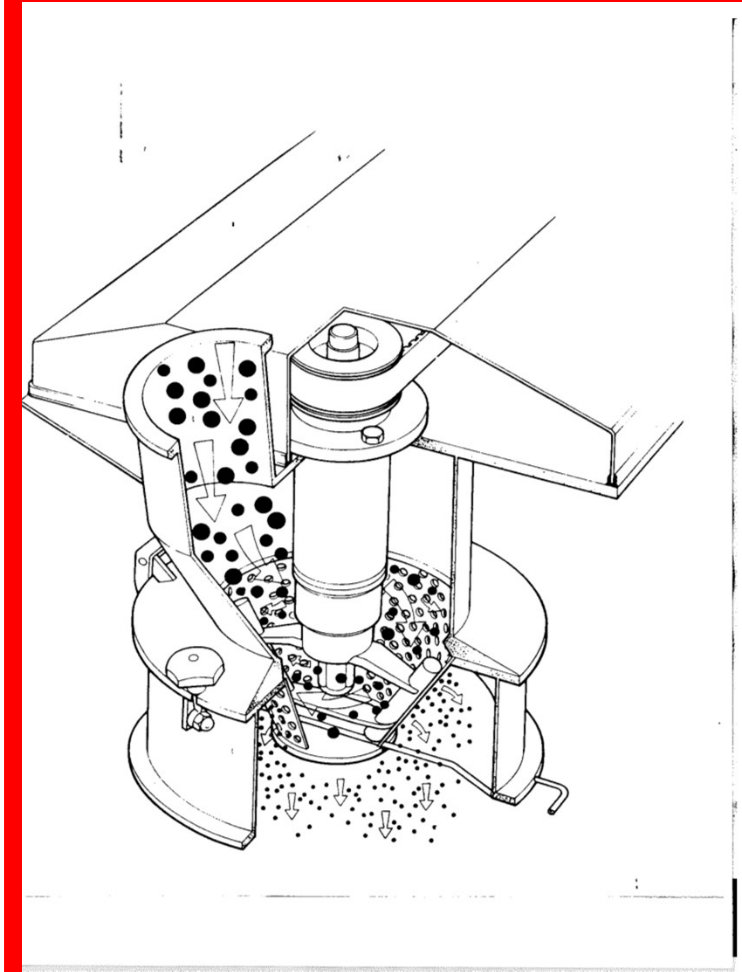
mixing → Granulation → Forced sieving → Tabletting

- Delumping to make uniform particle size distribution

Particle size reduction by forced sieving

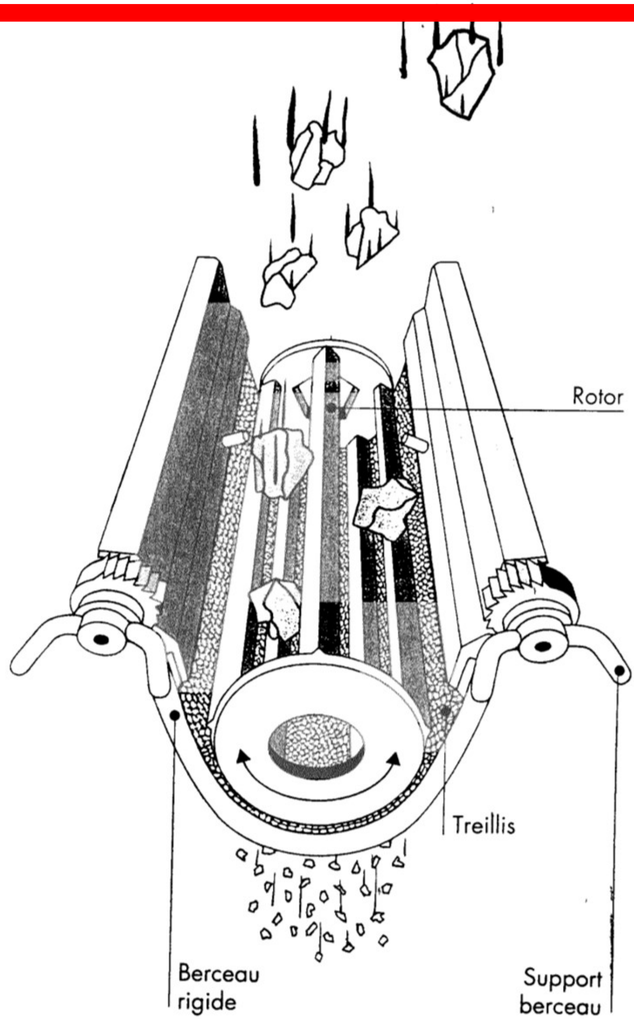
- **Cone mill**
  - *High speed rotor (1000 à 2000 rpm: up to 25 m/s)*
  - *Grid made from punched sheet*
  - *Technology to be processed at overfeeding regime*
  - *Critical process parameter*
    - ***Grid size***
    - ***Rotation speed***

https://youtu.be/B1gAq4a3sDI



Particle size reduction by forced sieving:

- **Bar mill**
  - Oscillating rotor at very low speed (0,5 à 2 m/s)
  - Grid made from wire mesh
  - Technology to be processed at overfeeding regime
  - Critical process parameters
    - **Grid size**
    - **Rotation speed**



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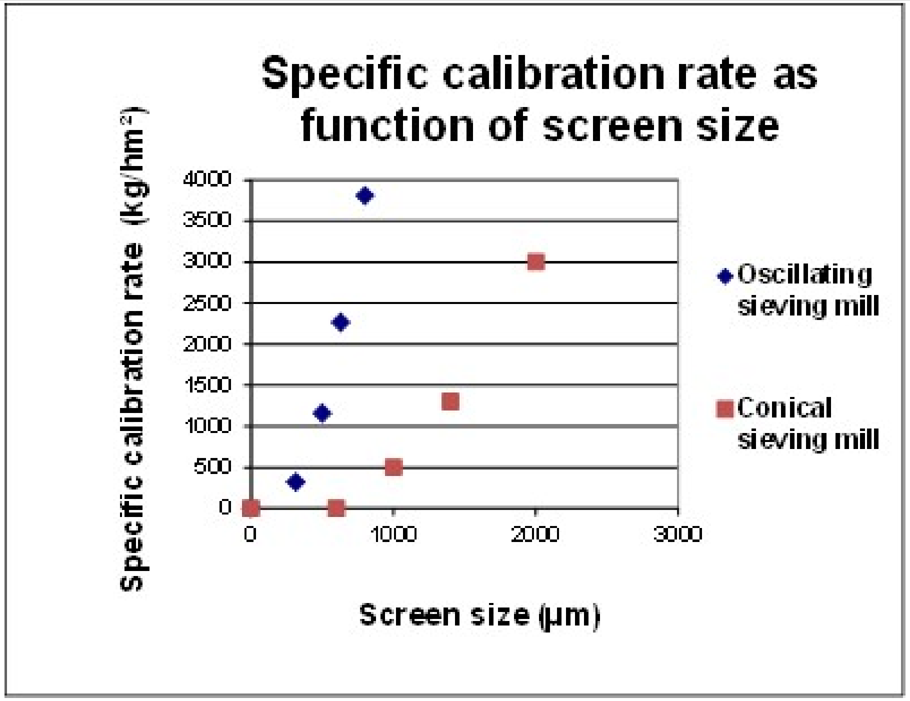
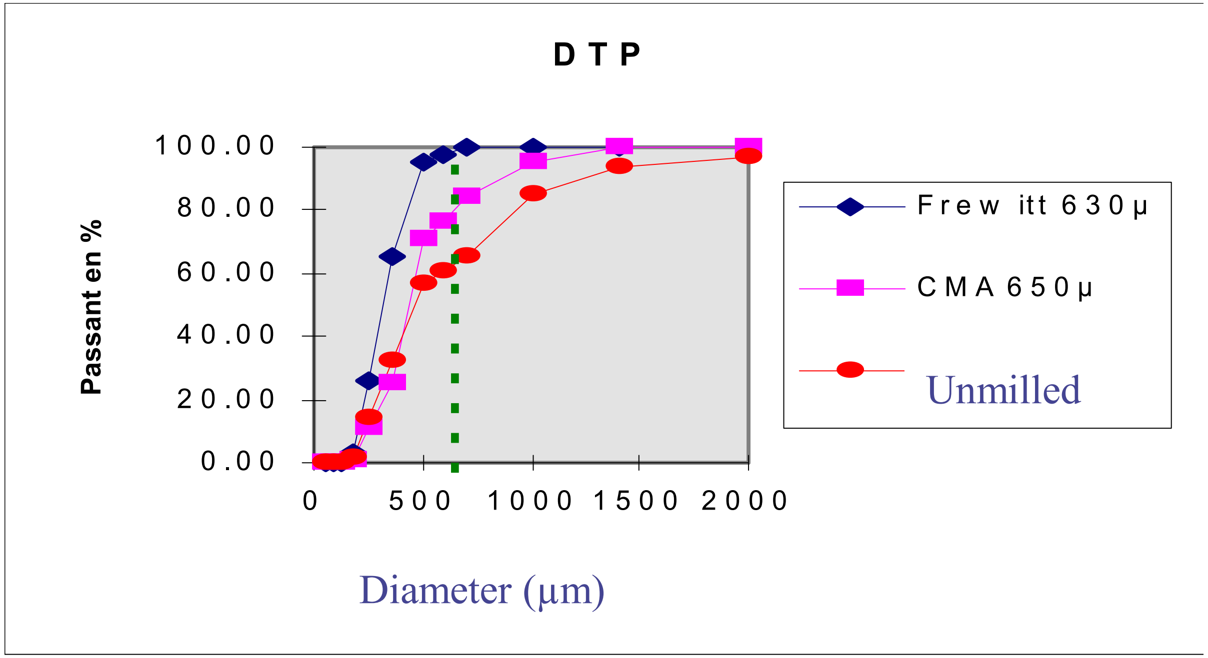
Particle size reduction by forced sieving: *Case study : API A*



The oscillating sieving mill leads to higher specific calibration rate when it compared to conical sieving mill. Indeed, a specific calibration rate of 3800 kg/h.m² was observed when using the oscillating sieving mill with screen size of 800 µm while, only 2000 kg/h.m² was obtained when using conical sieving mill with larger screen size (2000 µm

Particle size reduction by forced sieving: *Case study : API B*

- ***Particles size distribution***



- *The bar mill leads to a milled product with particles lower than 630 µm*
- *Even if the cone mill use grid size of 650 µm, it leads to a milled product with particles larger than 650 µm*

Particle size reduction by forced sieving: Case study : API B

❖ *Carr index, apparent density*

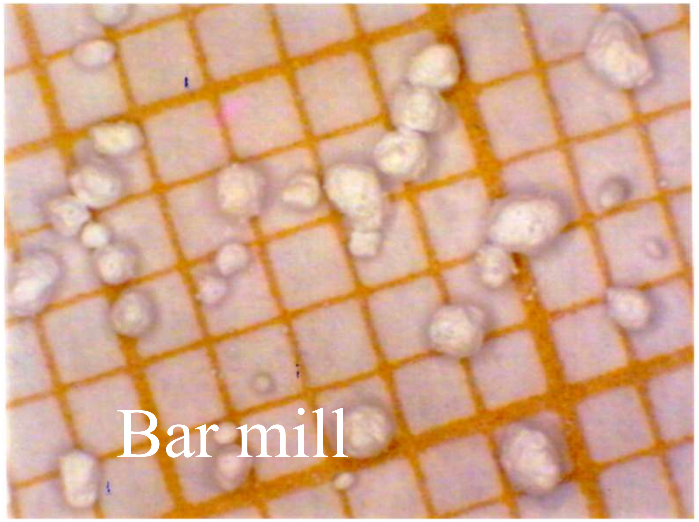
	Unmilled	Cone mill	Δ%	Bar mill	Δ%
Bulk density (g/ml)	0,276	0,207	- 25 %	0,237	- 14 %
Car index (%)	21,9	28,4	+ 29 %	19,2	- 12,3 %
% of particles > 630 µm	38 %	23,5 %	-	< 2 %	-

- *The cone mill has a negative impact on the flowability*

Apparent density = mass/ initial volume
Tapped density = mass / final volume after 500 tap
Carr index = (Tapped density – apparent density)*100/ tapped density

Particle size reduction by forced sieving: *Case study : API B*

❖ **Morphology**



- *Cone : Accumulation of electrostatic charges due to high shear rate (up to 25.103 s^{-1})*

Rotor has a diameter of: D (m)

Clearance between rotor and stator: e (m)

Rotation speed = RS (rpm)

1 rotation = pi*D

Particle size reduction by forced sieving:

❖ **Conclusion :**

- *The bar mill leads to high specific calibration rate*
- *The bar mill prevents the electrostatic agglomeration.*
- *The bar mill could enhance the flow properties.*
- *The bar mill helps the processability of drug product*

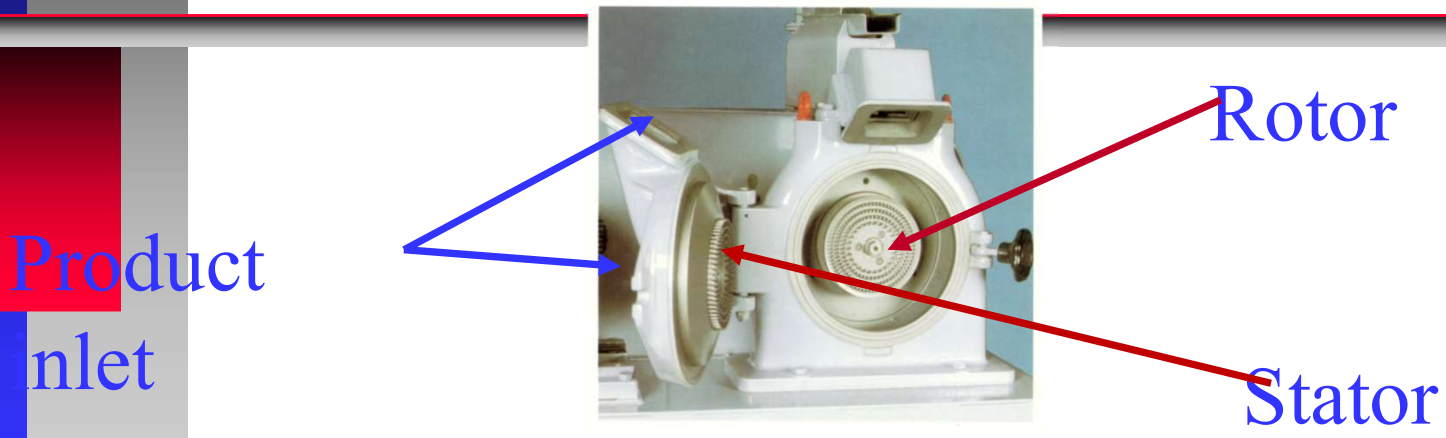
Methodology of milling or jet milling study

Mechanical milling

Particle size reduction by mechanical milling: Theory

- *The milling take place by mechanical action (impacts of particles with milling media (rotor and stator) or with others particles.*
- *3 technologies:*
  - *Pin mill*
  - *Hammer mill*
  - *Paddle mill*

Particle size reduction by mechanical milling: Pin mill



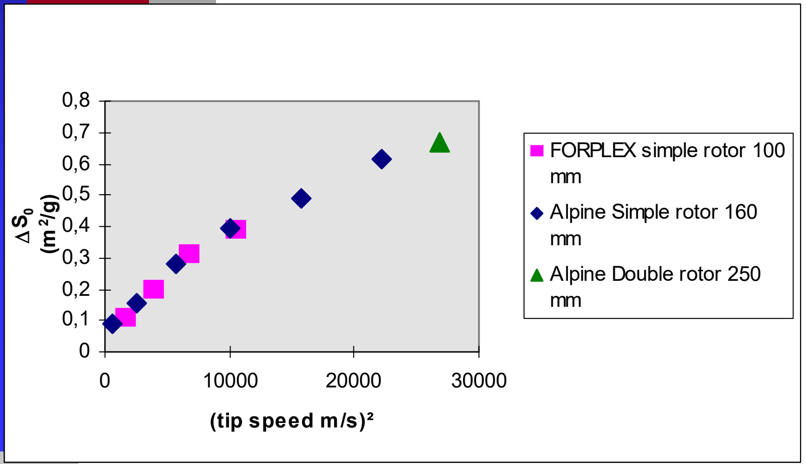
❖ ***Principle***

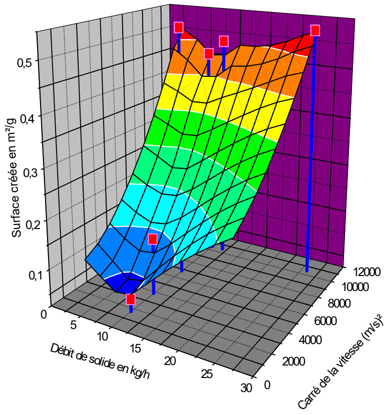
- *Relative movement of rotor part regard to a stator part. The rotor and stator are composed of 4 or 5 of pin (1- 2 cm length and few mm diameter) rows.*
- *The solid feeding takes place at the center. The milled product is evacuated at the outlet of the mill due to the centrifugation force.*

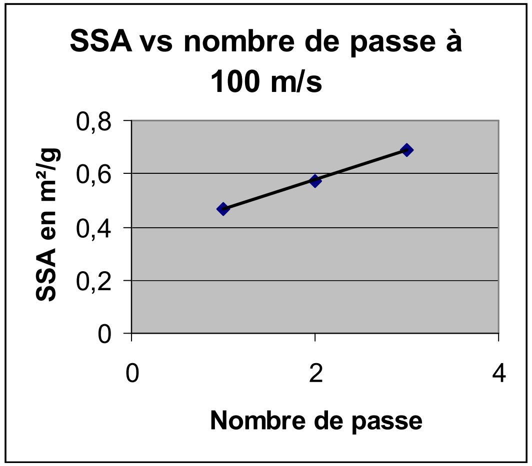
Particle size reduction by mechanical milling: Pin mill

- Key parameters :
  - Rotation speed
    - Standard tip speed from 50 up 100 m/s
    - High tip speed up 150 m/s
  - Number of passages
  - Solid flow rate

Particle size reduction by mechanical milling: Pin mill- Parametric study

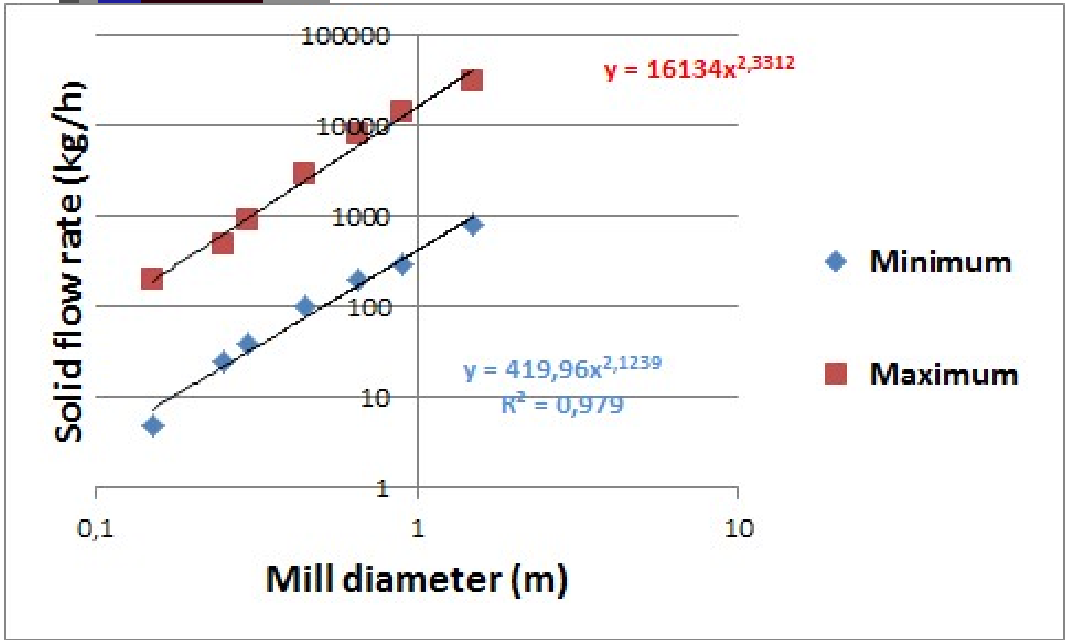


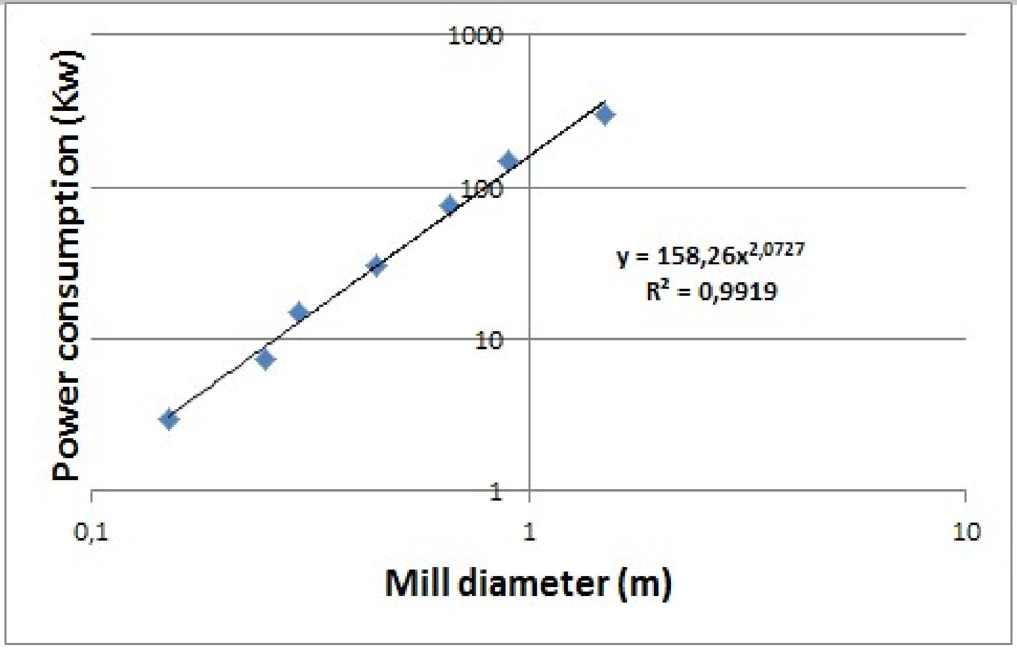




- ***Whatever the used scale, whatever the used technology the tip speed is the decisive factor.***
  - *The created SSA is proportional to the square of the tip speed.*
  - *No significant impact of the solid flow rate on the created SSA.*

Particle size reduction by mechanical milling: Pin mill- Scale-up





- **Scale-up rules**
  - $\Delta SSA \sim N^2$
  - Solid flow rate $\sim D^2$
  - Power consumption $\sim D^2$

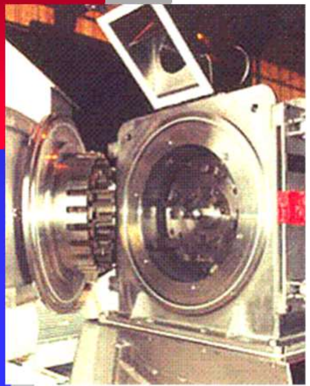
Particle size reduction by mechanical milling: *Pin mill- Scale-up*

- ***Milling trials performed using 100 mm pin mill***

Rtotation speed (rpm)	Solid flow rate (kg/h	d50 (µm)
0	4	116
4000	4	59,6
9000	4	35,1
13000	4	20,51
18000	4	12,11

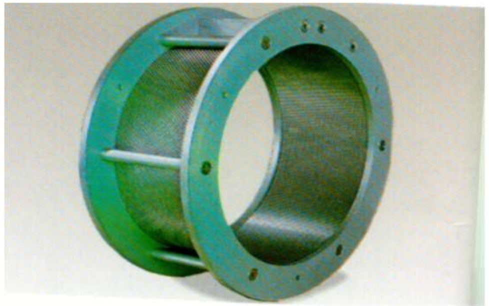
- *Graph ΔSSA ~ N²*
- *Extrapolate rotation speed to get 0.3 µm^{-1} as ΔSSA using 250 mm mill diameter*
- *Extrapolate the solid flow rate using 250 mm mill diameter*

Particle size reduction by mechanical milling: Paddle or hummer mill



Hummer

Paddles



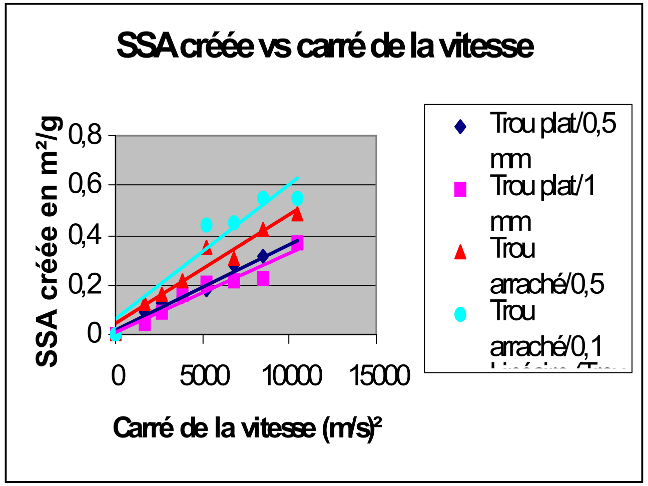
Grid (used for both technologies)

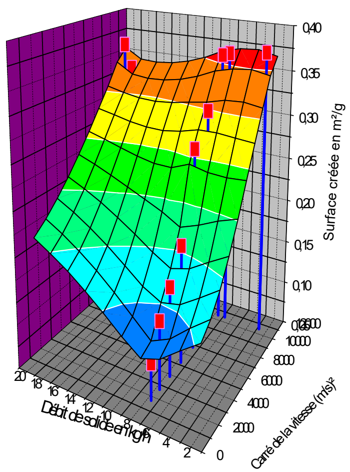
- ***Principle***
- *The solid feeding take place at the center. The milled product is evacuated through the grid at the outlet of the mill due to the centrifugation force*
- ***Less used in pharmaceutical industry due to the risk of grid clogging***

https://youtu.be/NSUbcndrCnI

Particle size reduction by mechanical milling: *Paddle or mill: Parametric study*

- ***Key parameters :***
  - ***Tip speed: The created SSA is proportional to the square of the tip speed***
  - ***Solid flow rate: No significant impact of the solid flow rate on the created SSA***
  - ***Gas flow rate: No significant impact of the gas flow rate on the created SSA but it has to be sufficient in order to ensure the solid cooling and it's transportation***
  - ***Grid type (holes shape, holes diameter, number of holes): impact significantly the physical quality of the milled product.***

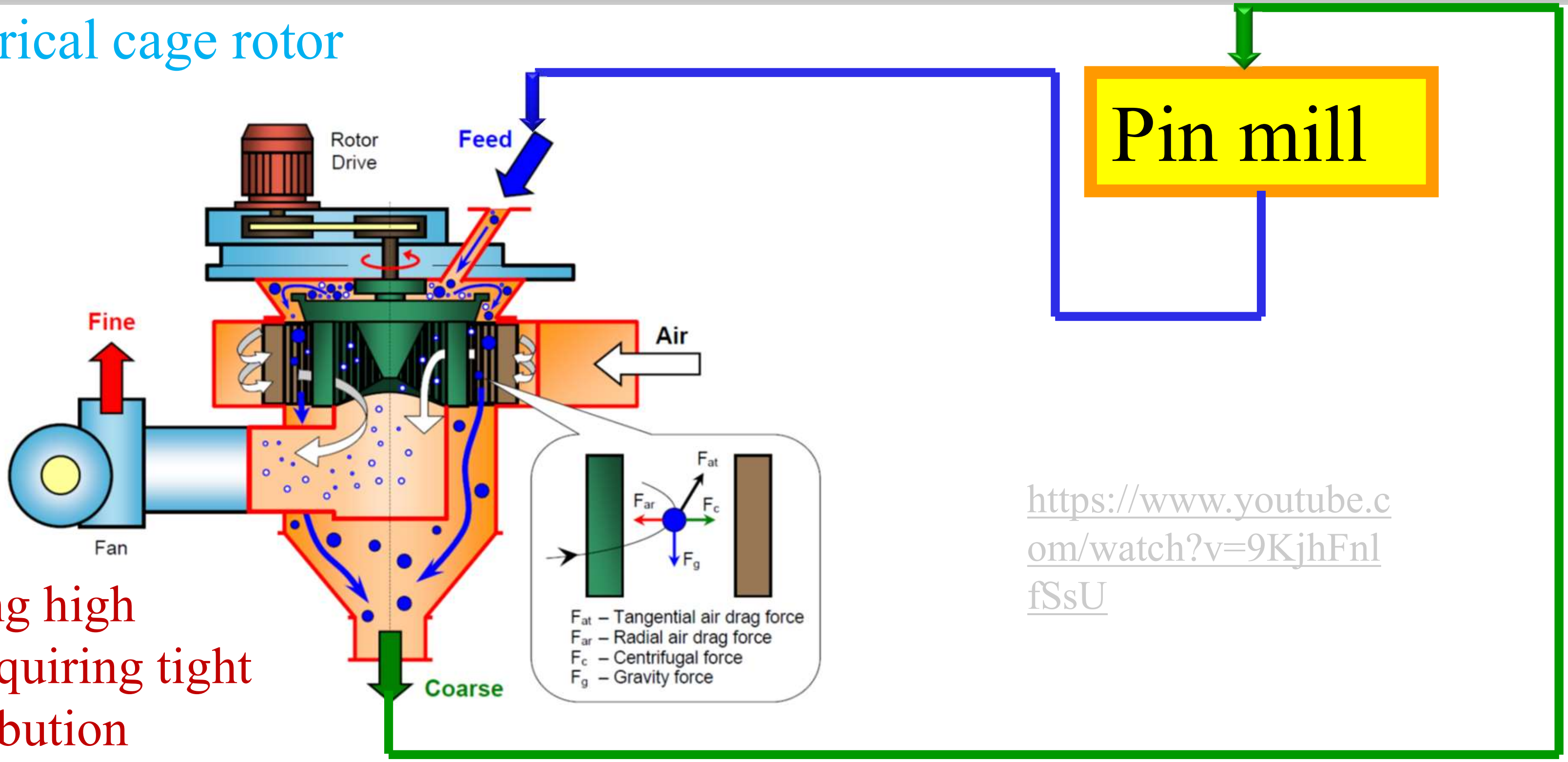




Particle size reduction by mechanical milling: *Pin mill equipped with dynamic selector*

https://youtu.be/N8JRwAf9Qfk

Cylindrical cage rotor



https://www.youtube.com/watch?v=9KjhFnlfSsU

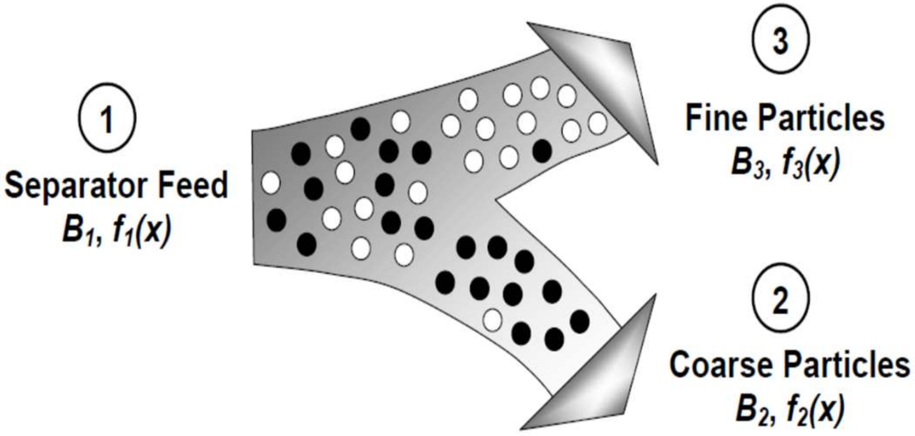
Plant for producing high tonnage of API requiring tight particle size distribution

Dissertation by Gleb Gennadievich Mejeoumov

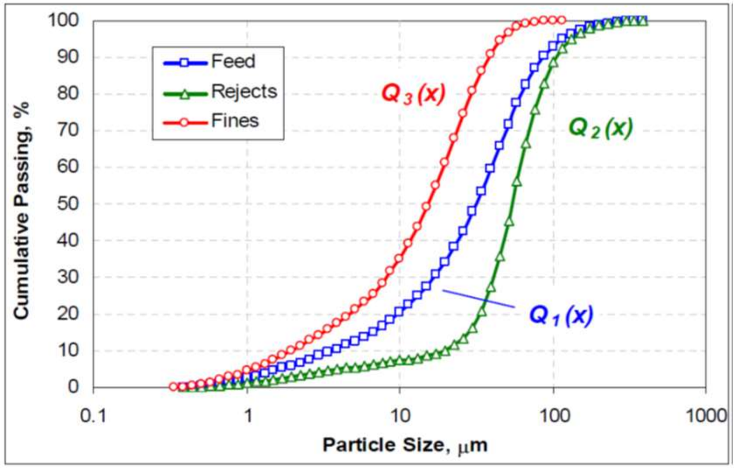
❖ *Principle*

- ***The product is introduced within the mill using à rotary valve. Then it's milled by mechanical action (impacts) of particles with milling media (rotor and stator) or with others particles.***
- ***The milled product is then carried towards the dynamic selecteur. The bigs particles are centrifuged and go back with the mill. The fine particles are transported by the gas to the filter***

Particle size reduction by mechanical milling: *Pin mill equipped with dynamic selector*



B: Material flow rate kg/h → $B_1 = B_2 + B_3$
F(x): Particle size distribution



- **Key parameters**
  - *Rotor speed*
    - *Increase → increase of centrifugal force → increase of fineness of fine fraction*
  - *Air flow rate*
    - *Increase → increase of aerodynamic force → decrease of fineness of fine fraction*
  - *Feed rate*
    - *Increase → can lead to conjuction of the selector*

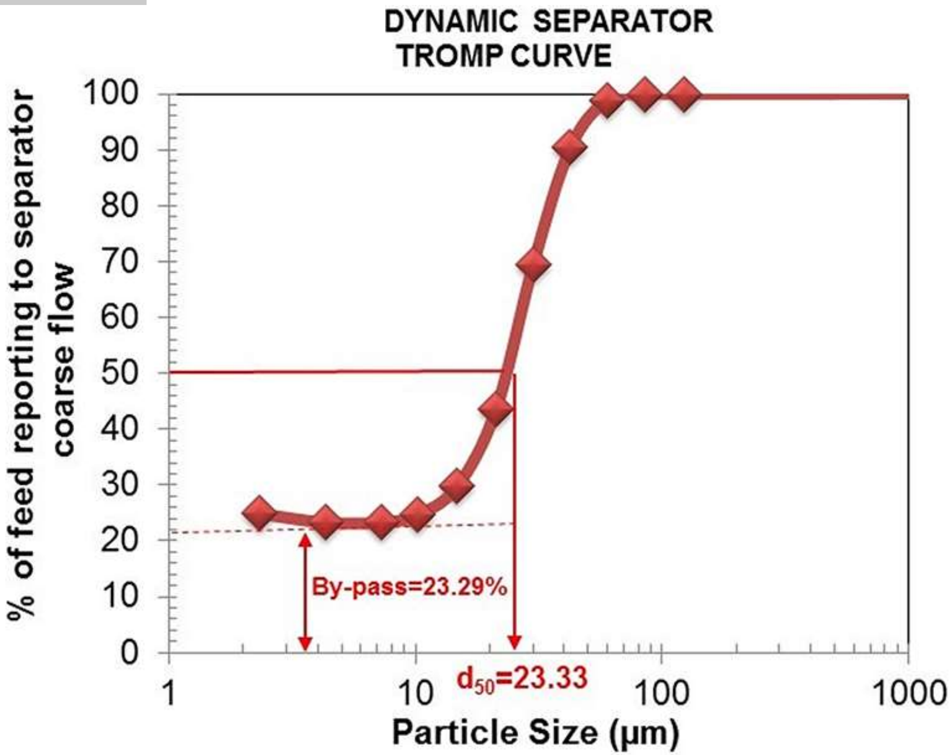
Particle size reduction by mechanical milling: *Pin mill equipped with dynamic selector*

$$B_1 \cdot f_{1i} = B_2 \cdot f_{2i} + B_3 \cdot f_{3i}$$

f_{xi} = portion of material in ith fraction

$$Tromp_i = \frac{B_2 \cdot f_{2i}}{B_1 \cdot f_{1i}}$$

Selection function



Cut size value: X_{50}

Sharpness of separation: X_{75}/X_{25}

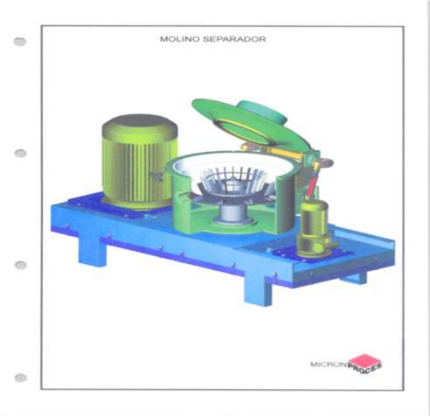
By-pass value: fraction that bypasses the classification action

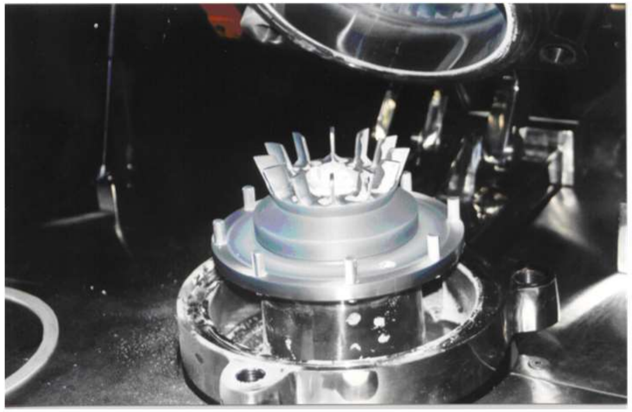
Partition coeffition: $B_3.f_{3i}/B_1.f_{1i}$

Grade efficiency curve

$$GEC = \frac{f_{3i}}{f_{1i}} \cdot \frac{f_{1i} - f_{2i}}{f_{3i} - f_{2i}} \cdot$$

Particle size reduction by mechanical milling: *Pin mill equipped with dynamic selector*





❖ Principle

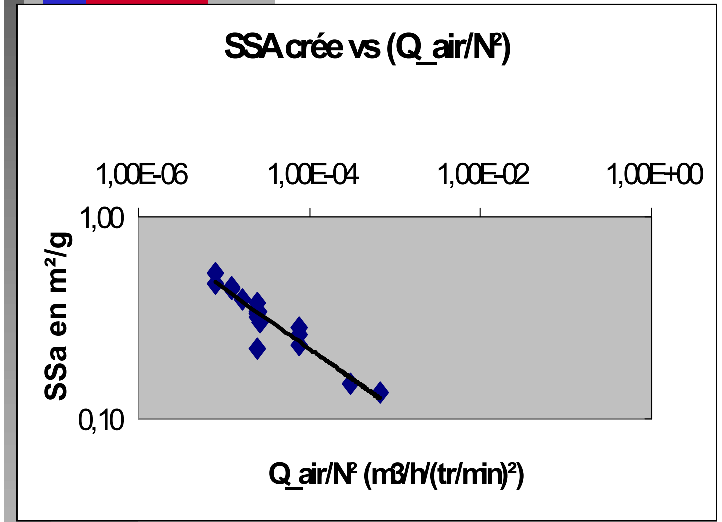
- *The product is introduced within the mill using à rotary vale. Then it's milled by mechanical action (impacts) of particles with milling media (rotor and stator) or with others particles.*
- *The milled product is then carried towords the dynamic selecteur. The bigs particles are centrifuged and and go back with the mill. The fine particles are transported by the gas to the filter*

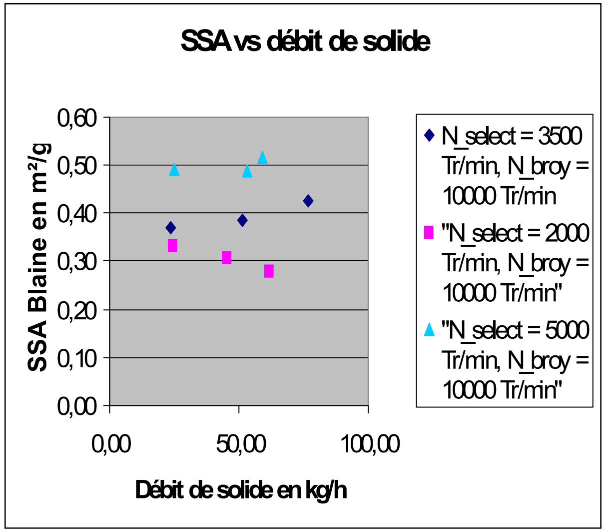
❖ Key parameters :

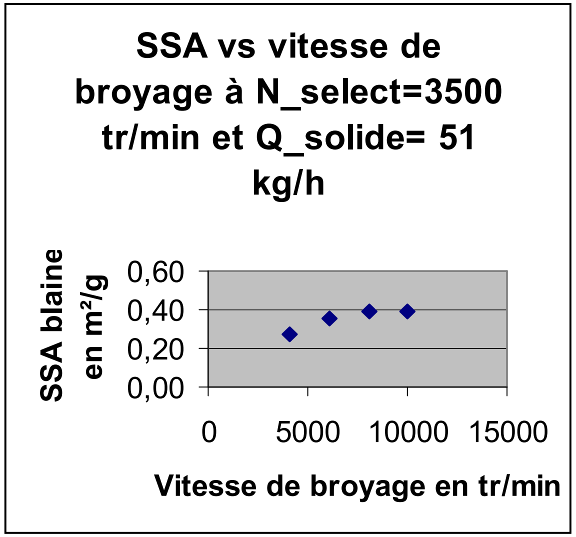
- *Mill rotation speed, selector rotation speed, solid flow rate, gaz flow rate.*

https://youtu.be/xlLSRM1N1e0

Particle size reduction by mechanical milling: *Pin mill equipped with dynamic selector-Parametric study*



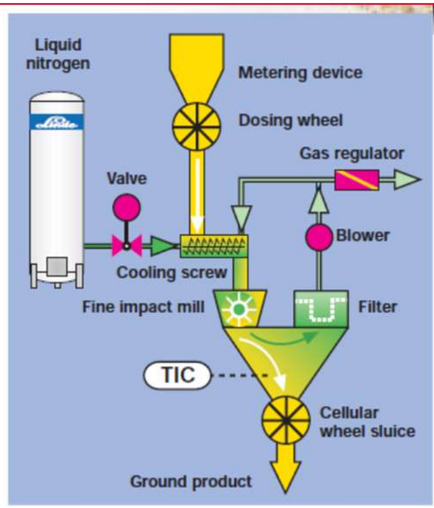


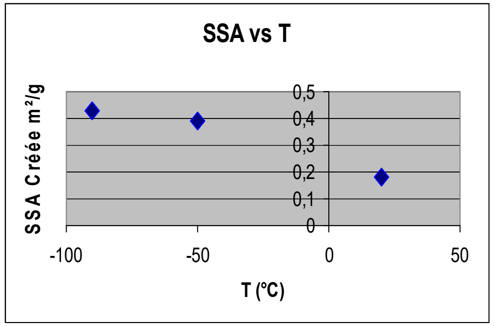


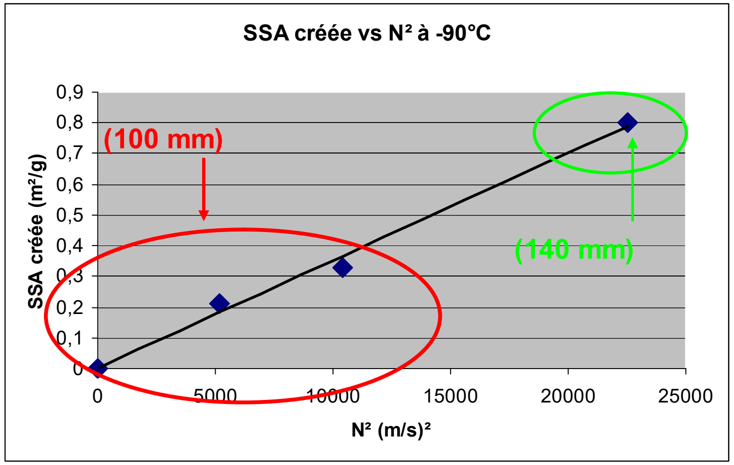
- *The physical quality of the milled product is mainly driven by the selector performances and the gas flow rate.*
- *The impact of the solid flow rate is not significant*
- *The mill rotation speed has a low impact on the physical quality of the milled product*

Particle size reduction by mechanical milling: Specific technolgies: Cryogenic milling

- **Cryogenic mechanical milling (down to -160° C)**
  - Used for product with low melting temperatur
  - Product sensitive to friction
  - Product with plastic behavior

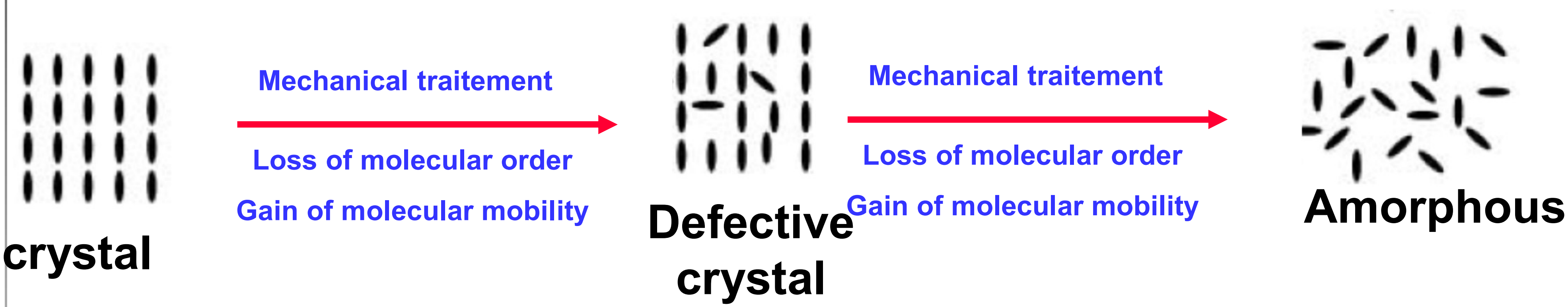






Particle size reduction by mechanical milling: Specific technologies: Amorphization by milling

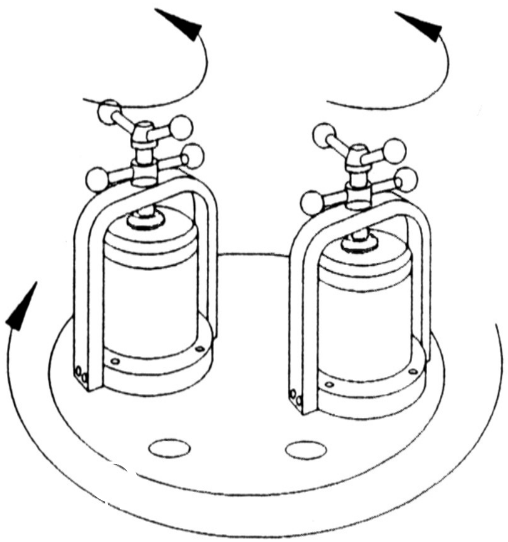
❖ ***Takes crystalline state away from equilibrium by progressively disturbing its crystal structure and increasing its free energy until the obtaining of totally amorphous product***

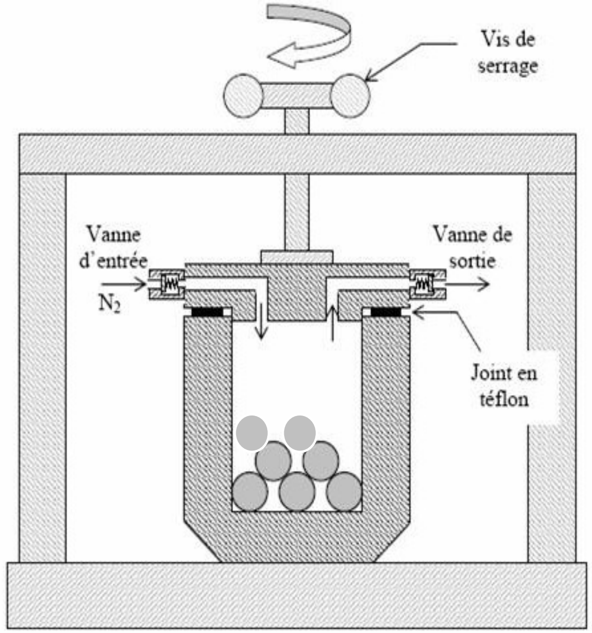


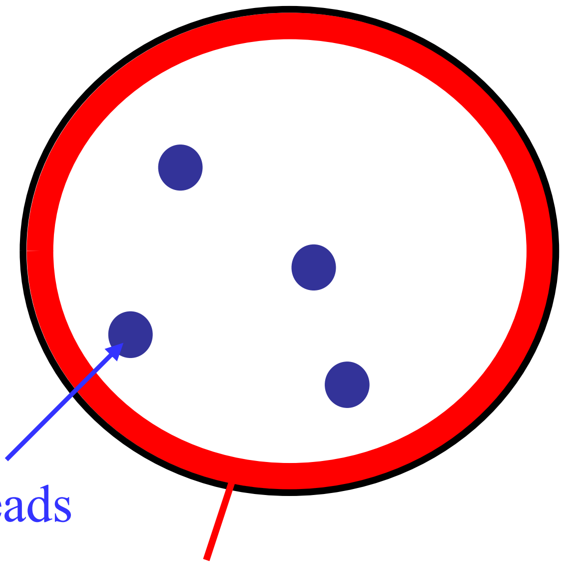
- ***Glass transition temperature (T_g) role***
  - *If $T_{milling} < T_g$: Amorphization*
  - *If $T_{milling} > T_g$: Polymorphic transition*

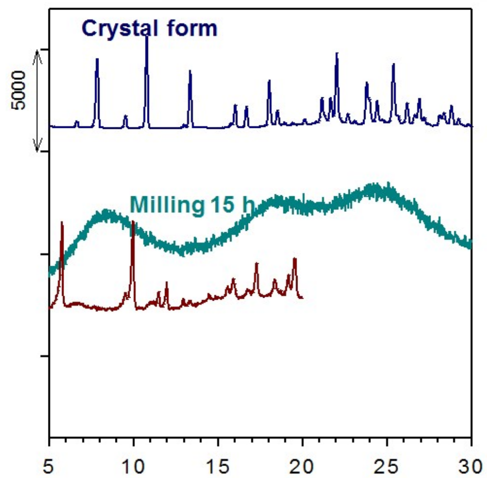
Particle size reduction by mechanical milling: *Specific technologies-Amorphization by beads milling*

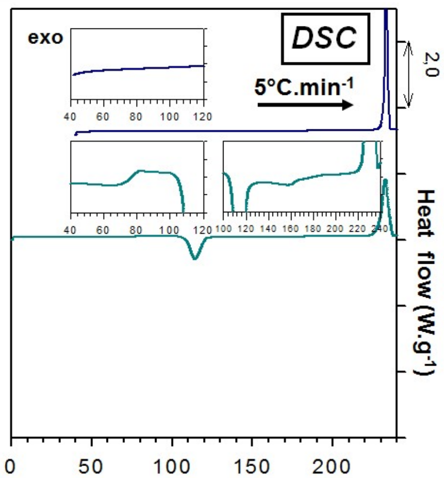
- Amorphisation by milling (API) or co-milling (API + excipient)



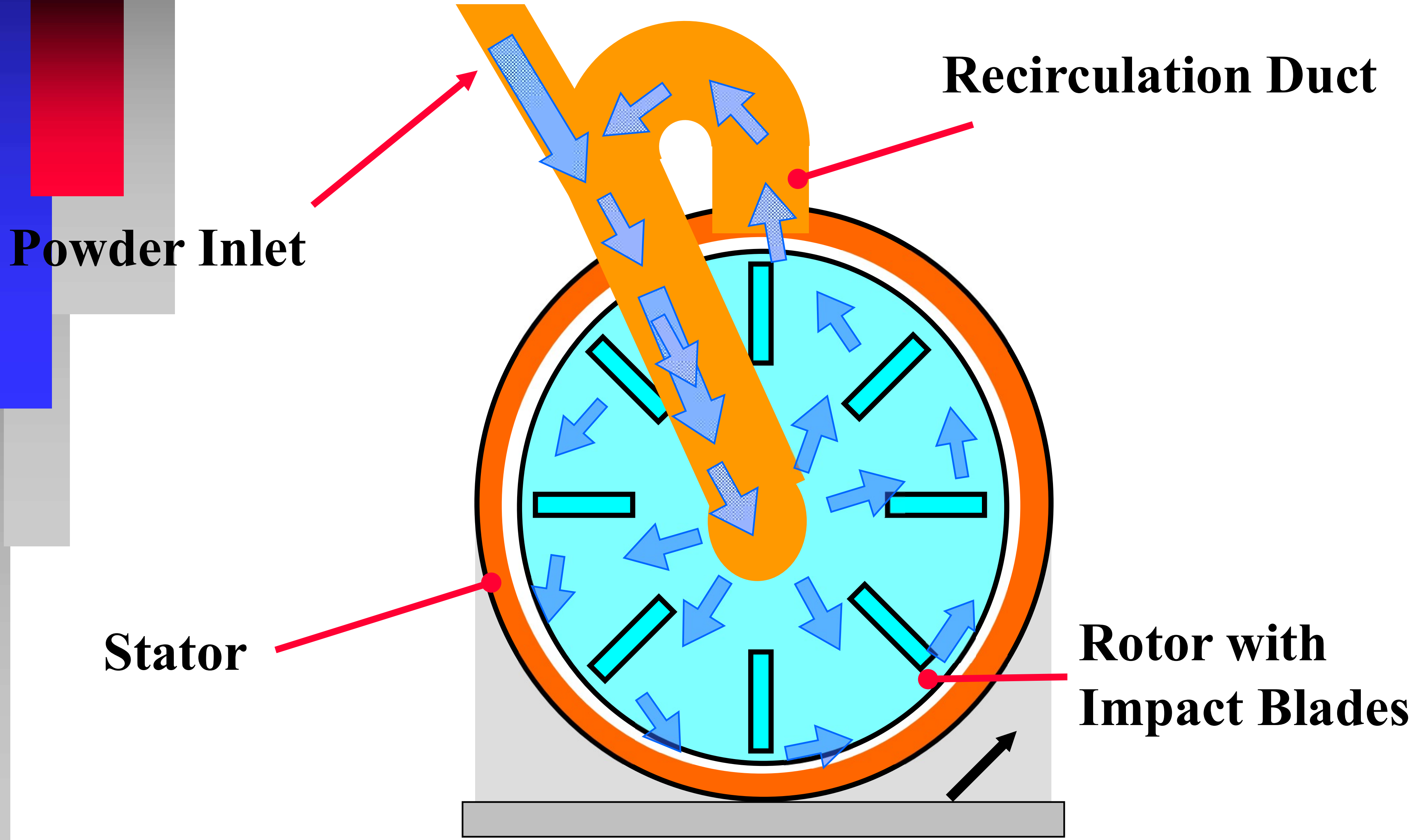








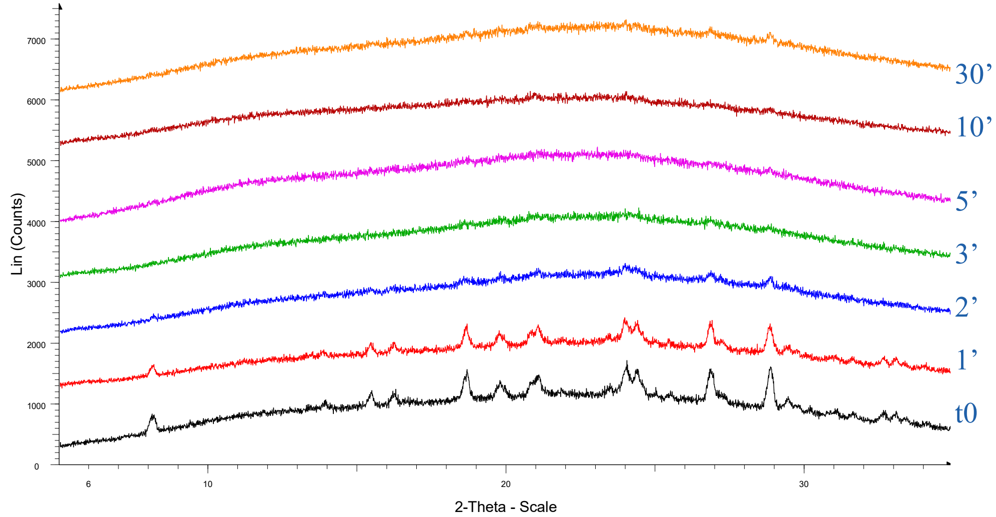
Particle size reduction by mechanical milling: *Specific technologies-Amorphization by Hammer mill*

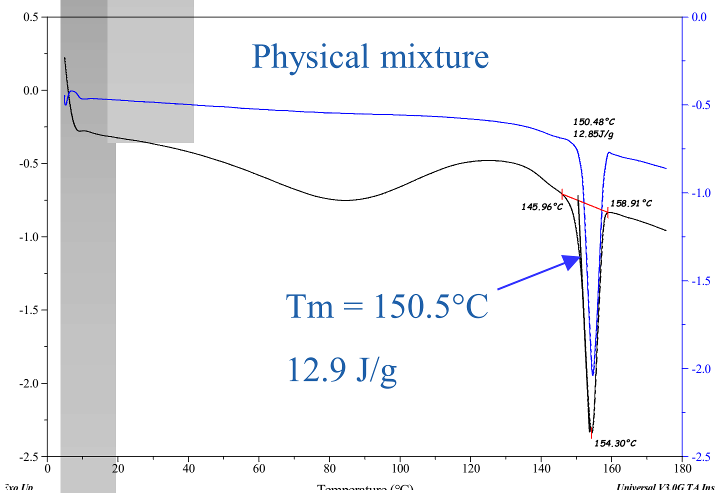


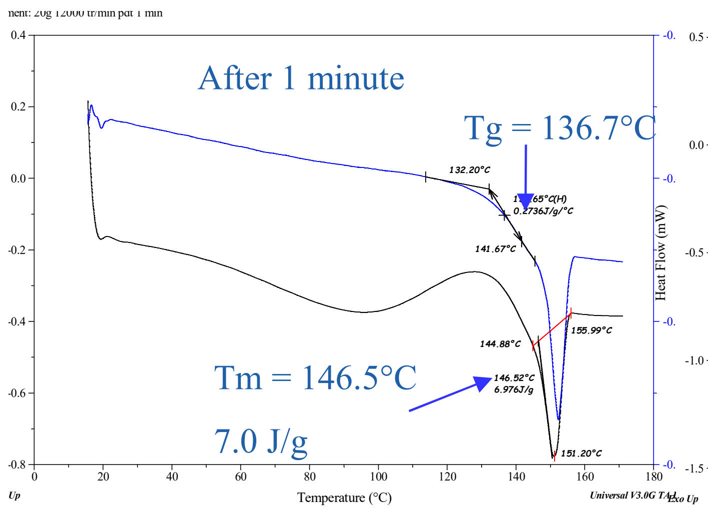
Particle size reduction by mechanical milling: *Specific technologies-Amorphization by Hammer mill*

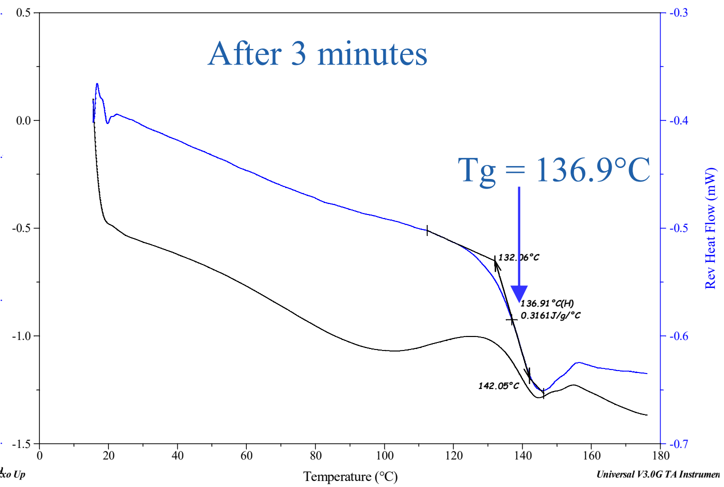
- **Kinetic results :**
  - **Amorphous after 3 minutes of milling or more**
  - **135.6°C < T_g < 137.3°C**

API A/HPMCP









Methodology of milling or jet milling study

Jet milling

Particle size reduction by jet milling:

Theory & applications

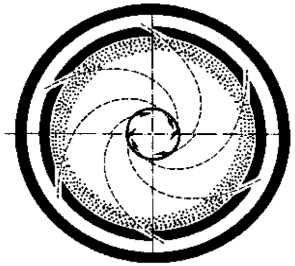
- *The different jet mills*
- *Applications*
- *Nozzles : theory and applications*
- *Critical parameters*
- *Population balances*
- *Effects on crystal structure*
- *GMP & Hygiene*

Particle size reduction by jet milling:

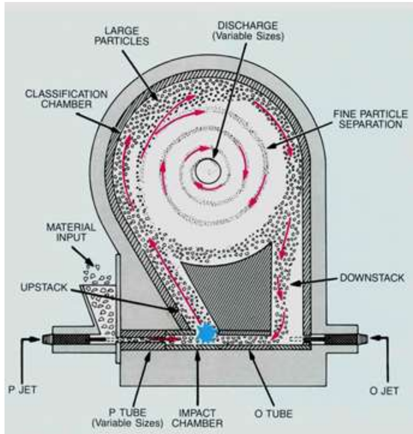
Pro's & con's

- ***Pros :***
  - *Ultra fine milling (1 to 15 µm depending of material and conditions)*
  - *No product contamination*
  - *No overheating of the material*
  - *Easy cleaning- easy cleaning validation*
- ***Cons:***
  - *Possible amorphisation : Surface area can decrease during storage*
  - *Hygien (respirable size) & safety (powder explosion hazards)*

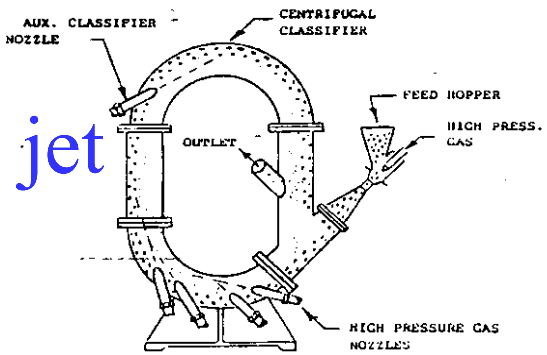
Particle size reduction by jet milling:
Different technologies



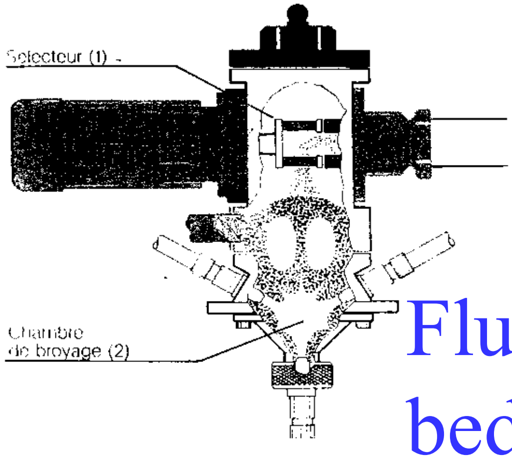
Spiral or pancake jet mill



Opposed jet mill



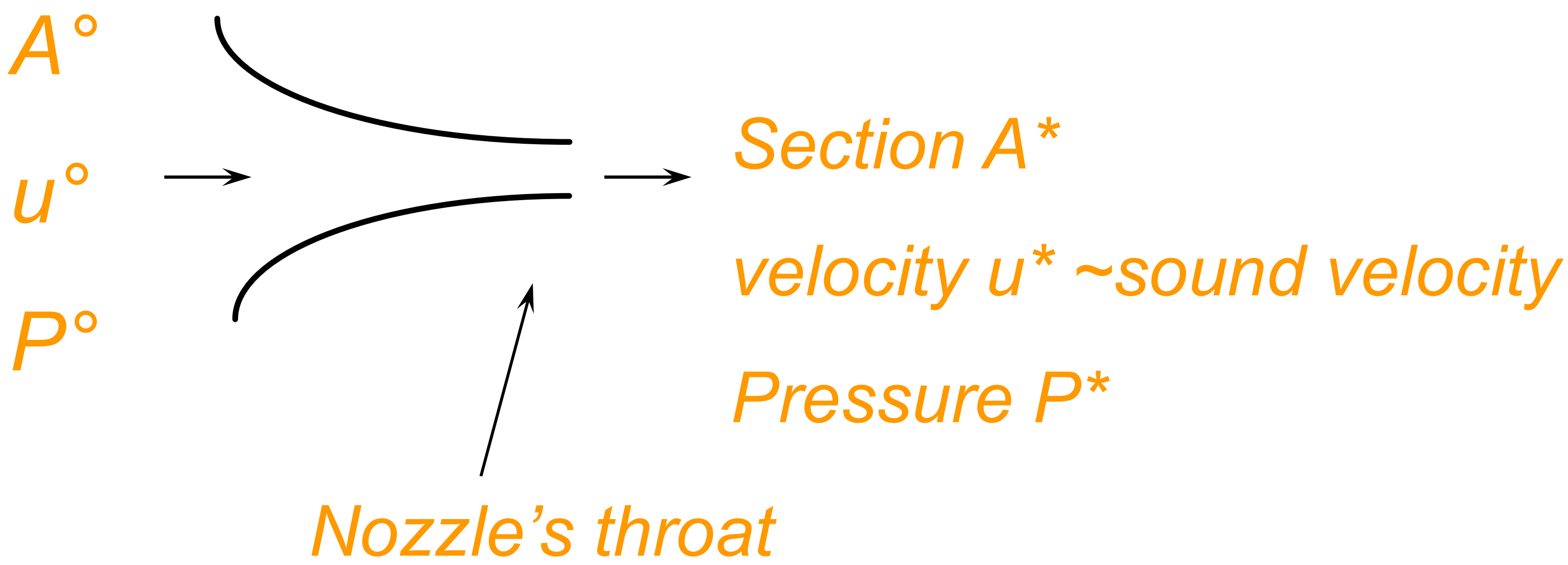
Loop jet mill



Fluidized bed jet mill

- ***The milling takes place due to the kinetic energy generated by the gas acceleration through the milling nozzles***

Particle size reduction by jet milling:
Nozzle's principle

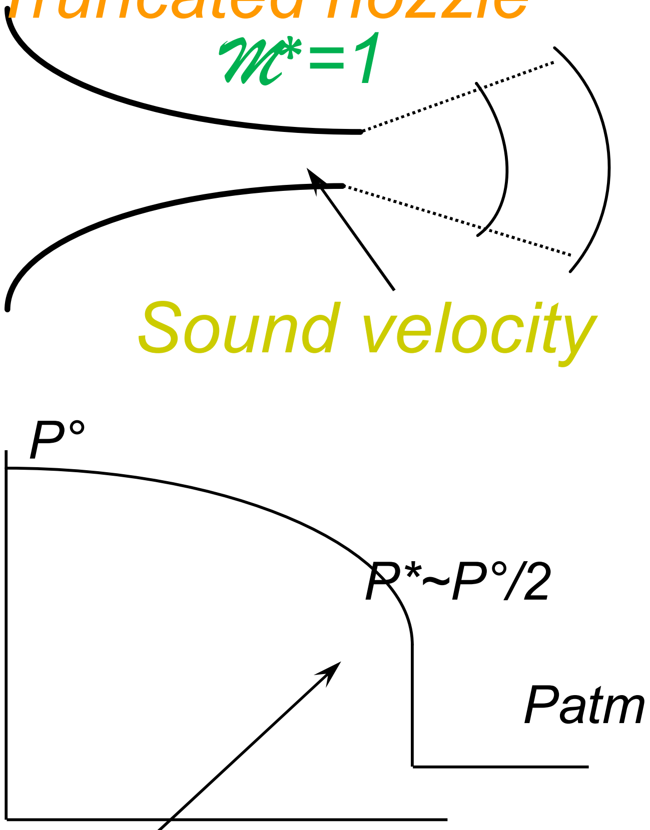


The gas is accelerated by expansion through the nozzle

Particle size reduction by jet milling:

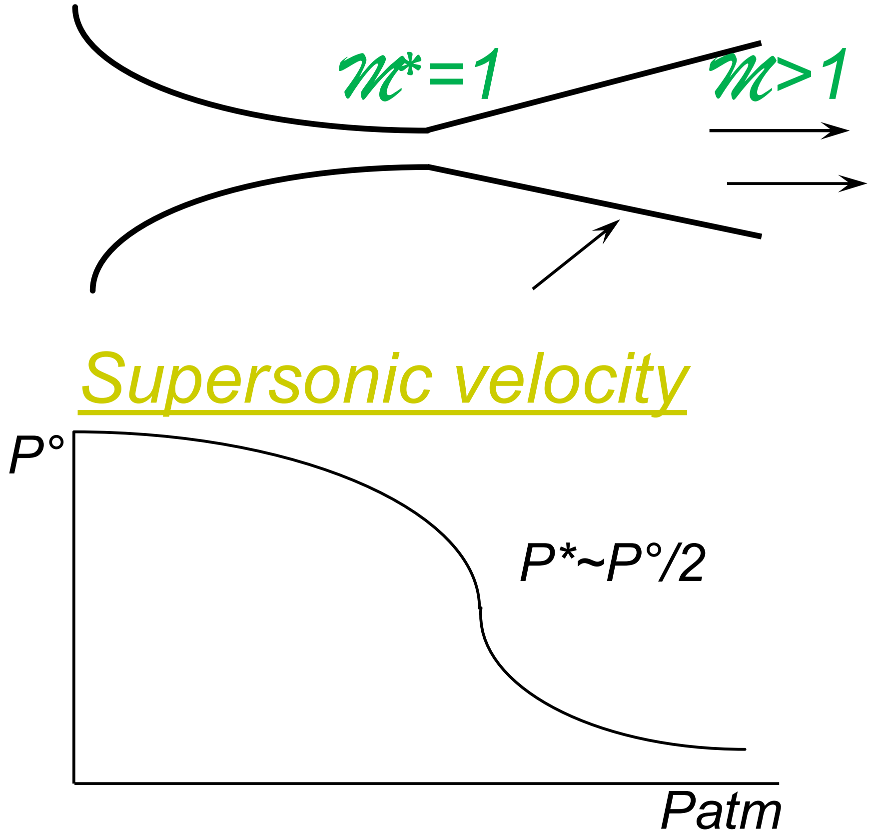
Truncated & de Laval nozzles

Truncated nozzle



Shockwave expansion

de Laval Nozzle



Continuous expansion in the divergent part of the nozzle

Particle size reduction by jet milling:

Physics : compressible flows

- **Fundamental equations for ideal case**
  - **Assumption**
    - *The gas flow within the nozzle is isentropic*
      - **Adiabatic without friction**
    - *The gas flow within the nozzle is quasi unidimensional*
  - **Mass conservation**

$$\dot{M} = \rho u A = Cte$$

- *For quasi unidimensional flow*

$$\frac{d\rho}{\rho} + \frac{du}{u} + \frac{dA}{A} = 0$$

$$\frac{1}{\rho}\frac{d\rho}{dx} + \frac{1}{A}\frac{dA}{dx} + \frac{1}{u}\frac{du}{dx} = 0$$

Particle size reduction by jet milling:

Physics : compressible flows

- *Perfect gas equation*

$$\frac{P}{\rho} = RT$$

- *Isentropic transformation*
  - *From first principle of thermodynamic*

$$H + \frac{1}{2}u^2 = H_0$$

> - *H_0 is stagnation enthalpy*
> - *For perfect gas*

$$CpT + \frac{1}{2}u^2 = CpT_0$$

Particle size reduction by jet milling:

Physics : compressible flows

$$\frac{P}{\rho^{\gamma}} = Cte \quad \gamma = \frac{Cp}{Cv} = \frac{Cp}{Cp - R}$$

- Cp: specific heat at constant pressure
- Cv: Specific heat at constant volume

- Stagnation properties
  - They are checked for any point of the flow and correspond to a state of stopping following an isentropic transformation

$$\frac{u}{c} = Mach$$

- u is the gas velocity and c is the sound velocity
- Mach is the Mach number

Particle size reduction by jet milling:

Physics : compressible flows

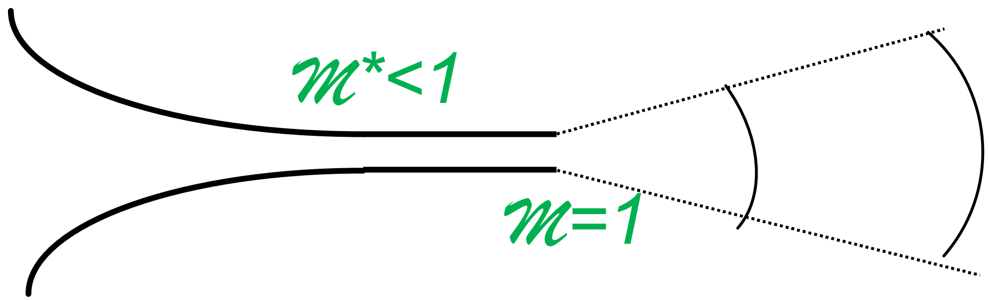
- **Therefore**

$$\frac{T_0}{T} = 1 + \frac{\gamma - 1}{2} Mach^2$$

$$\frac{P_0}{P} = \left(1 + \frac{\gamma - 1}{2} Mach^2\right)^{\frac{\gamma}{\gamma - 1}}$$

$$\frac{\rho_0}{\rho} = \left(\frac{P_0}{P}\right)^{\frac{1}{\gamma}} = \left(1 + \frac{\gamma - 1}{2} Mach^2\right)^{\frac{1}{\gamma - 1}}$$

Particle size reduction by jet milling:
Real nozzle



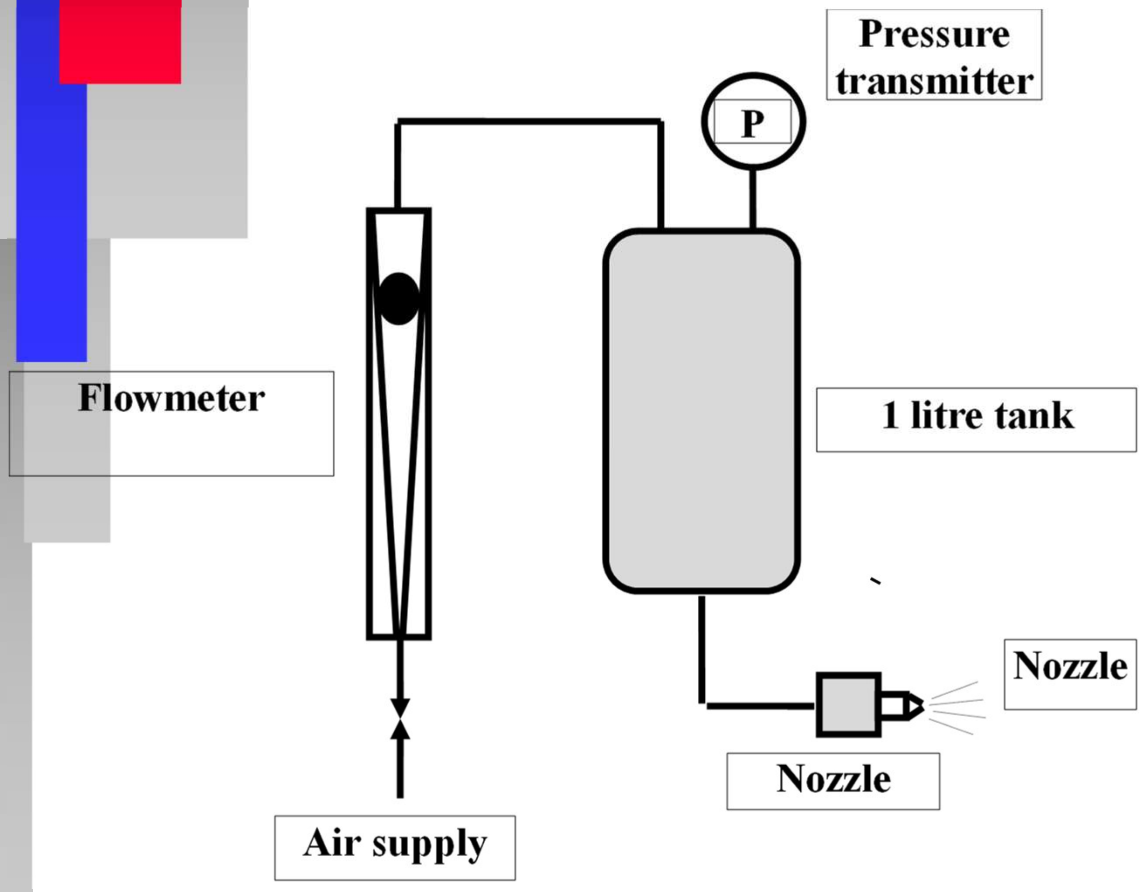
❖ **Machining quality of nozzle**

- ***Pressure drop by friction in the cylindrical part***
- ***Subsonic velocity at the throat (M* from 0,5 to 0,99)***
- ***Impact on kinetic energy and therefore on performances of particle size reduction***
- ***Nozzles are characterized in terms of Mach number***

Particle size reduction by jet milling:

Aerodynamic qualification

- ***Characterization of Mach number for each nozzle of the jet mill***



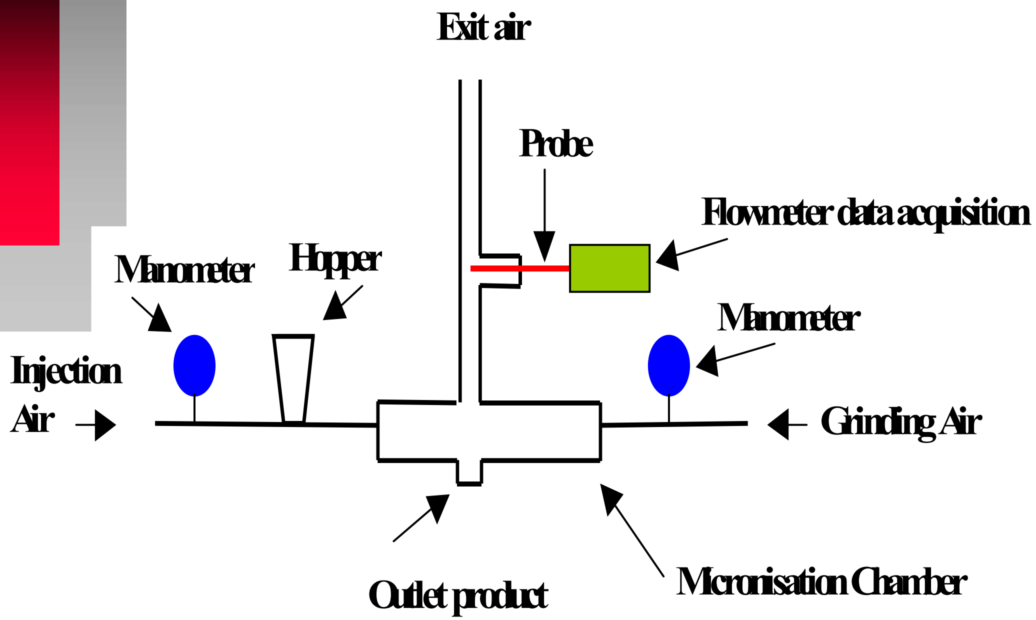
$$\frac{u}{c} = Mach$$

$$u = \frac{4flow}{\pi d^2}$$

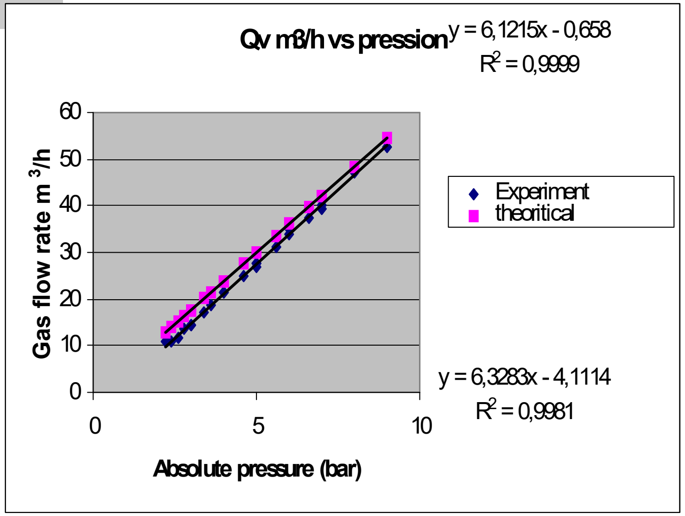
- ***Not always possible as most of the suppliers drill the nozzles directly in a ring***

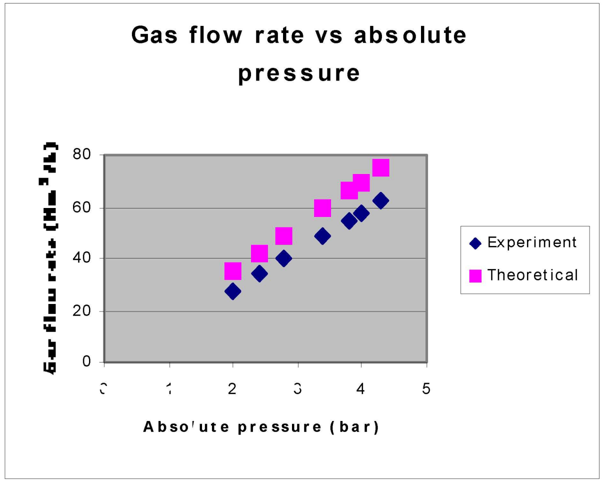
Particle size reduction by jet milling:

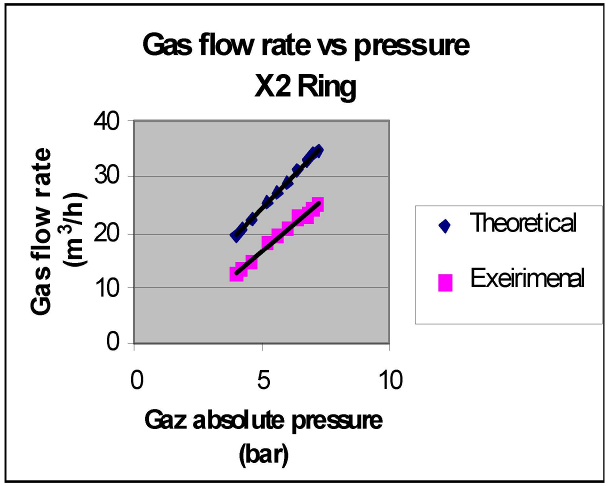
Aerodynamic qualification



When nozzles are directly drilled in a ring an average Mach number is mesured « Orifice coefficient »







Particle size reduction by jet milling:

Aerodynamic qualification

$0.52 \leq CO \leq 1$

↓

Machining quality

Size	Name	Grinding nozzles			Injection nozzles	
		d (mm)	number	CO	d (mm)	CO
Loop	Jet'Omizer Vitry OO	0,7	2	**0,83**	0,55	**0,53**
	Jet'Omizer Frankfürt	0,725	2	**0,78**	0,8	**0,76**
	Rinajet	0,75	2	**0,96**	0,75	**0,93**
	Loop 101S	2,05	2	**1,00**	1,4	**0,90**
1.5 inches	FPS 1,5	0,4	4	**0,87**	0,6	**NA**
2 Inches	Spoutnik	1,55	3	**0,80**	1,55	**0,66**
	FPS 2	0,8	6	**0,93**	0,6	**NA**
	MC50 Vitry	0,85	6	**0,82**	1,25	**0,94**
	MC50 Frankfürt	0,9	6	**0,74**	1,2	**0,75**
	Micronmaster	1,4	3	**0,97**	1,4	**0,93**
	Sturtevant	1,04	2	**0,90**	0,71	**0,89**
4 Inches	MC100	1,25	6	**0,75**	1,65	**0,95**
5Inches	FPS 5	1,25	6	**0,49**	NA	**NA**
8 Inches	APEX 8	2,05	8	**0,82**	1,65	**NA**
	CHRISPRO 8	1,5	15	**0,52**	3,7	**NA**
	FPS 8	1,5	8	**0,59**	1,65	**NA**
12 Inches	JETPHARMA 12	1,9	12	**0,93**	2,5	**1,00**
	1581	3	12	**0,87**	4,6	**0,73**
	50236	3	12	**0,91**	3,6	**0,67**
	02307.	3	12	**0,72**	5,7	**0,50**
	50609	3	12	**0,64**	5,7	**0,67**
20 Inches	372045	4,5	12	**0,53**	9	**0,70**
	372055	5,5	12	**0,60**	9	**0,66**

Particle size reduction by jet milling:

Jet energy

$$Mach = \frac{u}{c}$$

$$u = c = \sqrt{\frac{\gamma R T^*}{M}}$$

$$\frac{T^*}{T_0} = \frac{2}{\gamma + 1} = 0{,}833$$

$$Q_{gas} = \rho_0 u A_0 = \rho^* c A^*$$

$$\frac{\rho^*}{\rho_0} = \left(\frac{2}{\gamma + 1}\right)^{\frac{1}{\gamma - 1}} = 0{,}634$$

$$\rho_0 = \frac{P_0 M}{R T_0}$$

$$Q_{gas} = n * CO * 0{,}454 P_0 \sqrt{\frac{\gamma M}{R T_0}} d^2$$

Gas kinetic energy

$$E_c = \frac{1}{2} Q_{gas} c^2 = n * CO * 0{,}189 P_0 \gamma \sqrt{\frac{\gamma R T_0}{M}} d^2$$

Grinding specific energy

$$E_{sp} = \frac{E_c}{Q_{solid}} \propto \frac{P_0}{Q_{solid}}$$

Solid-gas ratio

$$\tau = \frac{Q_{solid}}{Q_{gas}}$$

Particle size reduction by jet milling:

Kinetic energy of the jet is derived from fluid mechanics

A*: nozzle section

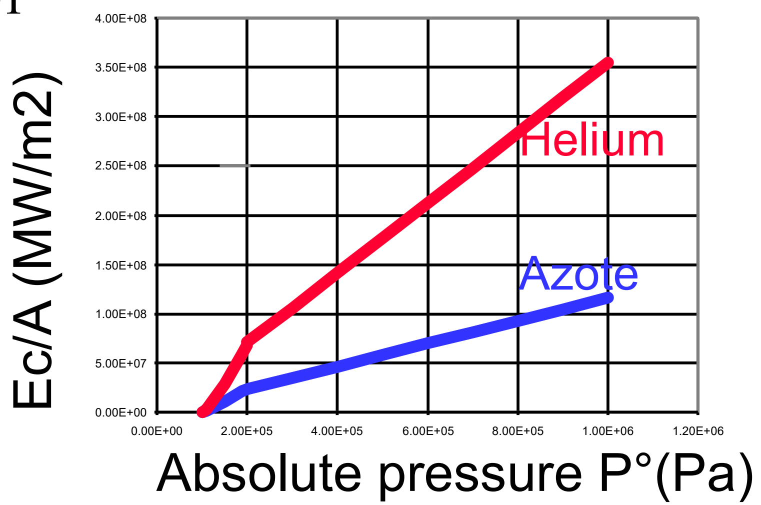
Orifice coefficient : nozzle quality

$$E_c = \frac{1}{2}.A^*.\rho^*.u^{*3} = \frac{1}{2}A^*.\rho°.(c°)^3.CO.\left(\frac{2}{\gamma+1}\right)^{\frac{3\gamma-1}{2(\gamma-1)}}$$

et

$$c° = \sqrt{\frac{R.T°}{M}}$$

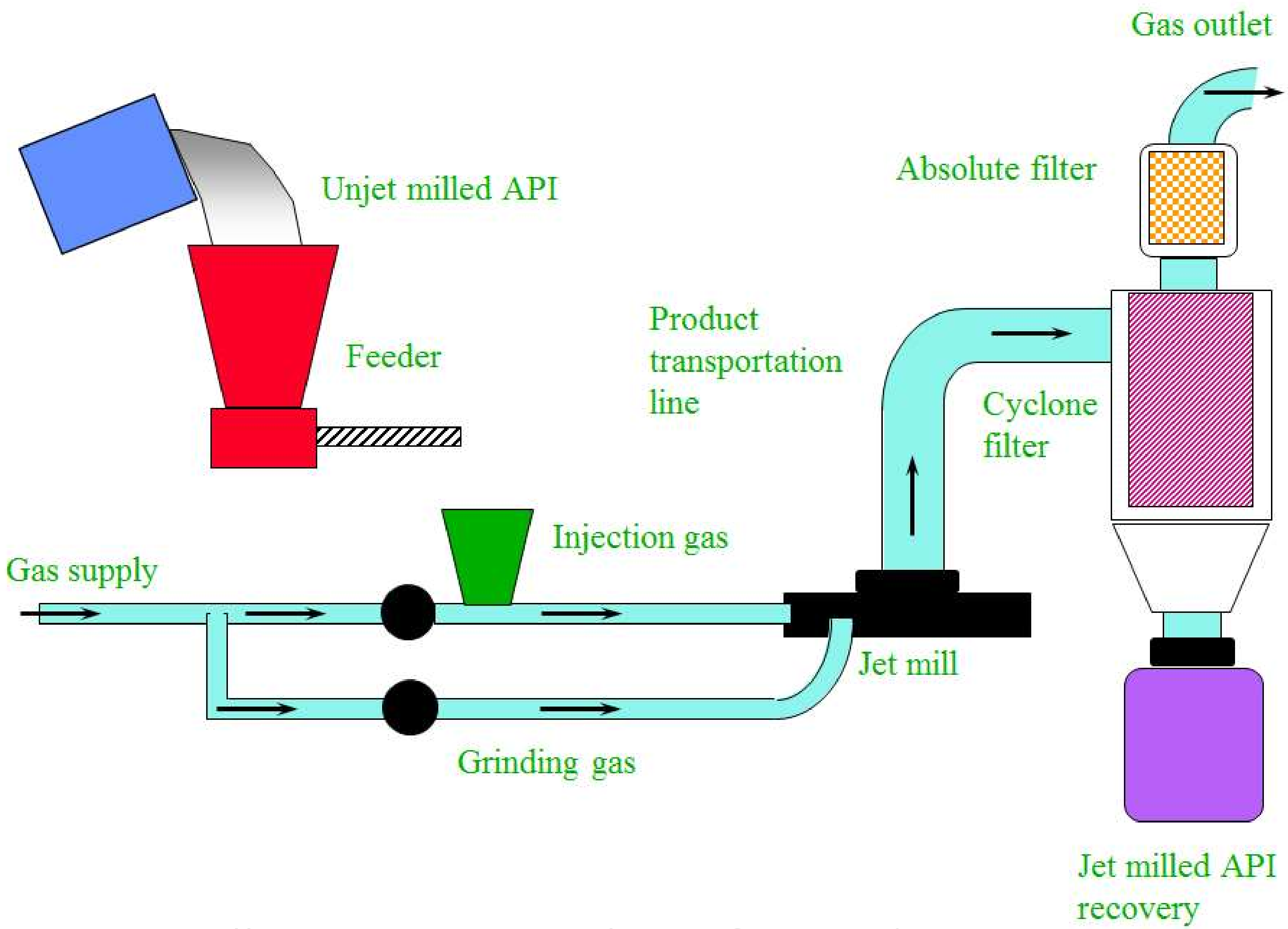
(sonic velocity)



Molecular mass --> Gaz nature influence (He vs N2 : Energy 3 times bigger)

Particle size reduction by jet milling:

Pancake jet Mill

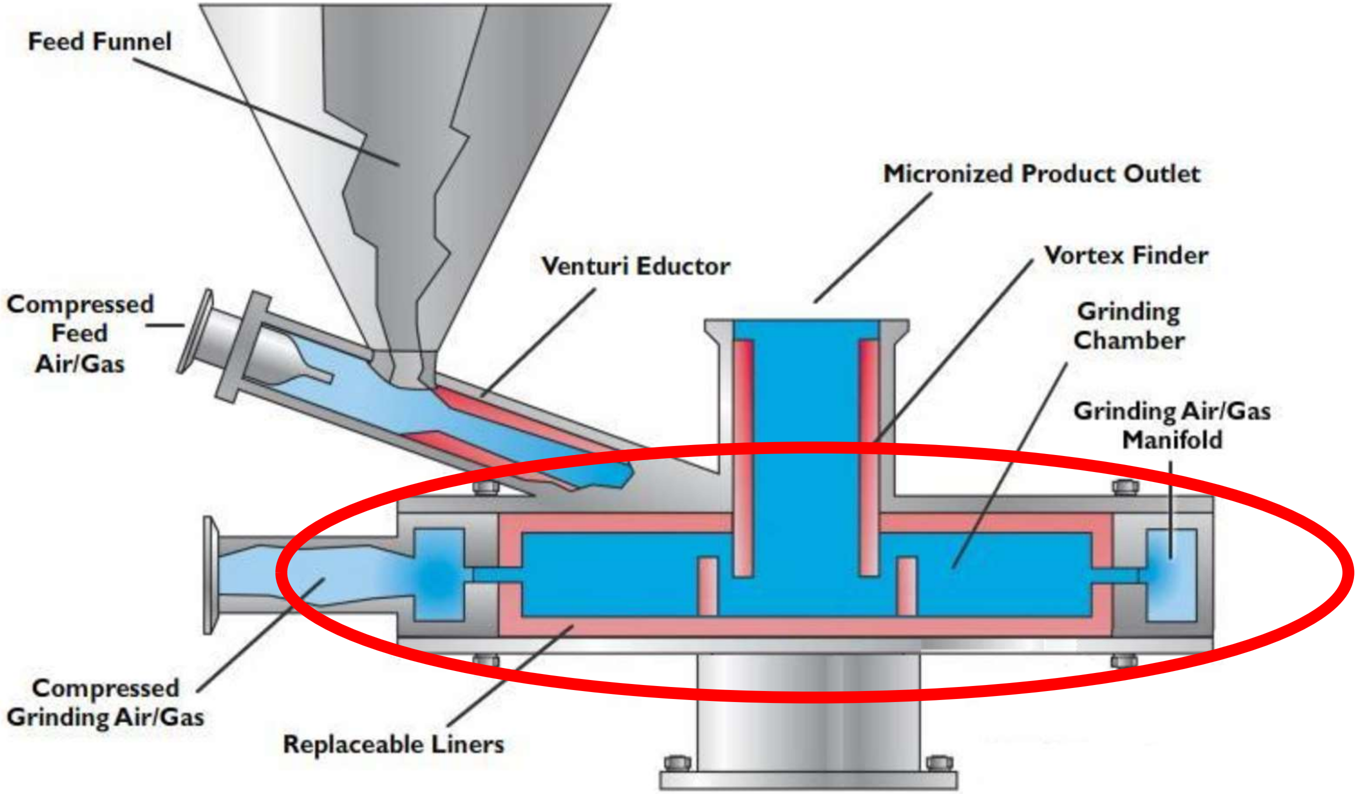


https://www.youtube.com/watch?v=wUYipPFMrKo

Microsoft
werPoint Presentati

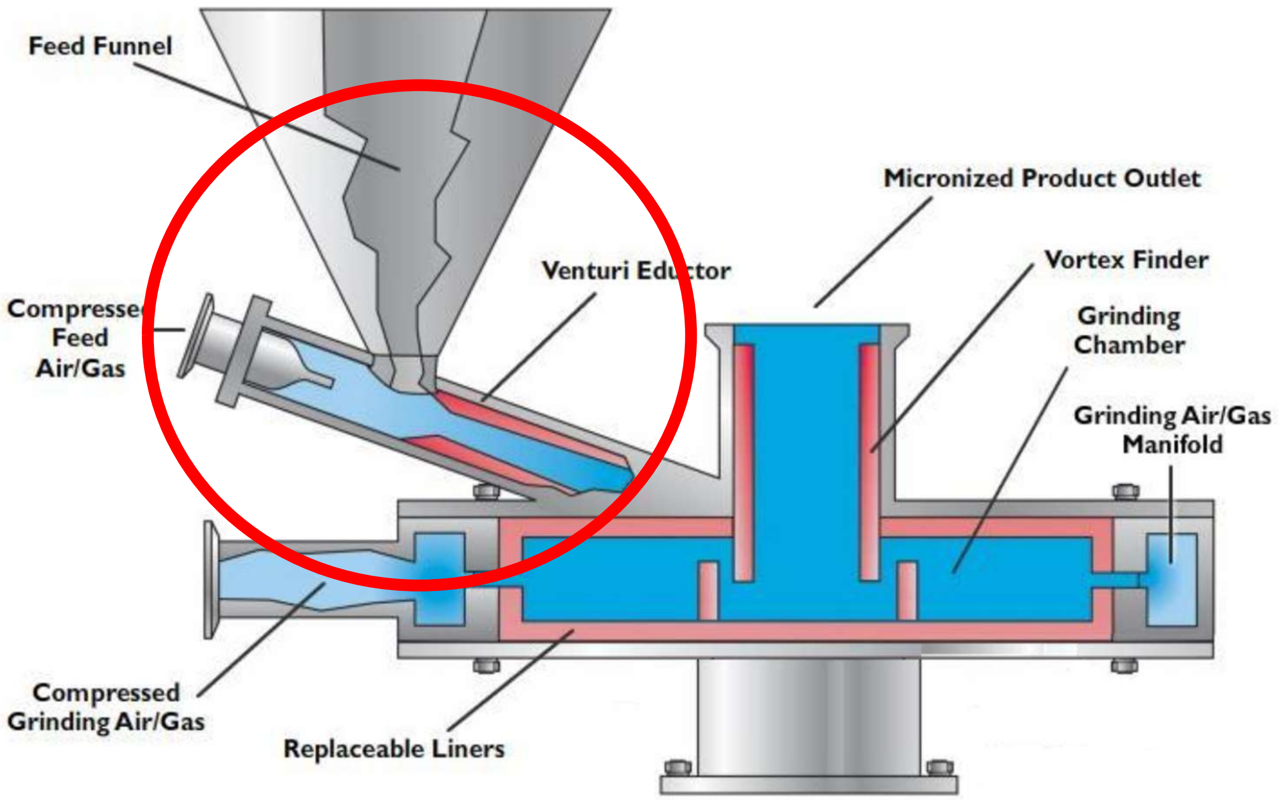
Particle size reduction : Pancake jet Mill

- The mill is made of:
  - A flat cylindrical milling plate :



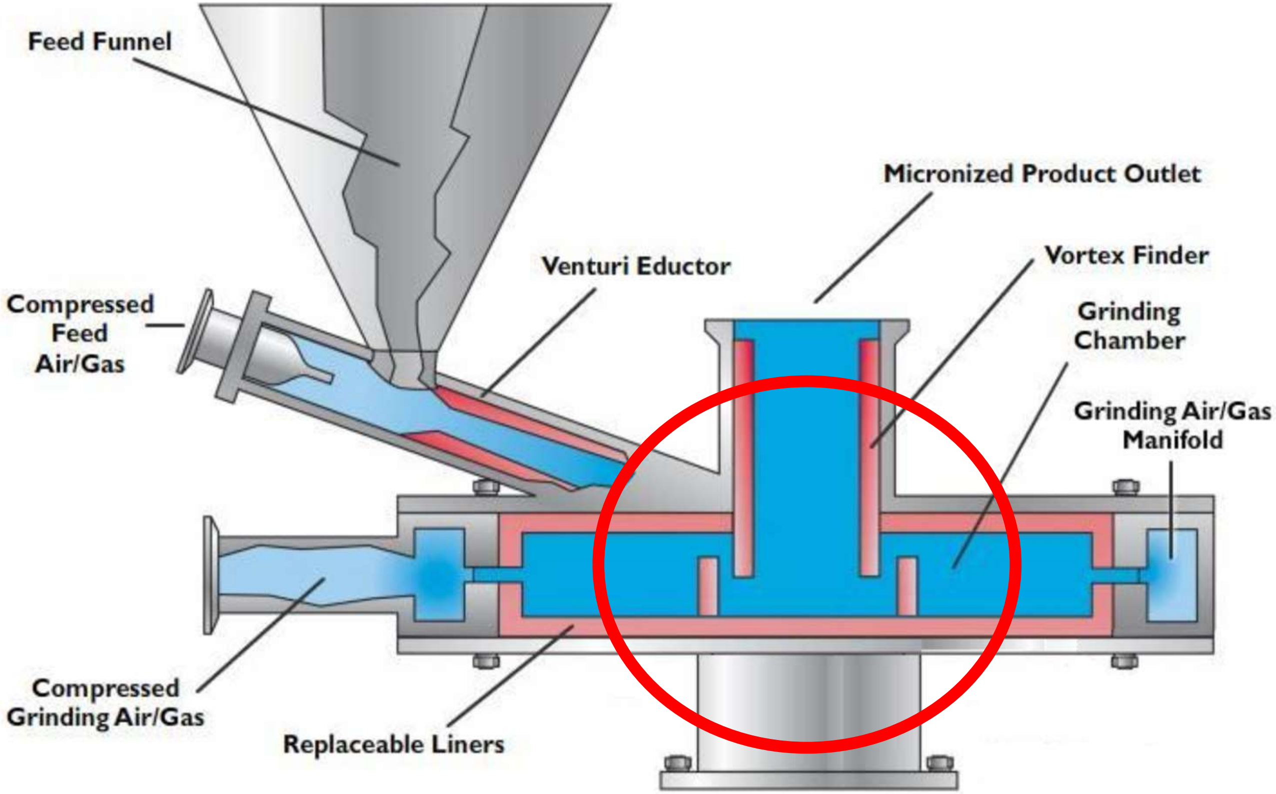
Particle size reduction : Pancake jet Mill

- ***The mill is made of:***
  - ***A powder feeding system (venturi) :***



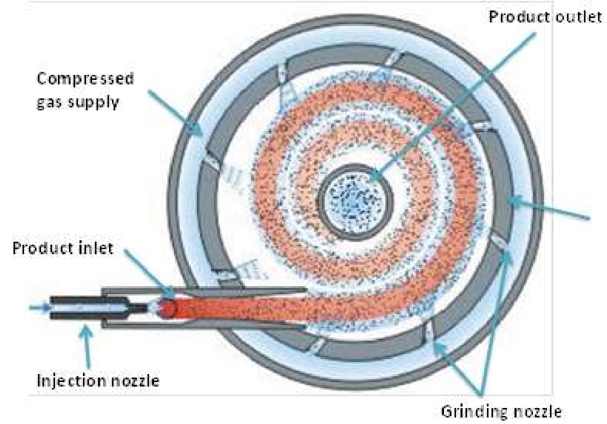
Particle size reduction : Pancake jet Mill

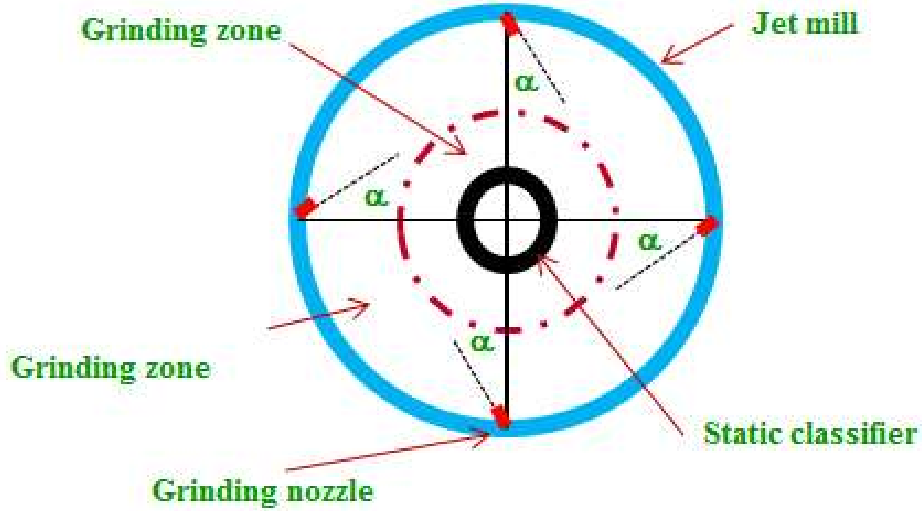
- The mill is made of:
  - A static classifier:



Particle size reduction by jet milling:

Pancake jet Mill-Aerodynamic mechanism





$l = k^* d_n$ $\quad\quad k = 10 \sim 20$

l = length of free jet $\quad\quad$ dn is the nozzle diameter

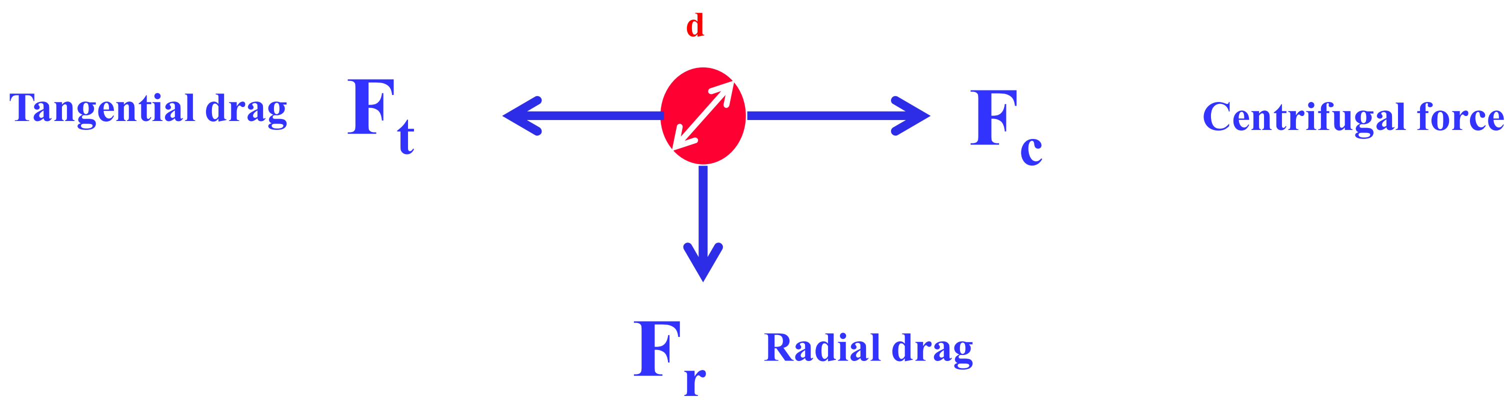
$$r = \frac{D}{2}\left[1 - 2 \times k\left(\frac{d_N}{D}\right)\cos\alpha\right]$$

r is the radius of the assumed boundary circle

The spiral jet mill cut size equation Rory MacDonald *et.al*

Particle size reduction by jet milling:

Pancake jet Mill-Aerodynamic mechanism



- ***Solid particles in the mill are subject to two competing forces***

$$F_c = \frac{\rho_s \times \pi \times d^3 \times v_t^2}{6 \times r}$$

Centrifugal force

$$F_t = \frac{A_p \times C_w \times \rho_g \times V_p^2}{2}$$

Centripetal force

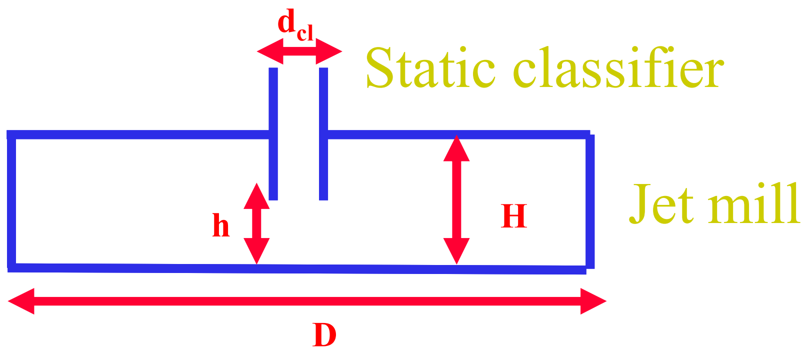
$$C_w = C_1 + \frac{24}{Re}$$

ρ_s: particle density
d: particle diameter
v_t: flow tangential velocity
r: particle position within the milling chamber
A_p: projected area of the particle in flow current
C_w: drag coefficient of the particle
ρ_g: gas density
V_p: normal component to flow of particle velocity
C_1= drag coefficient when Reynolds number tends toward infinity

The spiral jet mill cut size equation Rory MacDonald *et.al*

Particle size reduction by jet milling:

Pancake jet Mill-classification mechanism



$$v_r = \frac{Q_{gas}}{\pi d_{cl} h}$$

Assumption: constant spin ratio → $$\frac{v_t}{v_r} = k$$

$$d_{cut} = 3 C_w \rho_g r \frac{1}{4\rho_s} \frac{(v_t)^2}{(v_r)^2}$$

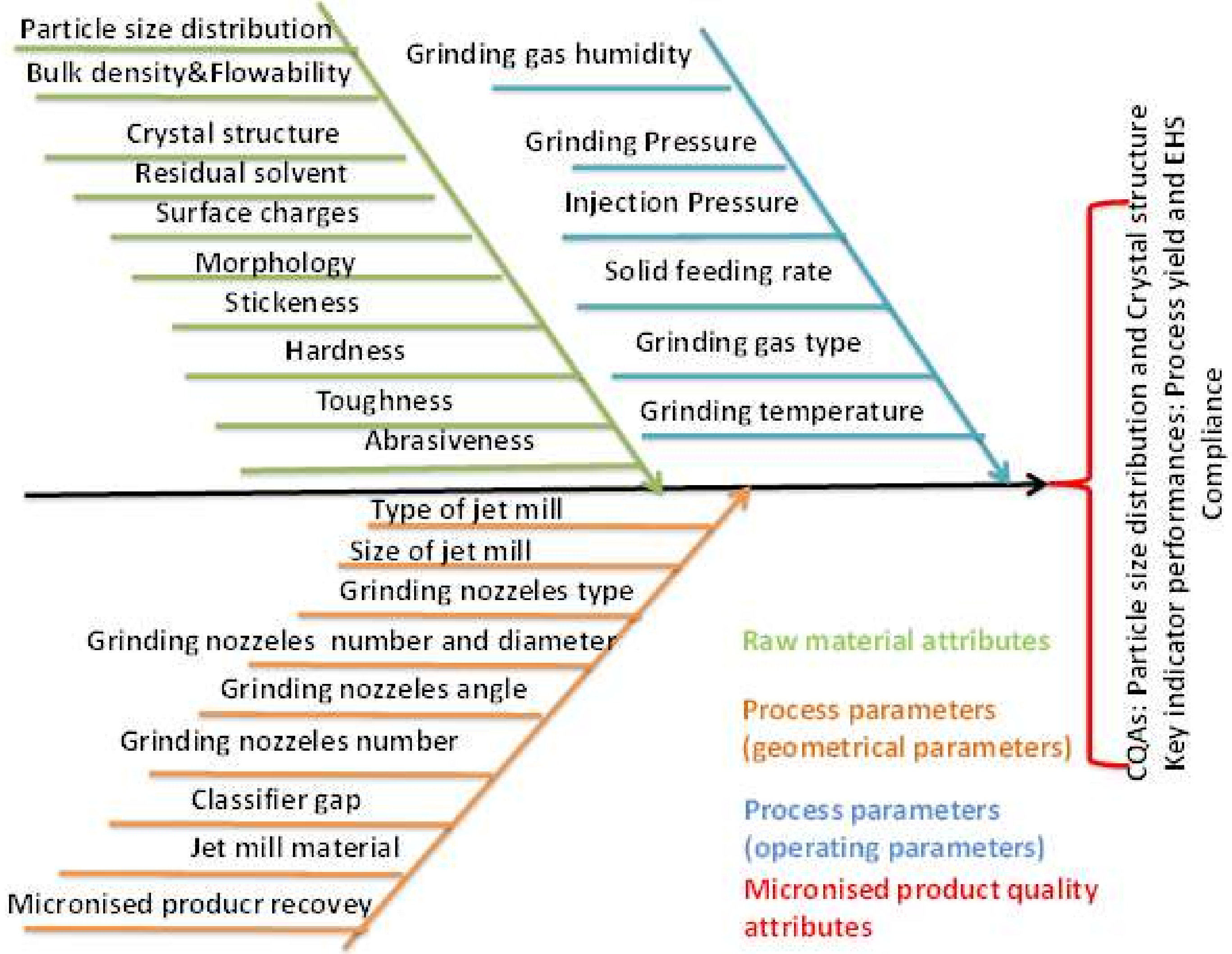
Increase of h → decrease of radial drag force → decrease of d_{cut}

The spiral jet mill cut size equation Rory MacDonald *et.al*

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

❖ **Key parameters**



Particle size reduction by jet milling:

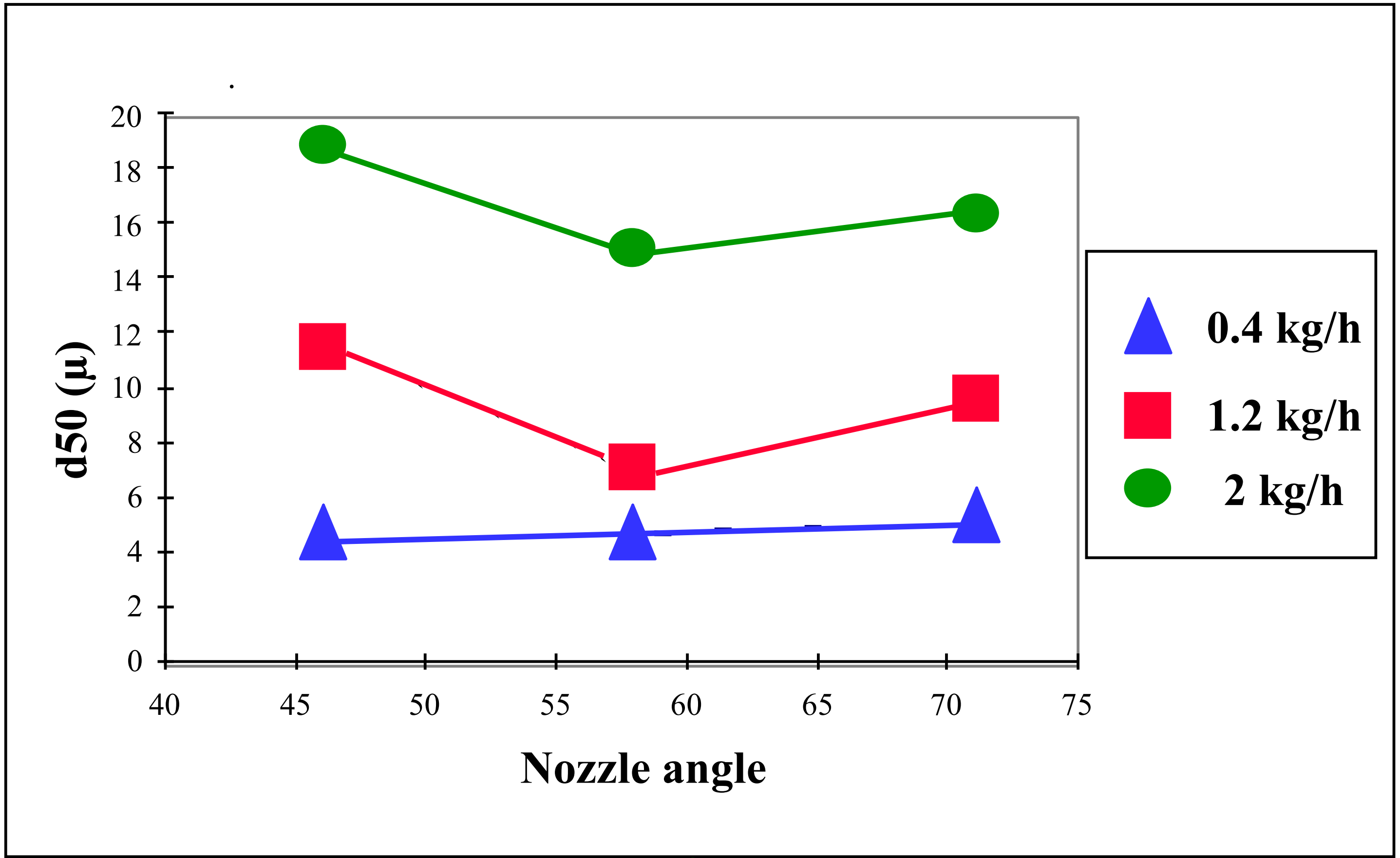
Pancake Jet mill-Parametric study

- **Key parameters**
  - Nozzle angle
  - Number of the nozzles
  - Nozzles diameter
  - Type of the nozzles (convergent vs convergent-divergent vs straight)
  - Gas type (Air, Nitrogen, Helium)
  - Grinding pressure
  - Solid flow rate

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

❖ **Nozzles angle impact at different solid flow rate**



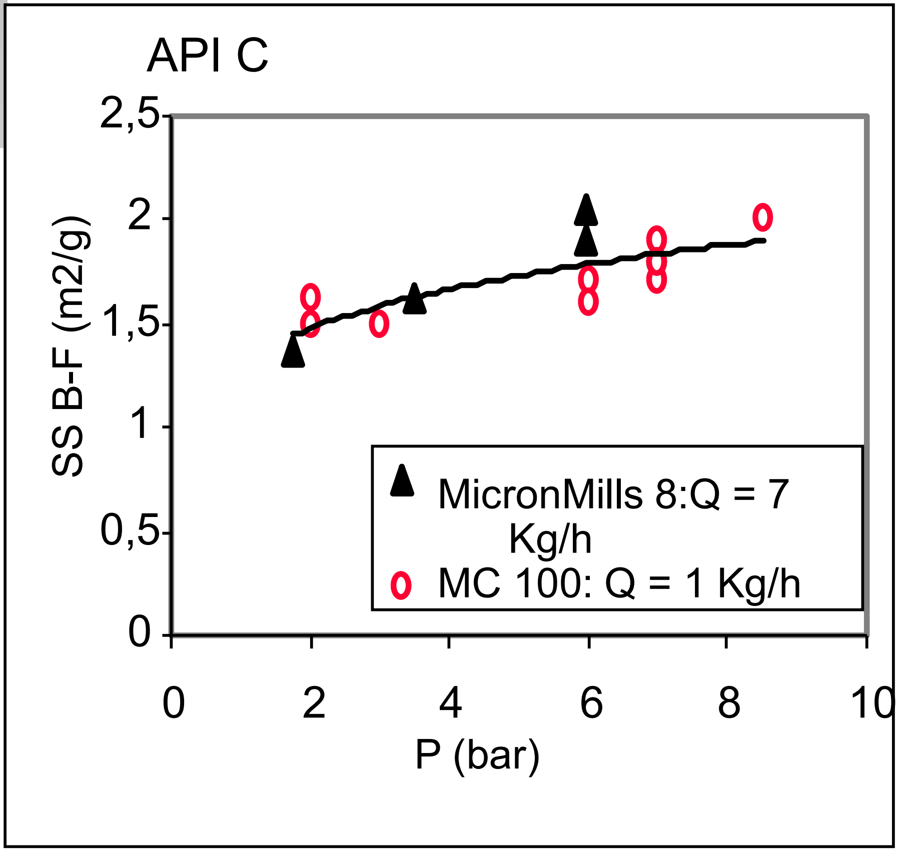
- **The nozzle angle has not a significant impact on the particles size but impact dramatically the solid build up within the jet mill**

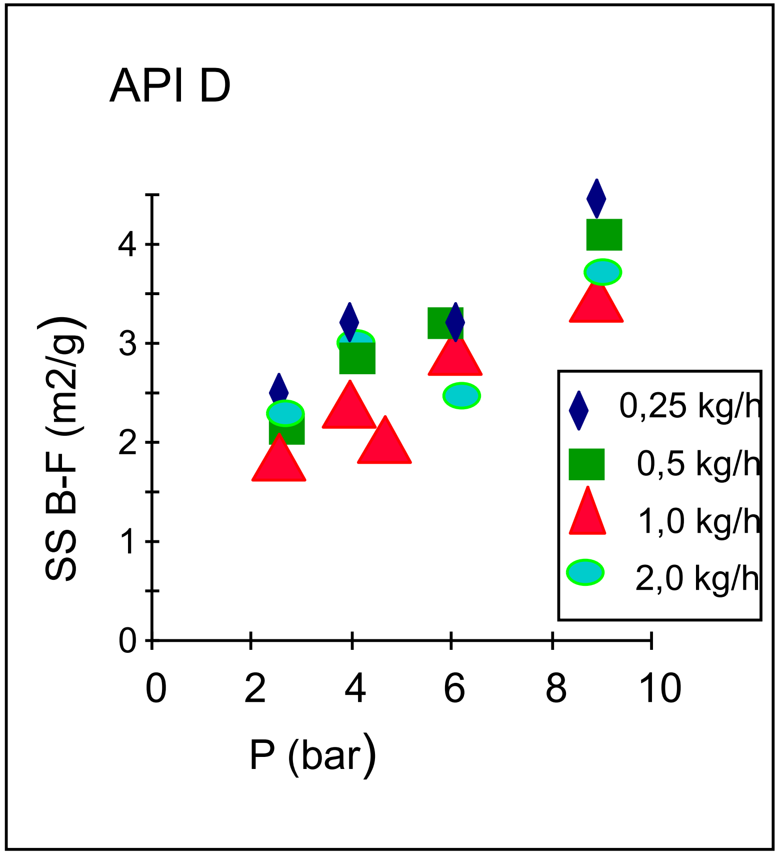
(from Smit et al.)

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

- Gas pressure impact





Higher the grinding pressure, higher the created specific surface area

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

❖ **Solid flow rate impact**

According Mohanty et Narasimhan

(kg/h)

$$\log Q \frac{\left(d_f - d_p\right)}{d_f} = mQ\left(\frac{1}{d_p^x} - \frac{1}{d_f^x}\right) + C$$

- *Where Q is the slid flow rate*
- *d_f is the feed particle size*
- *d_p is the particle size of micronized product*
- *C, m and x are constant related to product characteristics*
- *The exponent x is coming from the equation below*

$$\frac{dE}{dX} = -C \times \left(\frac{1}{X^n}\right)$$

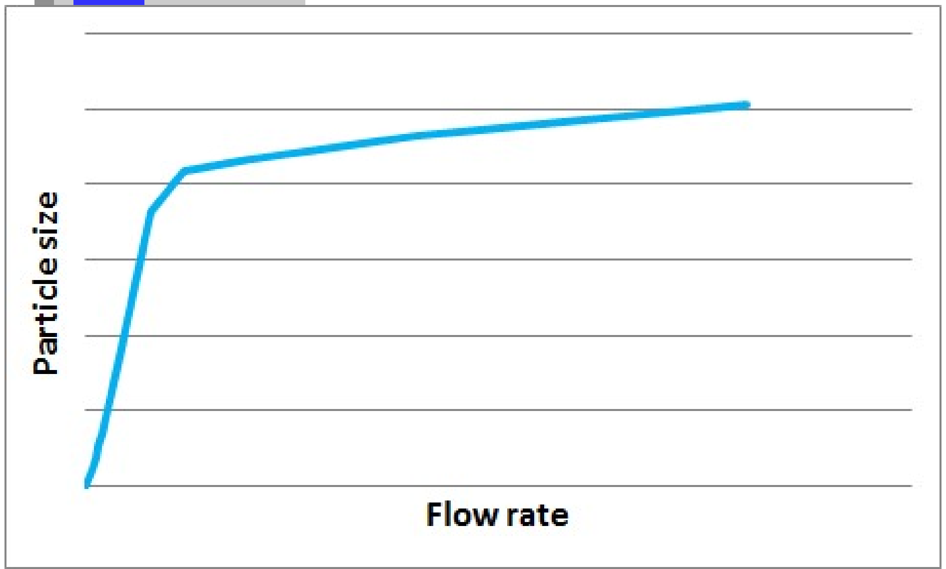
Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

❖ **Solid flow rate impact**

According Ramanujam et Venkateswarlu

- *The particle size increase continuously . The milling profile exhibiting two regimes. Each regime is driven by a power law*

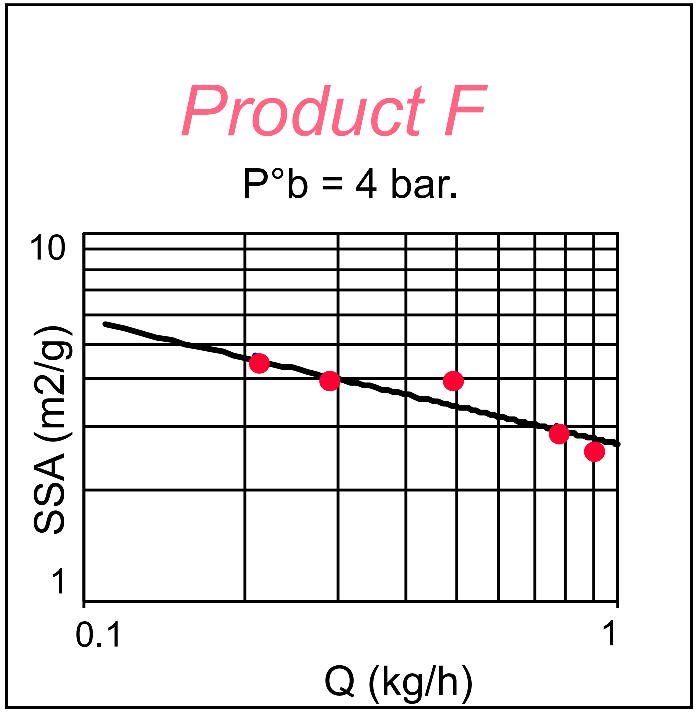


maximum value of the solid flow rate exists beyond which the behavior of the particles in the grinding chamber is very unstable resulting in a discontinuous output of the product and large fluctuations in the particle size.

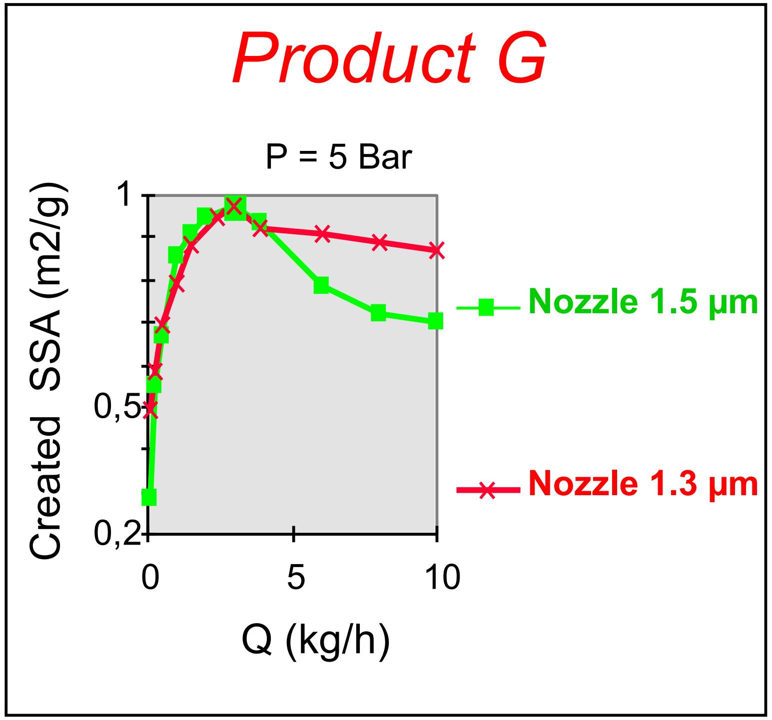
Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

- **Solid flow rate impact : 2 cases**



OR



Case 1: decrease in SSA when solid flow is increased

Case 2 : Existence of an optimal solid flow

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

- Injection pressure
  - This is parameter is poorly studied,
  - The most authors arbitrarily set it to 0.5 or 1 bar more than the grinding pressure to avoid a phenomenon of reflux in the venturi.
  - For Karl Sommer, the arrival of the gas-solid flow at the chamber causes, from a certain pressure, a disruption of the spiral flow which reduces the efficiency of grinding. He therefore recommends working at minimum feed pressure.
- Jet milling temperature
  - the speed of sound is proportional to the square root of the temperature, a high temperature will increase the speed of the gas in the mill and therefore the kinetic energy of the grinding gas

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

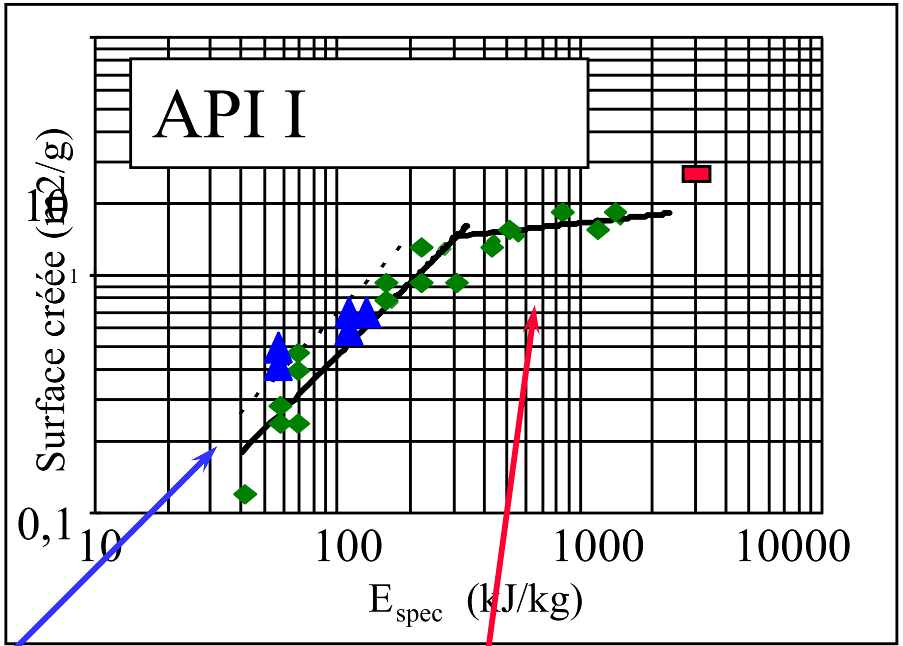
- **Impact of Energy**

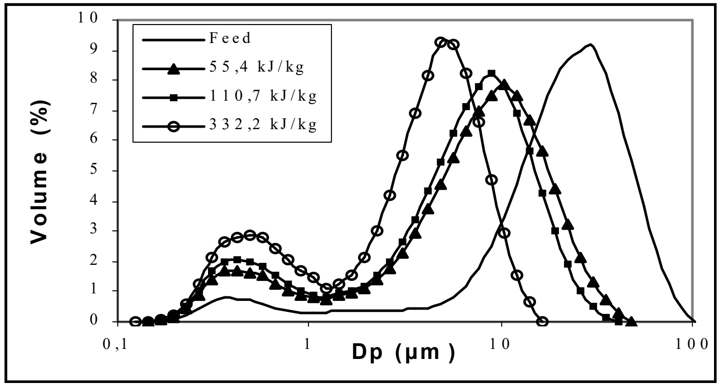
$$E_{spec} = \frac{E_c}{Q_{sol}} \approx \frac{P_{mill}}{Q_{sol}}$$

100 mm mill, N2

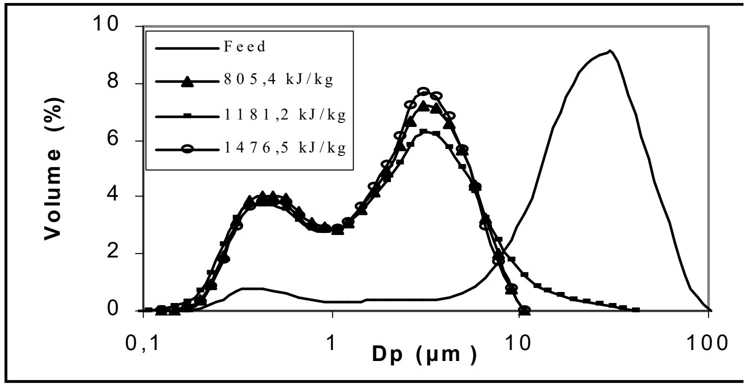
100 mm mill, He

500 mm mill, N2





Particle size distribution of product Z for low energy trials.



Particle size distributions of product Z for high energy trials.

Low energy : created Surface ~ E_{spec}, fragmentation regime

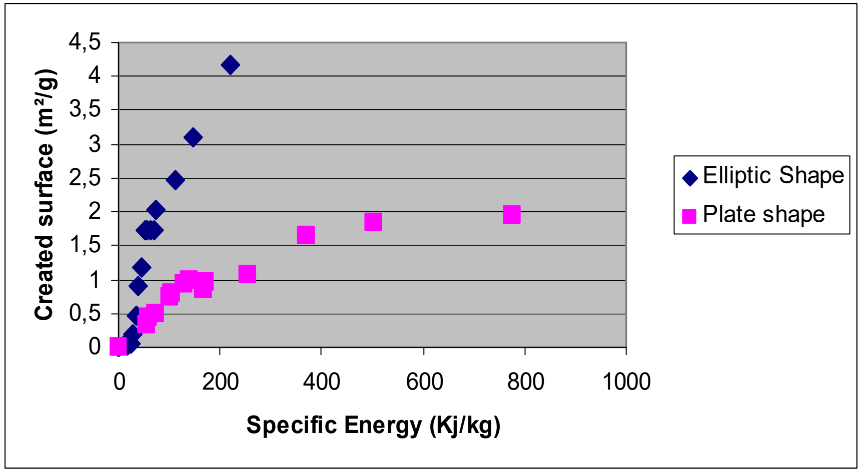
High energy : created surface ~ E_{spec}^{α}, α <<1,

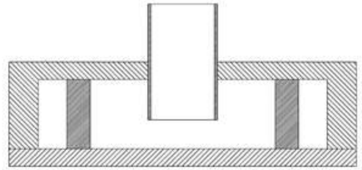
Attrition regime

Particle size reduction by jet milling:

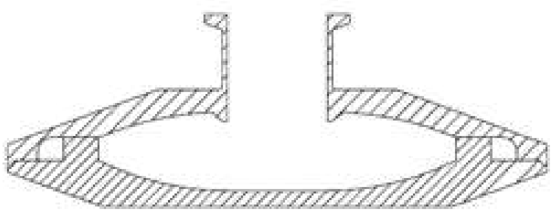
Pancake Jet mill-Parametric study

- **Impact of milling chamber shape**
  - **Ellipticale shape more powerfull than the plate one**
    - Lower Energy consumption
    - High productivity
    - Less build up





Plate



Elliptic

Role of classification?

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

- ***Dimensional analysis***

Ramanujam & Venkateswarlu correlation

$R_G = f\,(Re_b, R_M, R_d)$

- $R_G = SSA_p / SSA_f$
- $Re_{gn} = d_{gn}\, u_p / \mu_g$ (Reynolds number within grinding nozzle)
- $R_M = Q_p / Q_{gas}$
- $R_d = d_f / D_m$

$$R_G = \exp\left[K\left(R_d^{0.2}\right)\left(R_M^{p}\,\mathrm{Re}_{gn}^{q}\right)\right]$$

- ***This correlation shows a transition zone with different coefficients on each side***

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

- ***Dimensional analysis***

Sarma correlation

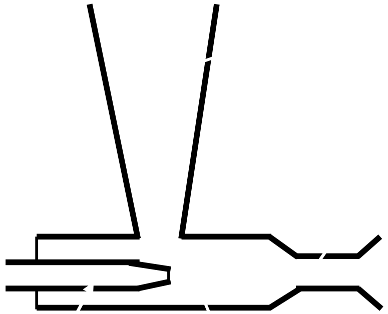
$$R_G = K\left(\mathrm{Re}_b\right)^q \left(R_M\right)^p \left(R_d\right)^s$$

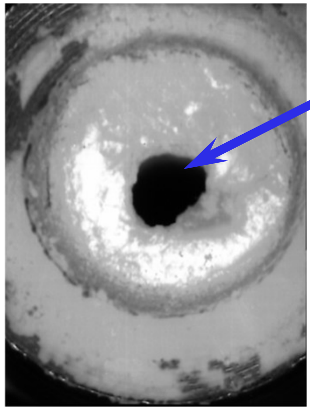
- ***The correlation was obtained from 48 trials carried out on a pancake jetmill wusing calcite.***
- ***Unlike the previous one, no transition zone was encountered.***

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

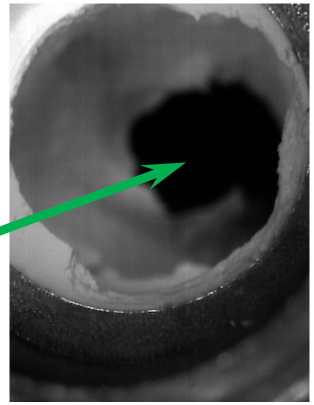
❖ *Material choice to solve adherence problems*





Stainless steel (12 min)

PTFE (37 min)



- *Venturi clogging (Product Y) : depends on the material used for the venturi*

Particle size reduction by jet milling:

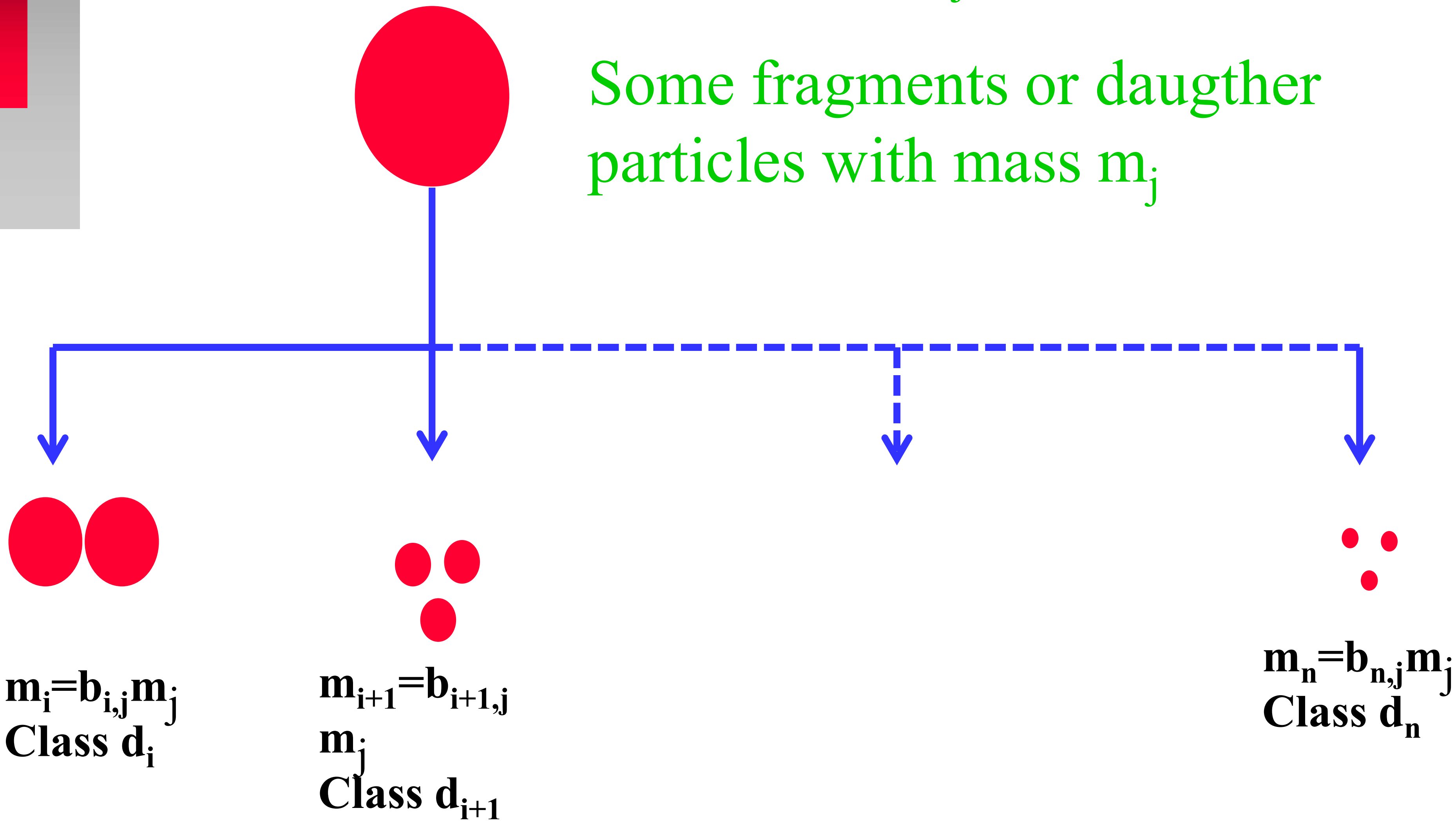
Pancake Jet mill-Parametric study

- Milling modeling and PSD prediction by using kinetic model
  - Kinetic model is based on mass-balance which uses a statistical analysis of collisions between particles, as well as for the breakage functions of the particles.
  - The method consists in dividing a particle-size distribution into several size classes indexed from 1 (coarse) to n (fine).
  - Then, two functions are defined:
    - S_i which represents the probability of breakage of particles in class i,
    - b_{ij} which represents the mass fraction of particles belonging to class j that is found after a certain milling time in class i

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

Mother particle j with mass m_j



Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

$$\frac{dw_i(t)}{dt} = -S_i w_i(t) + \sum_{j=1}^{i-1} b_{ij} S_j w_j(t))$$

w_i is the mass fraction of particles found in class i between time t and t+dt.

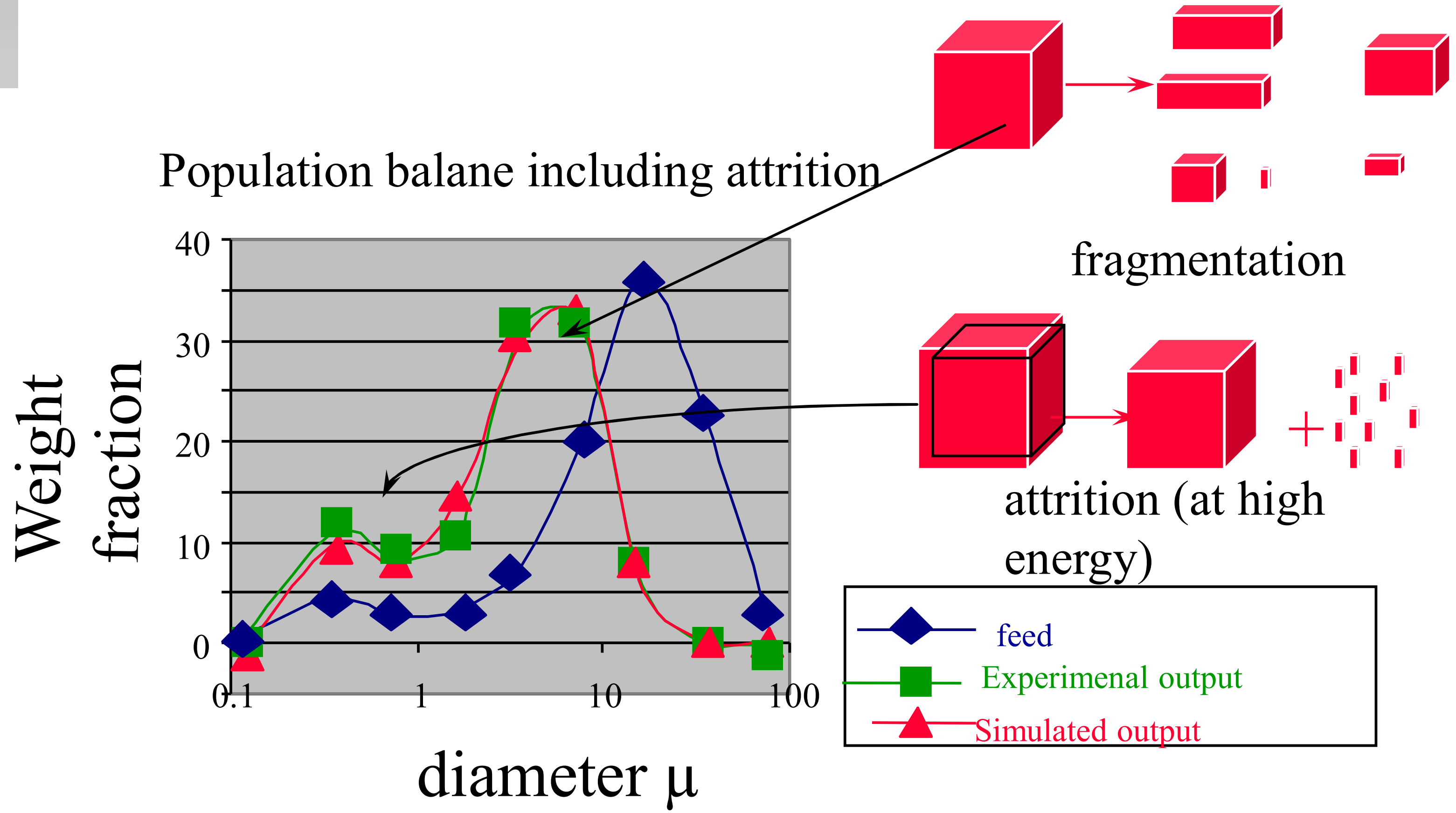
Solution of these n differential equations gives a prediction of the particle size distribution at different milling times,.

knowing the starting feed size $w_i(0)$, for given values of S_j an b_{ij}, which are determined experimentally

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

- ***Milling modelisation and PSD prediction by Population balances***



Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

- **Scale up rules:**

  Use Homothetic geometries

  $Q_{gaz} \sim D^{2}$

  $Q_{solide} \sim D^{2.2 \text{ to } 2.7}$

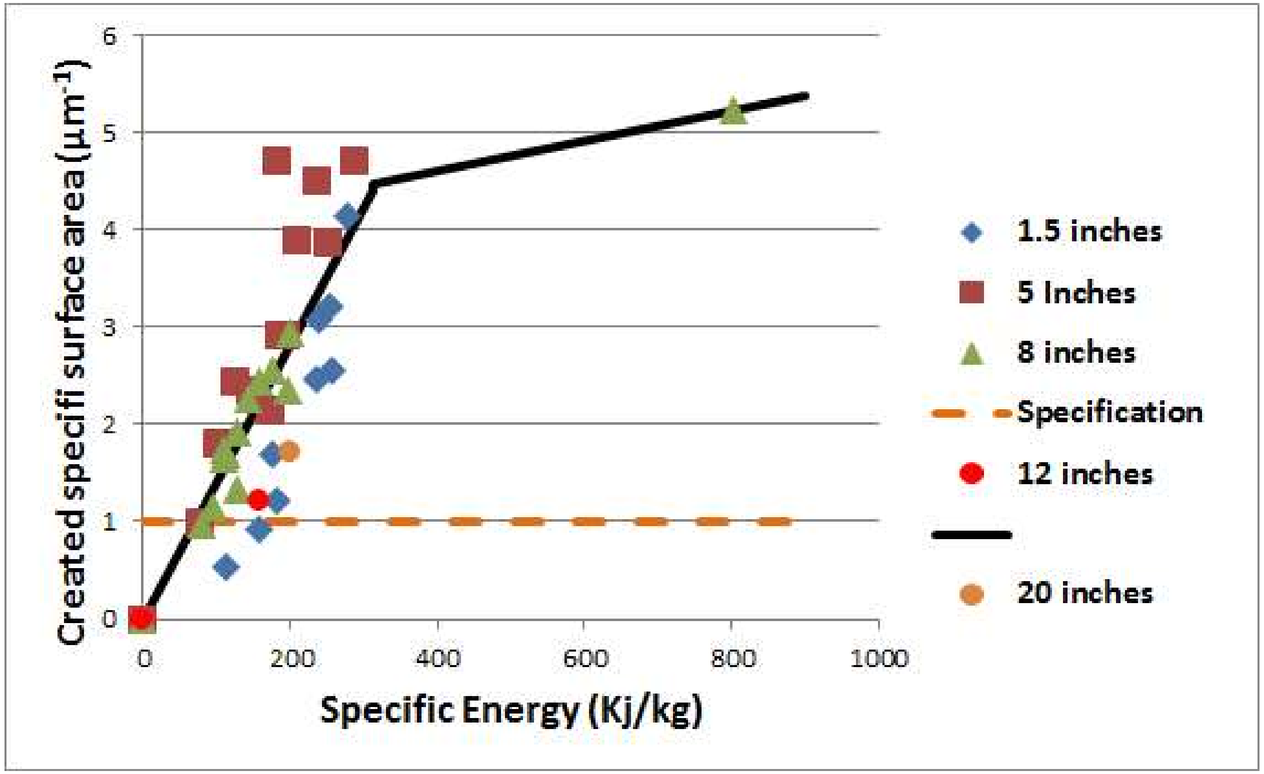
  $E_{spec} \sim D^{-0.2 \text{ to } -0.5}$

- **Rules checked from 100 to 500 mm & from 10 to 500 kg/h**

Particle size reduction by jet milling:

Pancake Jet mill-Parametric study

- Scale-up
  - Case study: Product C



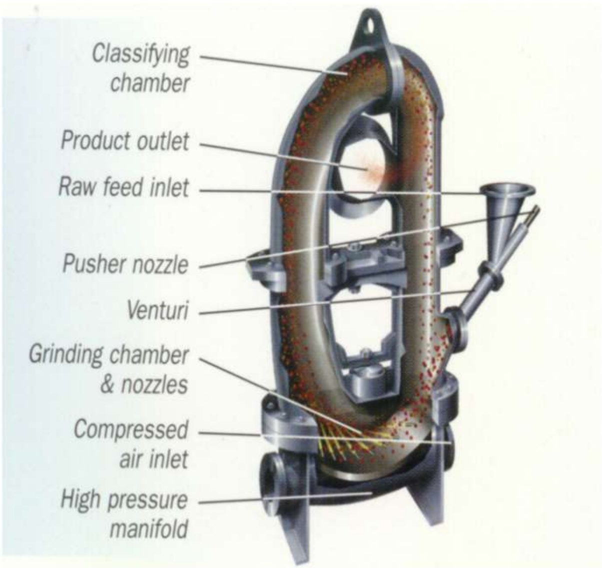
The milling profiles of different mills (1.5, 5, 8, 12 and 20 inches) led to a one master curve.

The specific energy approach is a very good scale-up's marker.

The scale-up factor between 1.5 inches and 20 inches is about 186 (130 kg/h for 20 inches and 0.7 kg/h for 1.5 inches)

Particle size reduction by jet milling:
Loop jet mill

- *Milling Zone at the bottom part*
- *Classification zone at the top part*
  - *The big particles will stay within the mill. They will go back to the milling zone.*
  - *The fine particles are ejected through the product outlet*



Particle size reduction by jet milling:

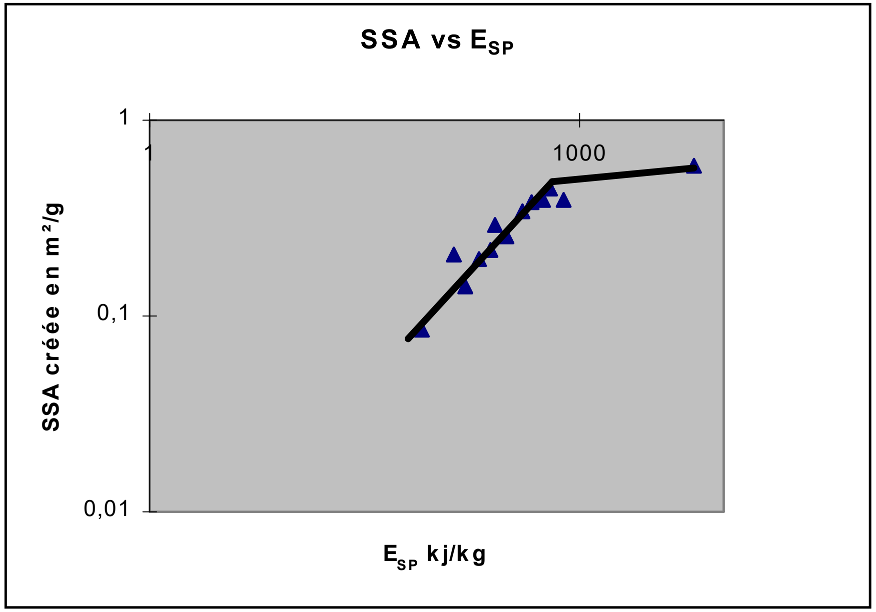
Loop jet mill_Parametric study

- **Key parameters**
  - Number of the nozzles
  - Nozzles diameter
  - Type of the nozzles (convergent vs convergent-divergent vs straight)
  - Gas type
  - Grinding pressure
  - Solid flow rate

Particle size reduction by jet milling:

Loop jet mill_Parametric study

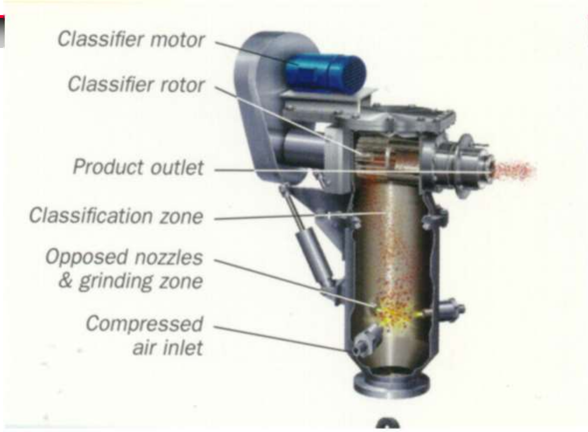
- **2 milling regimes**
  - **Low pressure : fragmentation**
  - **High pressure : attrition**
- **The created surface depends mainly on the specific energy.**

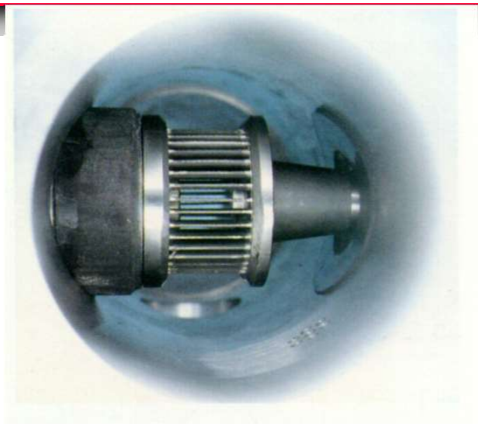


$$E_{sp} = \frac{E_{cin}}{Q_{solide}} \propto \frac{P_{abs}}{Q_{solide}}$$

Particle size reduction by jet milling:

Fluid bed jet mill





Principle:

- *The jet mill is composed of a milling chamber and a dynamic selector*
- *The milling chamber is composed of fluidization bed equipped with 3 nozzles positioned in order to have convergent jets toward the center of chamber where the milling take place*
- *The big particles will stay within the mill. They will go back to the milling zone.*
- *The fine particles are ejected through the dynamic selector (squirrel cage)*
-

Particle size reduction by jet milling:

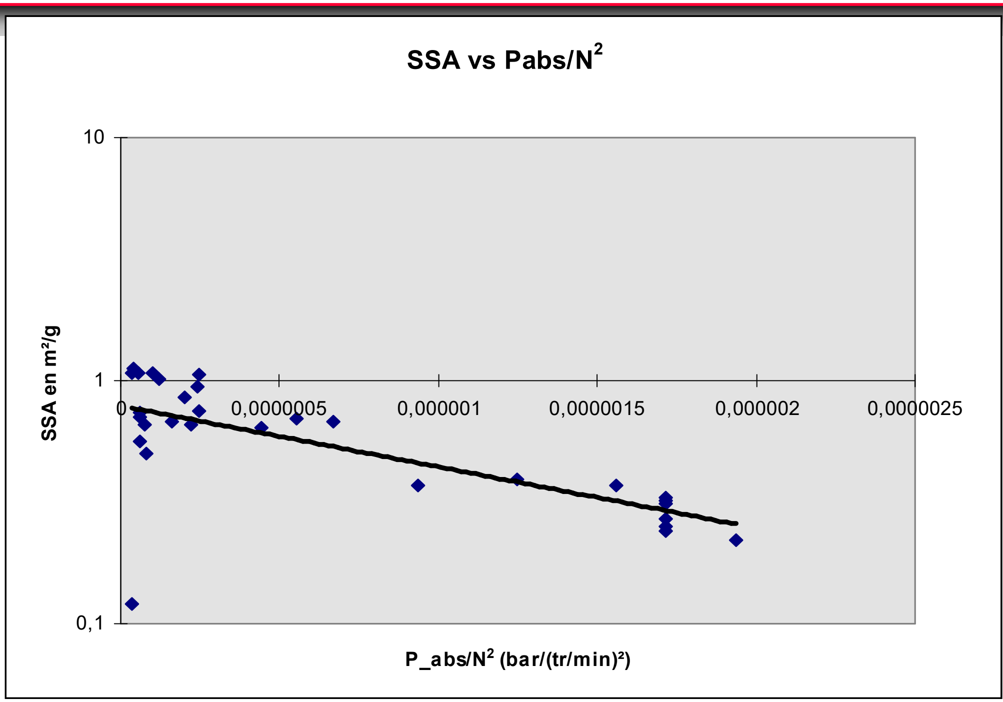
Fluid bed jet mill: Parametric study

Key parameters :

- *Grinding pressure*
- *Selector rotation speed*
- *Solid flow rate*
- *Nozzles diameter*
- *Type of the nozzles (convergent vs convergent-divergent vs straight)*
  - *Gas type*
  - *Grinding pressure*
  - *Solid flow rate*

Particle size reduction by jet milling:

Fluid bed jet mill: Parametric study

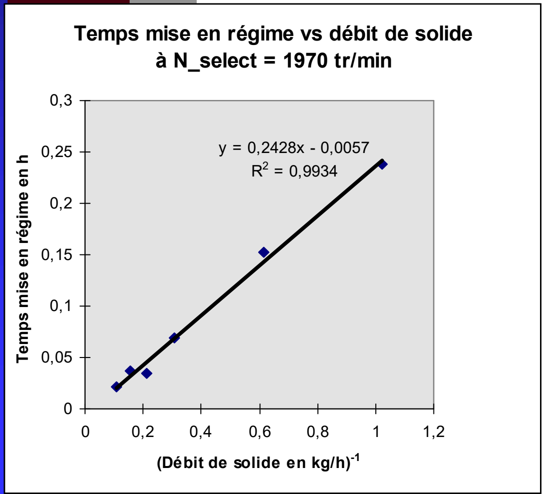


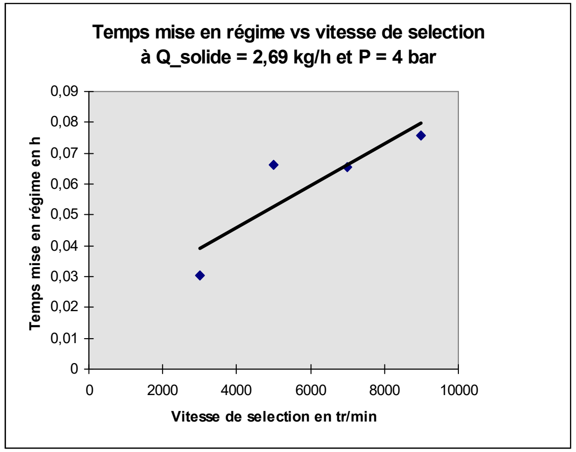
$$SSA = Cte \ at \ \frac{P}{N^2} = cte \, ; \frac{P}{N^2} \propto \frac{Drag \ forces}{Centrifuge \ forces}$$

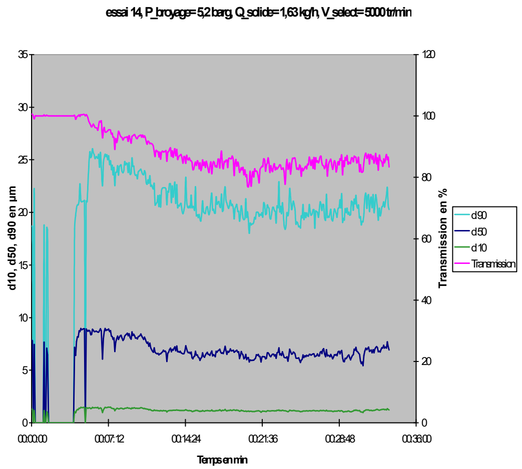
- **The physical quality of the milled product is mainly driven by the selector performances and the gas flow rate.**

Particle size reduction by jet milling:

Fluid bed jet mill_Parametric study



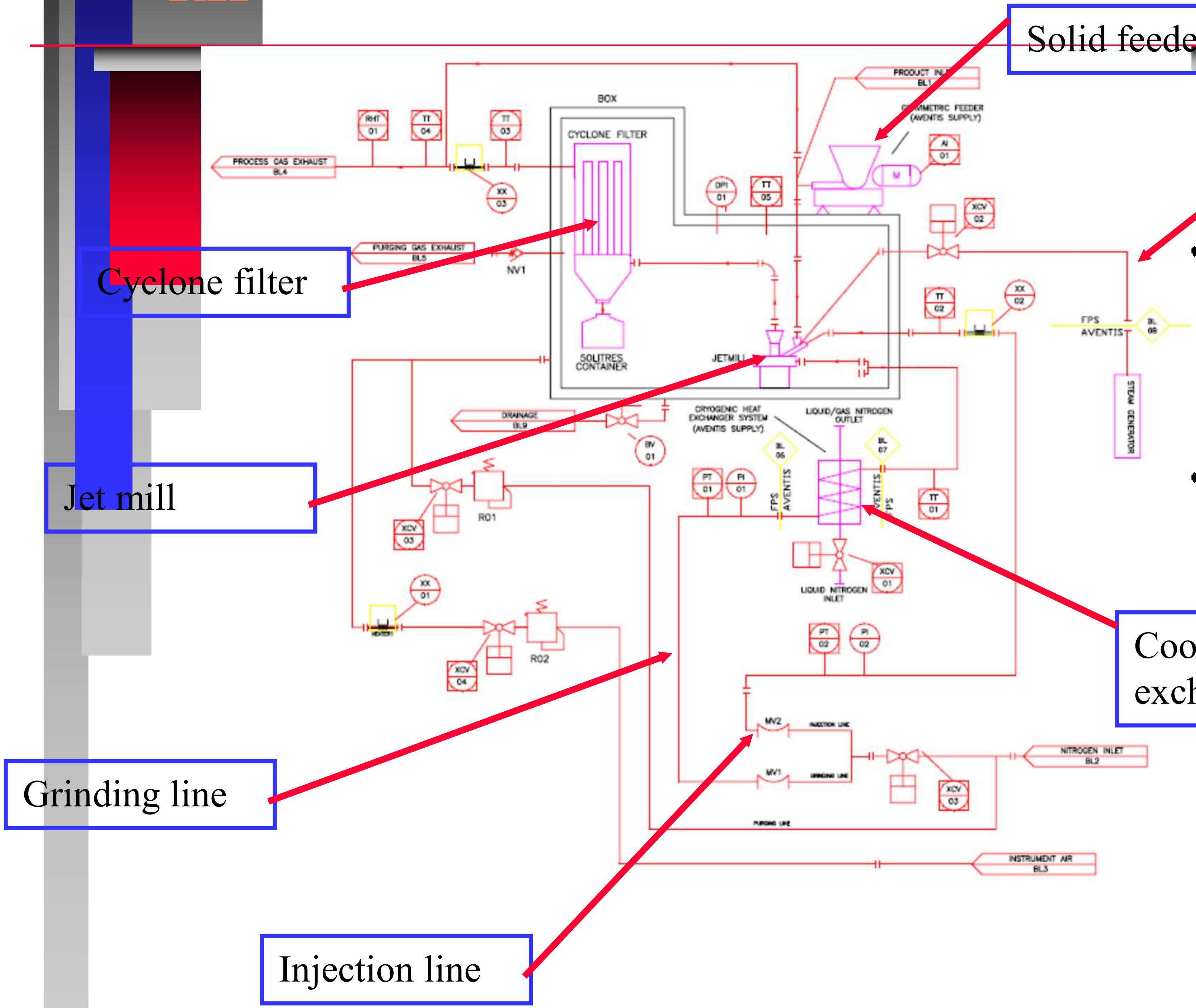




- *High hold-up within the mill (approx 240 g)*
- *Long time to reach the steady state (f(flow rate, Rotation speed of the selector))*
- *High variability of the physical quality of the milled product during processing*

Particle size reduction by jet milling:

Specific technologies_Cryogenic jet milling or jet milling under RH



- ***Cryogenic jet milling (T< -20° C)***
  - ***Enhancement of jet milling performances***
  - ***Amorphization (T< Tg)***
- ***Micronisation under HR***
  - ***Avoid the amorphisation (Tg < T)***

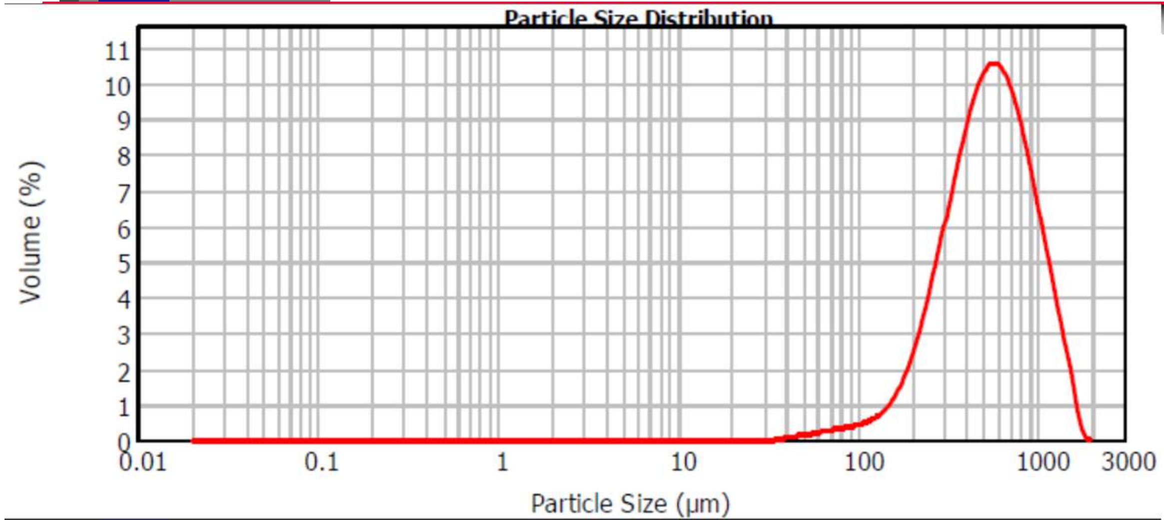
Particle size reduction by jet milling:

Specific technologies_Cryogenic jet milling or jet milling under RH

- **Micronisation at low temperature**
  - avoid the risk of melting low-melting materials
  - make fragile soft or ductile materials
  - Improve amorphization process (T<Tg)
- **Micronization under controlled relative humidity**
  - The objective of micronization under controlled HR is to avoid amorphization of the API during jet milling
  - Jet milling takes place between 50-90 % RH within chamber.
  - Pure superheated steam is introduced (to avoid condensation) at the venturi, where it is mixed with the preheated feed gas typically in the range 40-50 ° C (as is introduced much steam at the venturi it is necessary to overheat the gas to avoid condensation).
  - The flow of steam is controlled by a pump which introduces the liquid water into the boiler. Moisture is controlled by an HR probe at the output of the system.

Particle size reduction by jet milling:

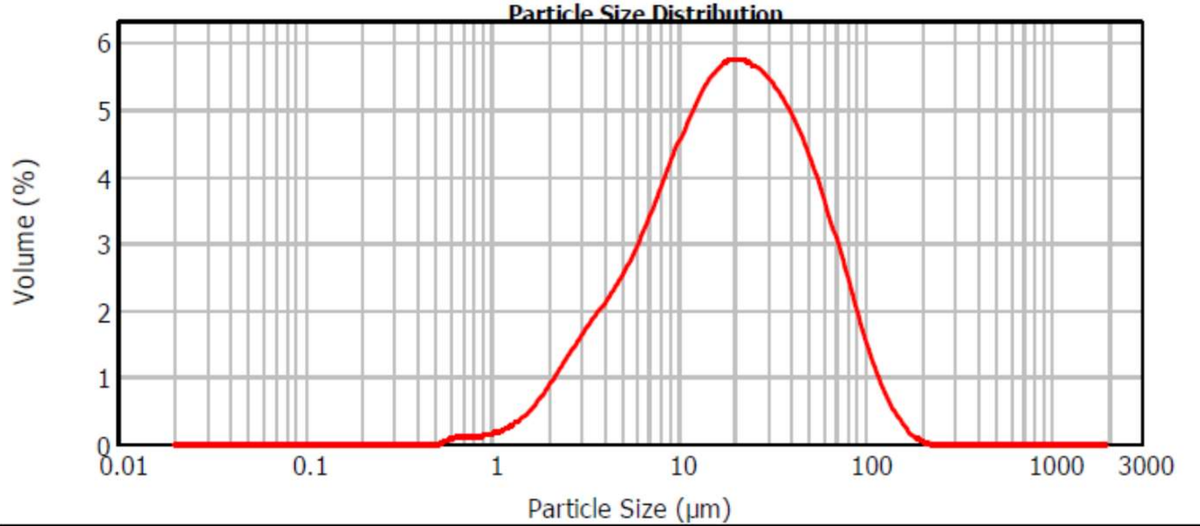
Specific technologies_Cryogenic jet milling or jet milling under RH



d10 = 244.6 µm d50 = 540.7 µm d90 = 1071.4µm

Koliphor P407
Polymer exhibiting plastic behavior
Cannot be milled at RT

Loop jet mill @ -130°C



d10 = 4.3 µm d50 = 19.0 µm d90 = 64.3 µm

Technologies comparison

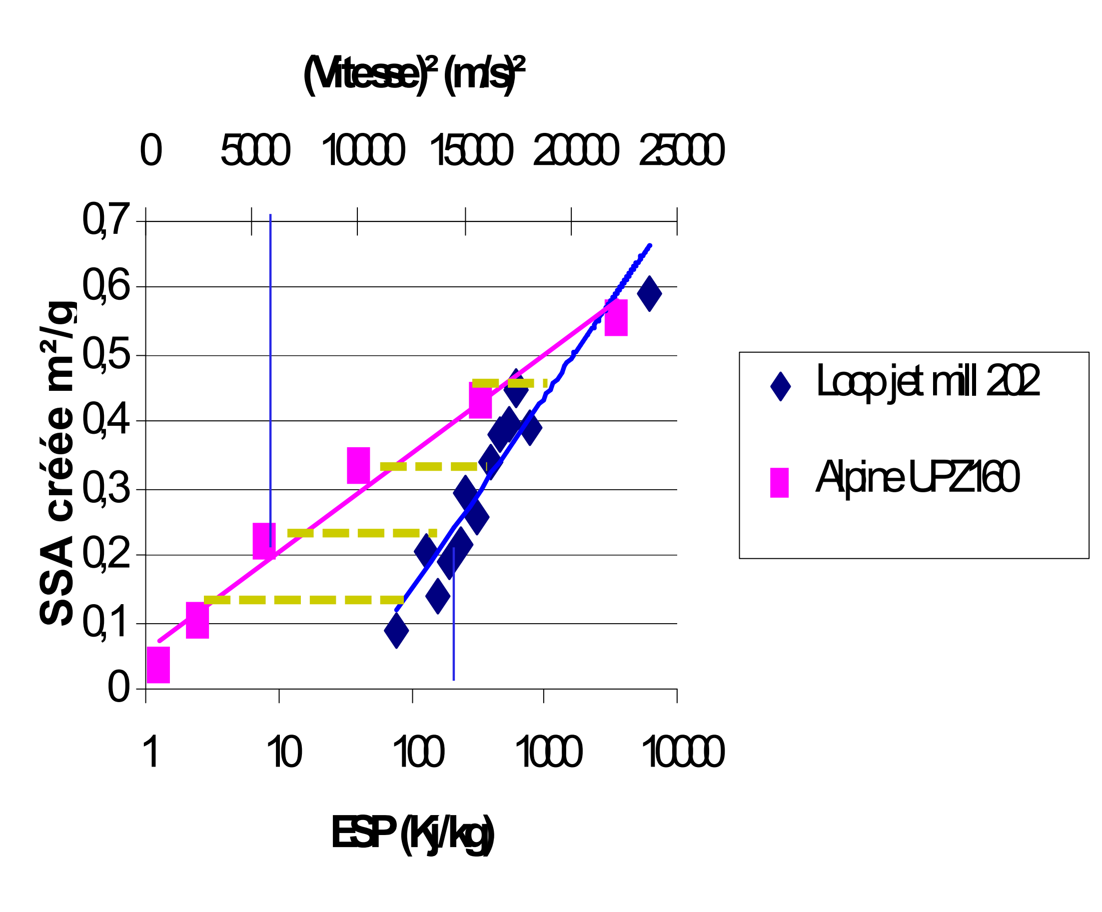
Particle size reduction :

Technologies comparison

- *Pancake vs loop jet mill : The pancake jet mill leads to a finer milled product (d50 < 10 µm) than the loop jet mill (d50 ≥10µm)*
- *In same cases a narrow particles size distribution could be obtained by pin mill or loop jet mill*
- *The loop jet and the pin mill could have an overlapping in terms of milling performances. In this case the loop jet mill has to be used as first intention (easy cleaning, easy maintenance etc…)*
- *The pin mill has to be preferred to hammer or paddles mill because he is less sensitive to clogging (No grid)*
- *The fluid bed jet mill has to be avoided (High variability of the physical quality of the milled product, complex maintenance, complex cleaning*
- *The hammer mill to be used for cryogenic milling which require high residence time*

Particle size reduction:

Technologies comparison_ loop jet mill vs Pin mill



Loop jet mill: the important parameter is the specific energy

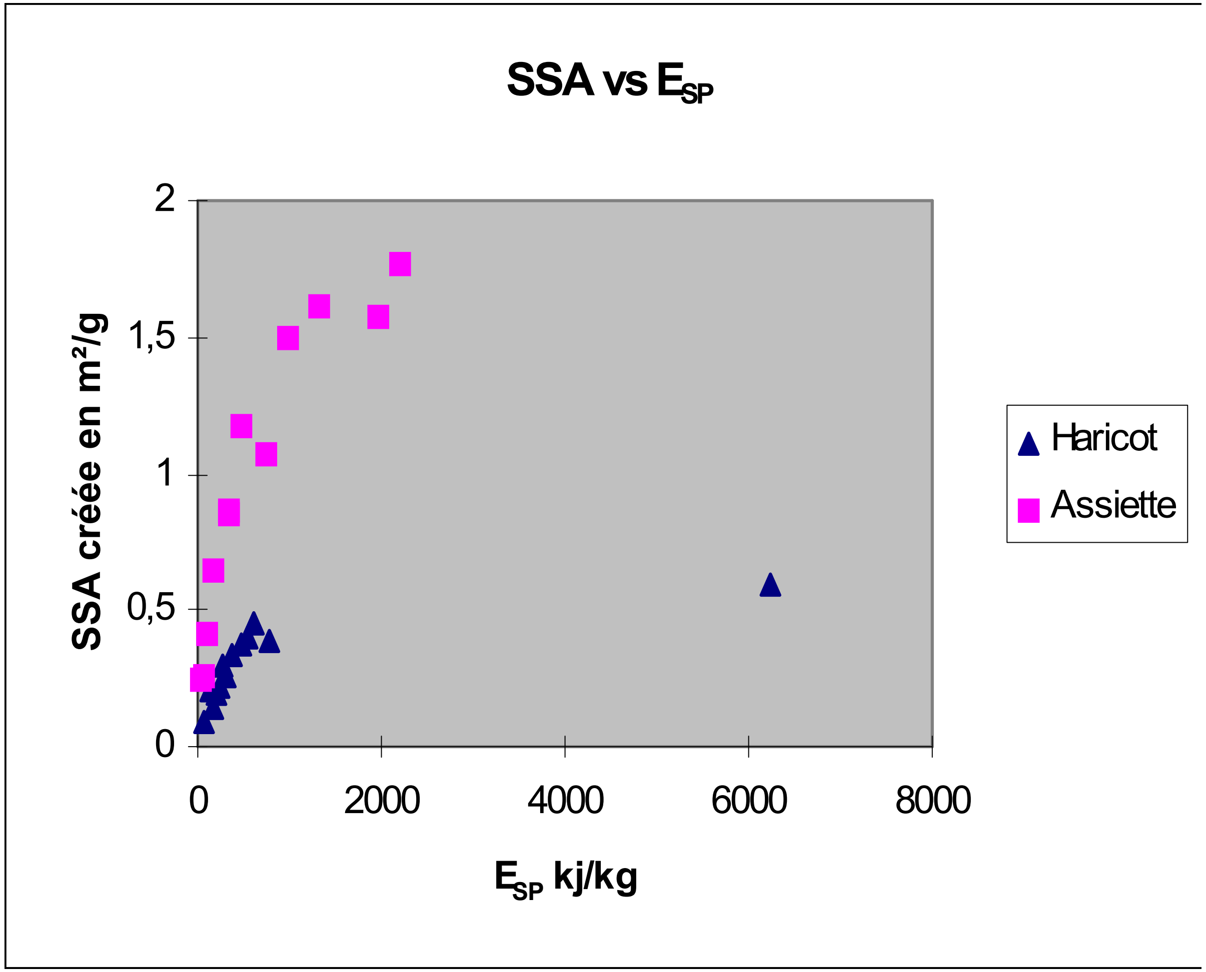
Pin mill: the important parameter is the (tip speed)²

Loop jet mill can lead to equivalent specific surface area than pin mill

Loop jet mill doesn’ required any complex maintenance plan

Particle size reduction:

Technologies comparison_ loop jet mill vs Pancake jet mill



Pancake Jet mill is able to produce much higher created specific surface area

Methodology

Particles size reduction:

Milling studies Planning during development

- **Pre-clinical phase:**
  - Basic data acquisition at miniature scale
  - Feasibility study at lab scale
  - As function of the targeted particle size the technology is selected
  - Parametric study :
    - impact of different process parameters on the physical quality of the API (PSD, SSA, apparent density, flowability, shape, etc….)
    - Impact on drug product quality attributes (Physical properties, biopharmaceutical properties)
  - Physical stability study
    - Monitoring of PSD or SSA at different relative humidity ((0, 60, 75/80 % RH) and ambient temperature during 1 week, 2 months and 3 months.

Particles size reduction:

Milling studies Planning during development

- *EHS study*
  - ***Operator protection***
  - ***Environment protection***

❖ **Before phase IIb:**

- *Technical trials at pilot scale*
- *Manufacturing of techno-batches*
  - ***Different particles size distribution***
  - ***Impact on drug product quality attributes (Physical properties, biopharmaceutical properties)***
  - ***Target or specification set up***
- *Manufacturing of GMP batches according the fixed target or specification*
- *Industrial transfer*

Particle size reduction:
Methodology of milling or jet milling

- Characterization of unmilled product (SSA, PSD, density, DSC, microscopy…)
- As function of the target particle size : selection of parameters to be tested according the suitable technology
- To perform the parametric study – ideal case

- **Mechanical milling :**
  - To study the impact of the rotation speed on the PSD / SSA
    - Milling using 3 or 5 levels of rotation speed at constant solid flow rate
  - To study the impact of the solid flow rate speed on the PSD / SSA (less important)
    - Milling using 3 or 5 levels of solid flow rate at constant rotation speed
  - Plot created SSA vs (rotation speed)2 and slid flow rate using 3D digaramm

Particle size reduction:
Methodology of milling or jet milling

- **Jet milling:**
  - Study the impact of grinding pressure on the PSD / SSA
    - Milling using 3 or 5 levels of grinding pressure at constant solid flow rate
  - Study the impact of solid flow rate on the PSD / SSA at constant pressure
    - Milling using 3 or 5 levels of slid flow rate at constant grinding pressure
  - Plot created SSA vs (P+1)/Q

❖ Observation of the build –up within the mill

❖ Characterization of milled product (SSA, PSD, density, DSC, microscopy…)

❖ Stability evaluation of the milled product

Particle size reduction:
Methodology of milling or jet milling

- ***When the process has reached a certain "maturity", realisation of techno-lots, with product from pilot plants (possibly supplier) close to industrial technology :***
  - ***batches with different PSD***
  - ***Robustness of upstream step ?***
  - ***Different suppliers ?***
  - ***Impact on expected usage properties***
  - ***Allows the choice (or tuning) of the target or specification***
- ***With well defined objectives/specifications, before transfer to industrial units :***
  - ***Include long duration trial with definitive set-up***

Particle size reduction:
Methodology of milling or jet milling

- **Finalisation of the study :**
  - **Development report**
    - Recommended technology
    - Domain studied,
    - Laboratory operating procedure for the manufacture batch record
    - Recommended operating range
    - Difficulties encountered (including materials compatibility)
    - Unstudied points still to be considered
  - **Safety study**
    - A document formalized between the donor and receiver is mandatory, informing him of all the risks associated with the process.
  - **For a commercial or clinical use :**
    - Quality agreement
    - Technical agreement

Particle size reduction:

Mechanical milling: Value chain

50 mm pin mill

(Btach size: 50 g

- Support to candidate selection and formulation screening

- PK and tox batches manufacturing

100 mm pin mill

Batch size: 100 up 1000 g)

- Process development,
- GLP tox Batch
- Technical and GMP batches

150 mm pin mill

Batch size: Up to 30 kg)

- Process tuning and scale-up activities
- Commercial manufacturing

Particle size reduction:

Mechanical milling: Value chain

1.5 inches or Qmill 0 jet mill

(Btach size: Up to 10 g

•Support to candidate selection and formulation screening

•PK and tox batches manufacturing

4 inches or Qmill 1 Jet mill

Batch size: up to 3 kg)

•Process development,

•GLP tox Batch

•Technical and GMP batches

≥ 8 inches or ≥ Qmill 2

Batch size: Up to 30 kg)

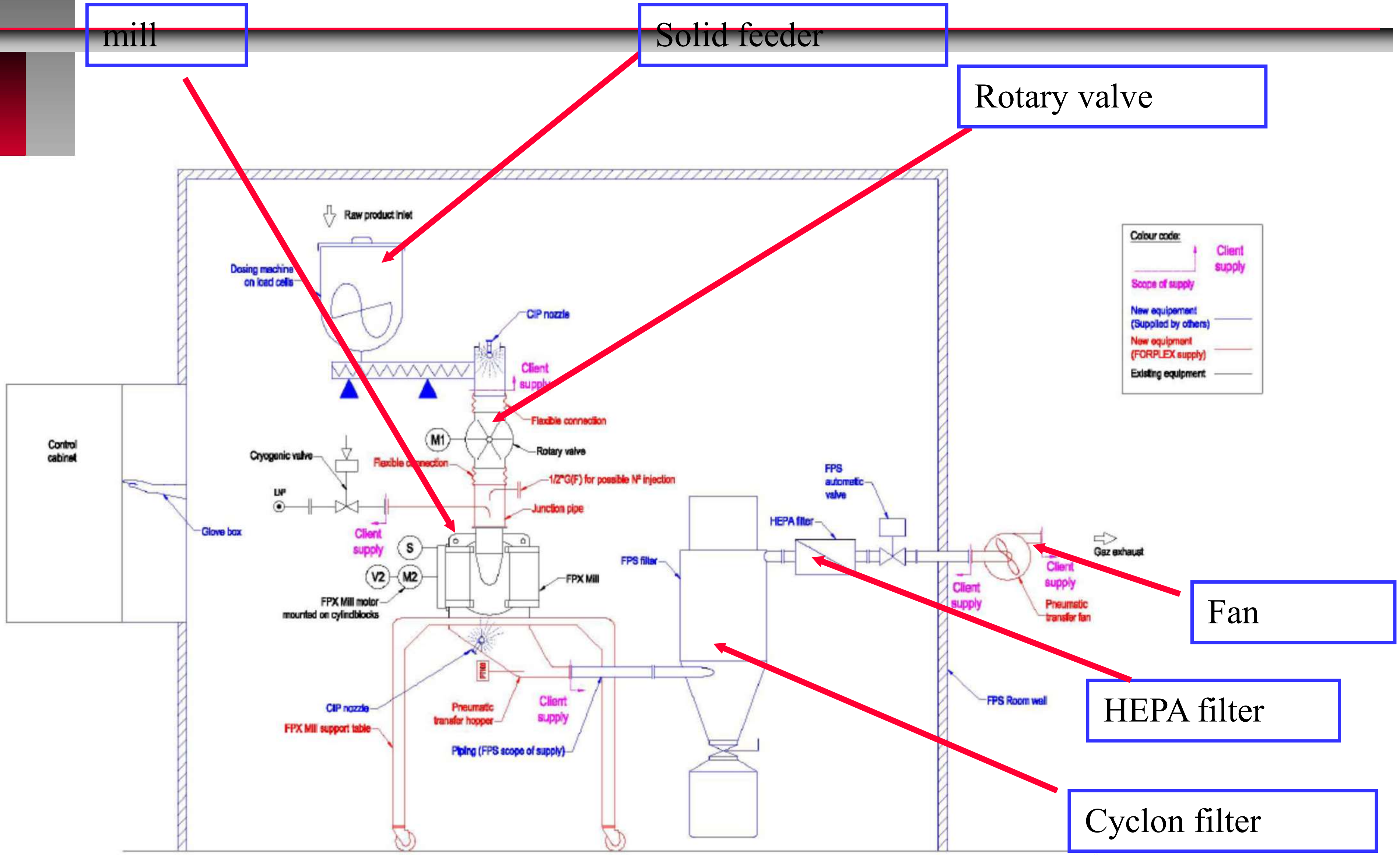
•Process tuning and scale-up activities

•Commercial manufacturing

Mill and jet mill environment

Particle size reduction:

Mechanical milling: Global configuration



Particle size reduction:
Solid feeding

❖ *Vibrating channel*

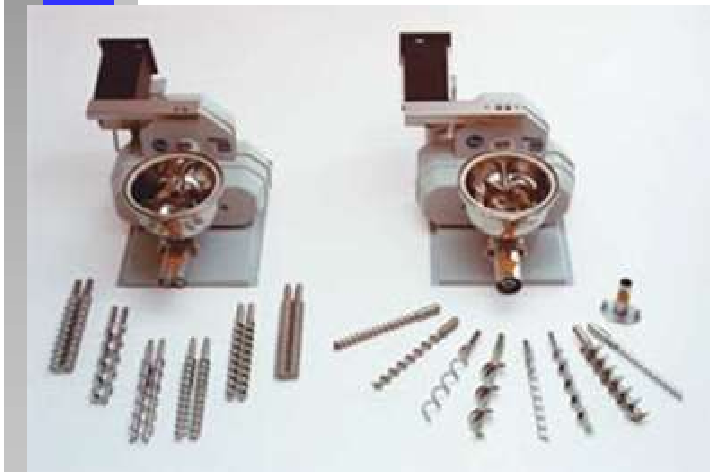
- *Suitable for a product having good flowabailty.*
- *Gravimetric feeder is preferable for jet milling as the solid flow rate is in relationship with specific energy*
- *The volumetric feeder could be used for mechanical milling as the impact of the solid flow rate on particle size is not significant.*

Particle size reduction:

Solid feeding

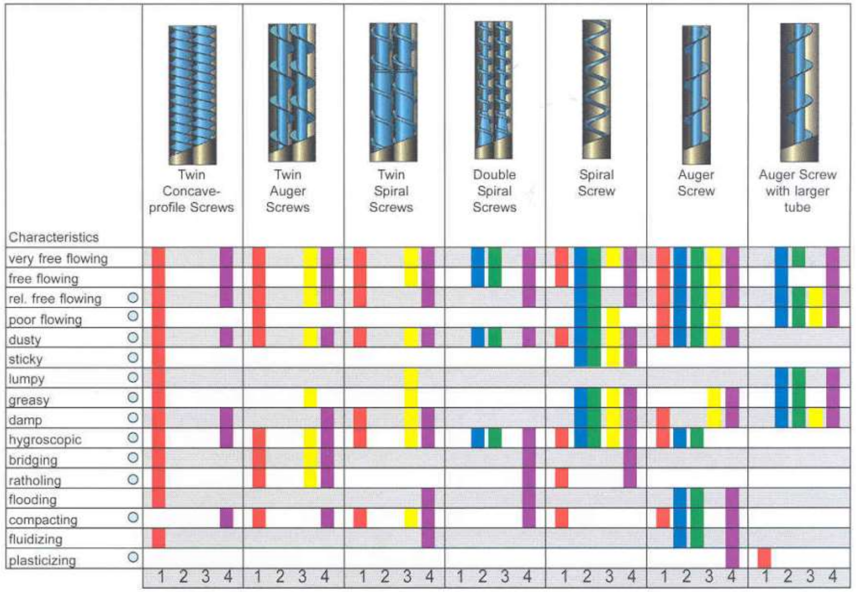
❖ Screw feeder

- ***The selection of the screw will depend on the physical quality of unmilled product***



Exchangeable Feed Screws in Single and Twin Screw Feeders

The table at right provides a rough classification of bulk material characteristics suitable to certain types of screw designs. Where flow characteristics are unkown or inconsistent, feeding tests are recommended.



Legend: 1 Powder; 2 Pellets; 3 Granules; 4 Fibers; 5 Flakes; ○ requires agitator

A colored dot in the table means: essentially suitable

Digi-Drive® is the world's first digital volumetric control. It's easier to use, improves feeding accuracy, and extends motor life.

Particle size reduction:
Solid feeding

Agitated hopper (positive cone)

Agitated hopper Negative cone): Prevent arching

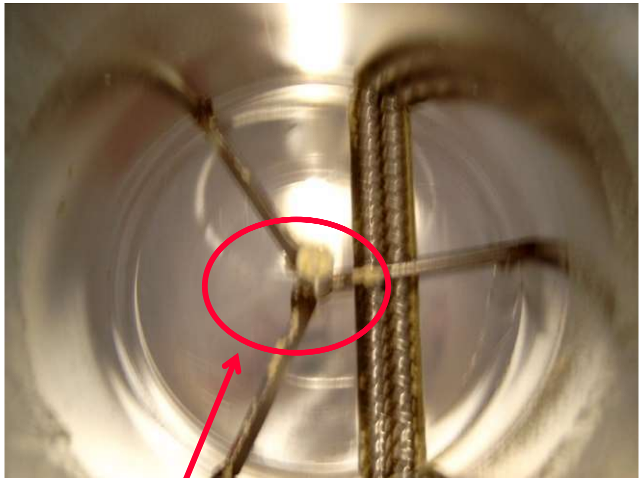
Lid equipped with vertical

Agitator

Particle size reduction:

Solid feeding

- ***Flat bottom is preferable in order to minimize the hold-up***



Hold-up

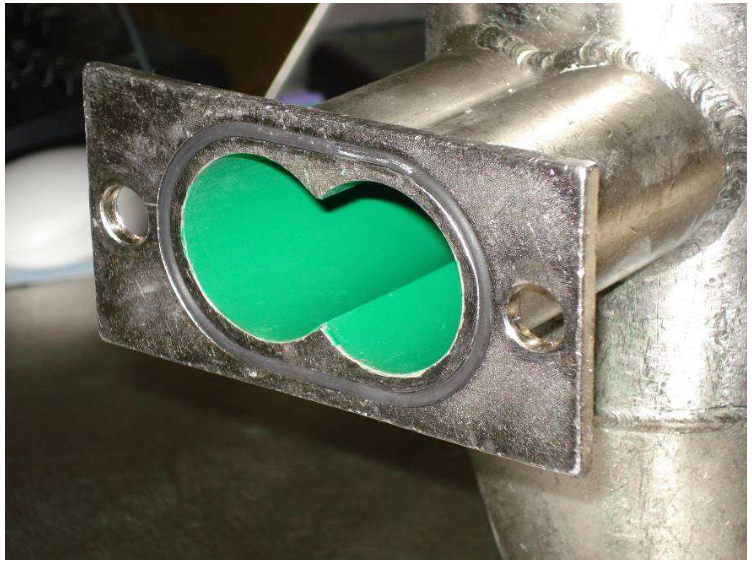
Particle size reduction:

Solid feeding

- ***Problem : melting of the product, blocking of the screws after 5 minutes run***
- ***A working solution :***
  - ***Surface coating on feeding pipe:***

    Non sticking polymer coating (FDA approved)

    Tuned screws



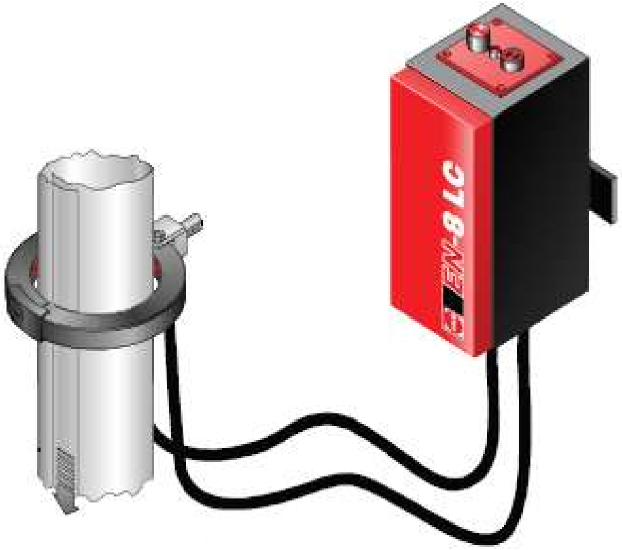
Particle size reduction:

Solid feeding

Static electricity:

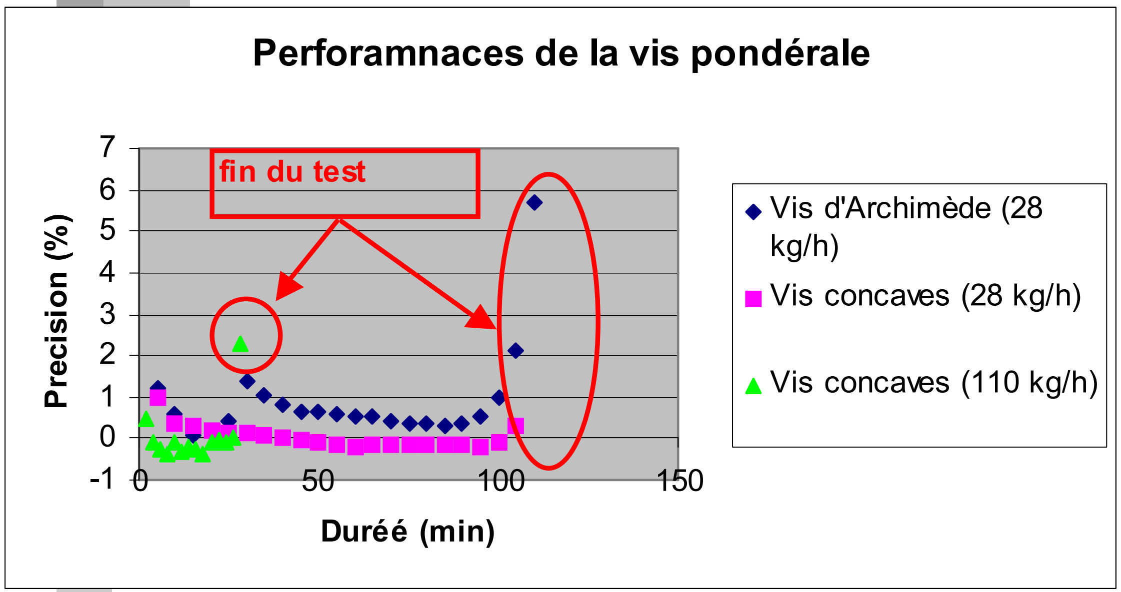
- *On-line discharge*

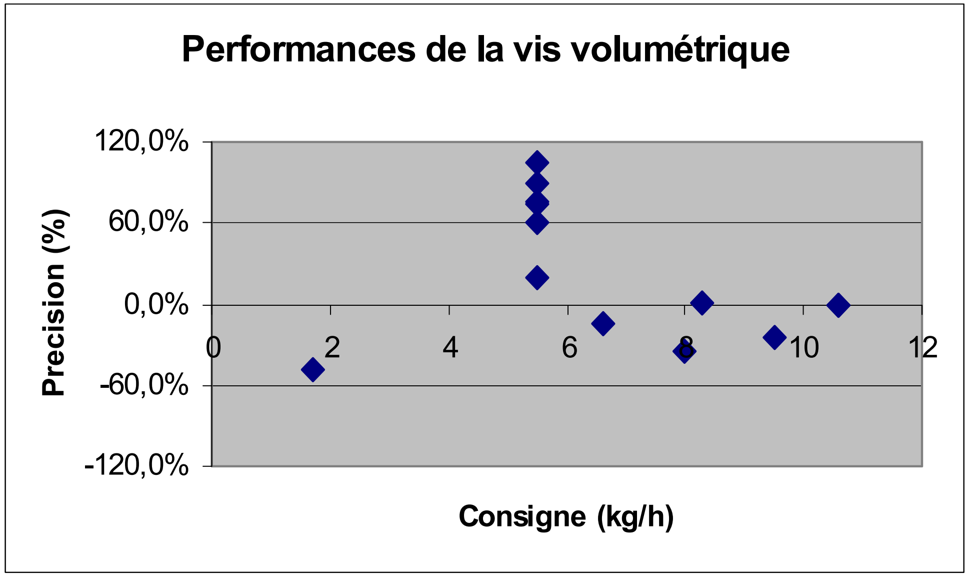
HAUG Ionisation – zur Beseitigung elektrostatischer Ladungen



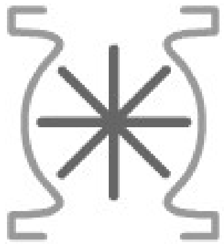
Particle size reduction:
Solid feeding

- ***The gravimetric feeder leads to high accuracy and consequently to better control of the solid flow rate and the productivity***





Particle size reduction:
Solid feeding



❖ Rotary valve

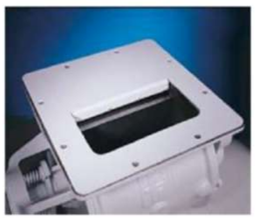
- *Suitable for a free flowing material.*
- *To be used only at the inlet of mechanical milling or the outlet of the cyclone filter*
- *Suitable for mill which is sensitive to overfeeding*
- *Different option for the rotary valve rotor*

Closed End Rotor

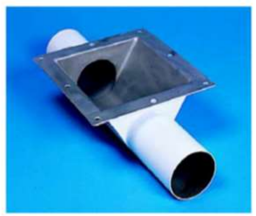
Removable Wear Bars

Shallow Pocket Rotor

Beveled Rotor Blades



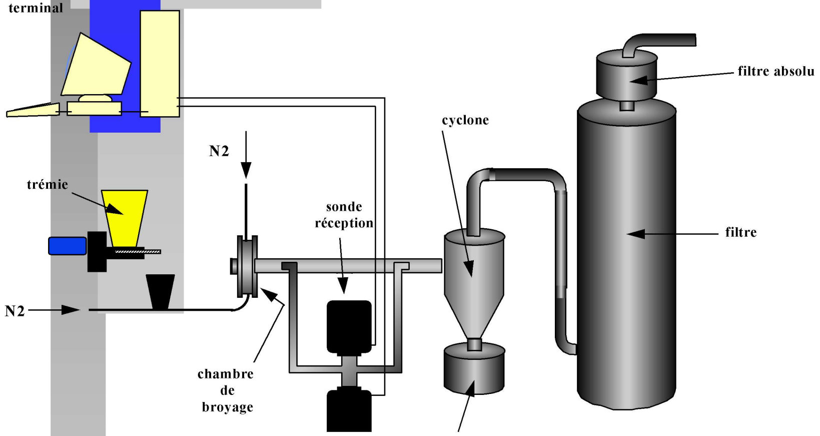
Inlet Baffles



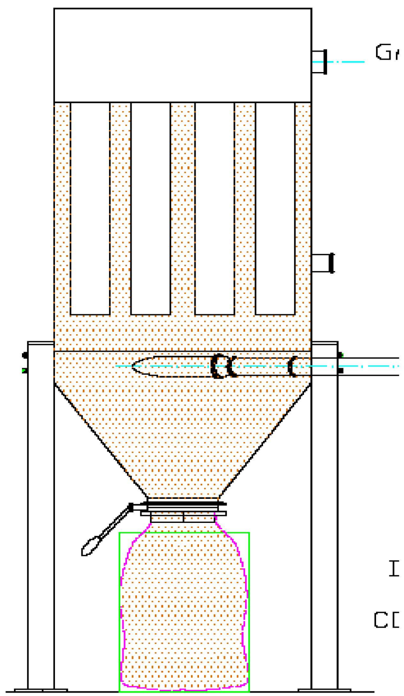
Drop Through Adaptors

Particle size reduction:

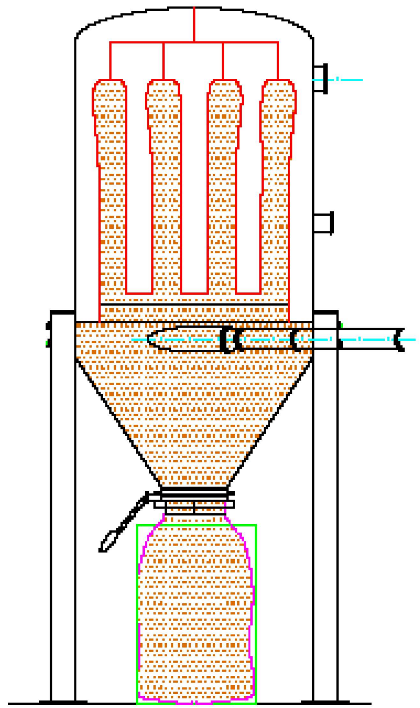
Milled product recovery



Combination of cyclone and cartridge filter



Cartridge filter



Filter sleeve "Octopus"

Particle size reduction:

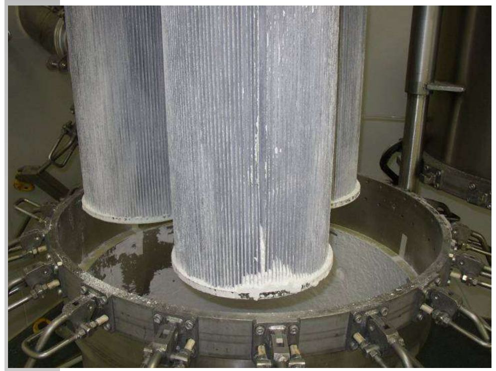
Milled product recovery_Cyclone combined with cartridge filter

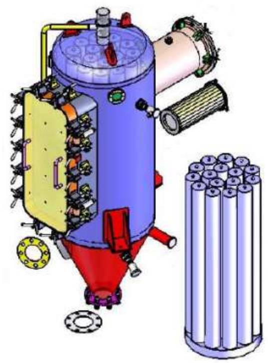
- ***2 fractions of milling product to be handled***
  - ***Coarse particles recovered at the bottom of the cyclone***
    - ***Will depend on the cyclone performances***
  - ***fines particles recovered at the bottom of the cartiridge filter***
- ***Impact of milling yield***
- ***Will required mixing step for the 2 fractions***

Particle size reduction:

Milled product recovery_Cartridge filter

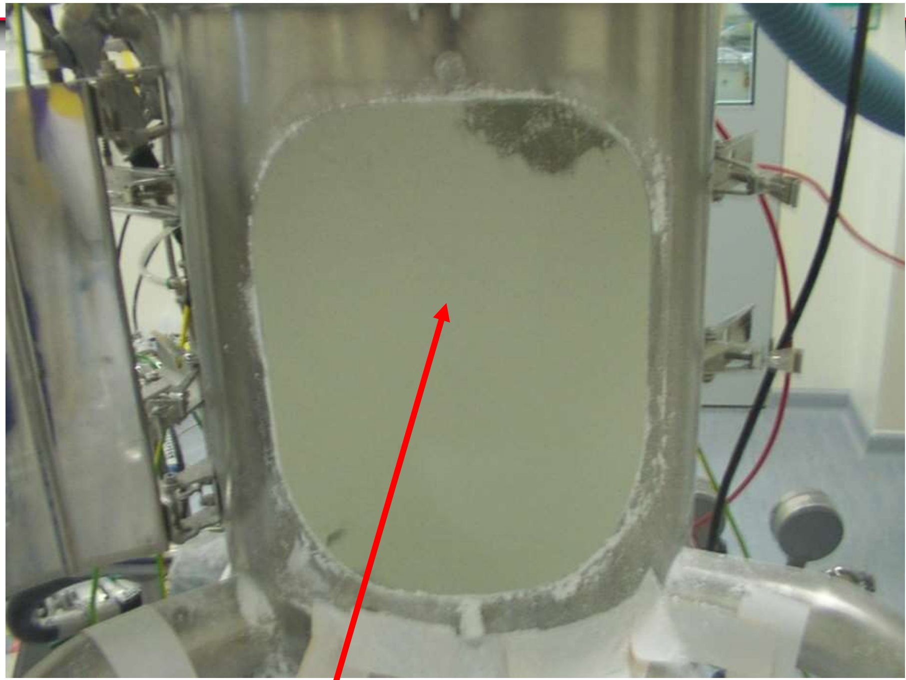
- ***The most usual filtration systems are :***
- ***Sleeve filters :***
  - *Cleaning by shaking*
  - *Number of sleeves dependant of product characteristics*
  - *Better yield (low deposit on the filter)*
- ***Cartridge filters***
  - *Separation by gas back-pressure*
  - *better surface/volume ratio*
  - *For filter sleeves, the type of cloth is more critical :*
    - *Strong mechanical constraints*
    - *Metallic fibres used*





Particle size reduction:

Milled product recovery_Cartridge filter



Inlet of the cyclone filter

Inside of the cyclone filter

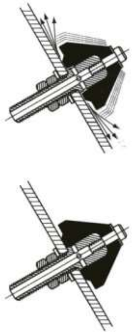
- *Milling yield impacted by the hold-up*
- *hold up mainly due to the build up*
- *Not suitable for sticky material*

Particle size reduction:

Milled product recovery_Cartridge filter

PHASE SOUS PRESSION

PHASE HORS PRESSION

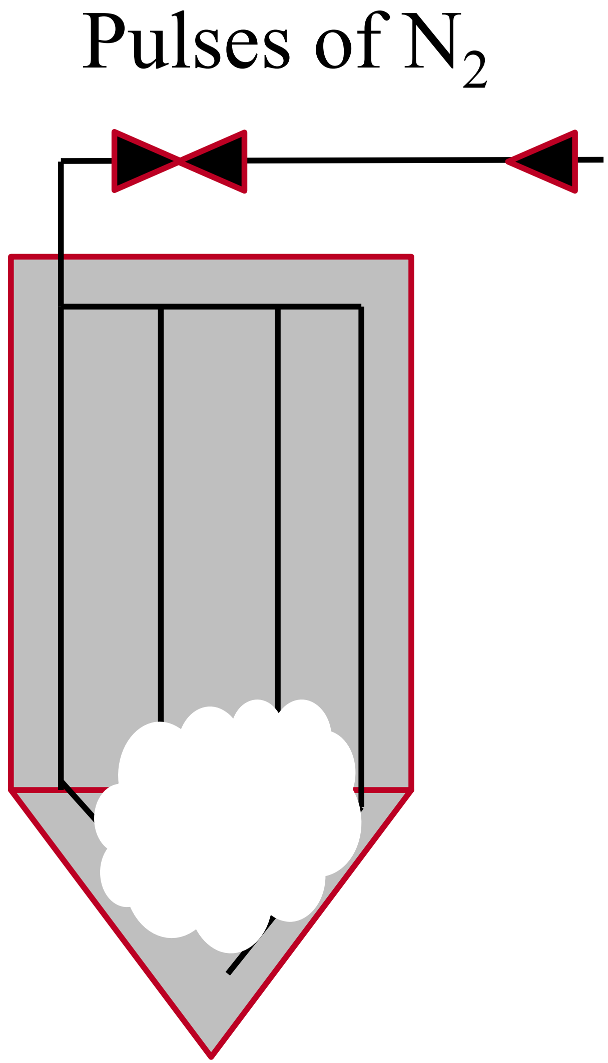


- **Silos can be equipped with rotary valves**
- **When designing the unit, don't forget the conditioning step :**
  - *In containers, no feed-rate limit*
  - *In drums, take into account the drum change, 6 to 10 minutes x 25 kg, so a productivity maximal of 100 to 120 kg/h*
- **Hoppers can be equipped with flowability aids systems to improve the flowability, however, trials need to be performed to see if the product is not compacting under constraint (pneumatic vibrator), in that case, aerating is needed :**

Particle size reduction:

Milled product recovery_Cartridge filter

❖ ***Improvement of flowability : Gas pulsing***



Particle size reduction:

Milled product recovery_Sleeve filter « Octopus »

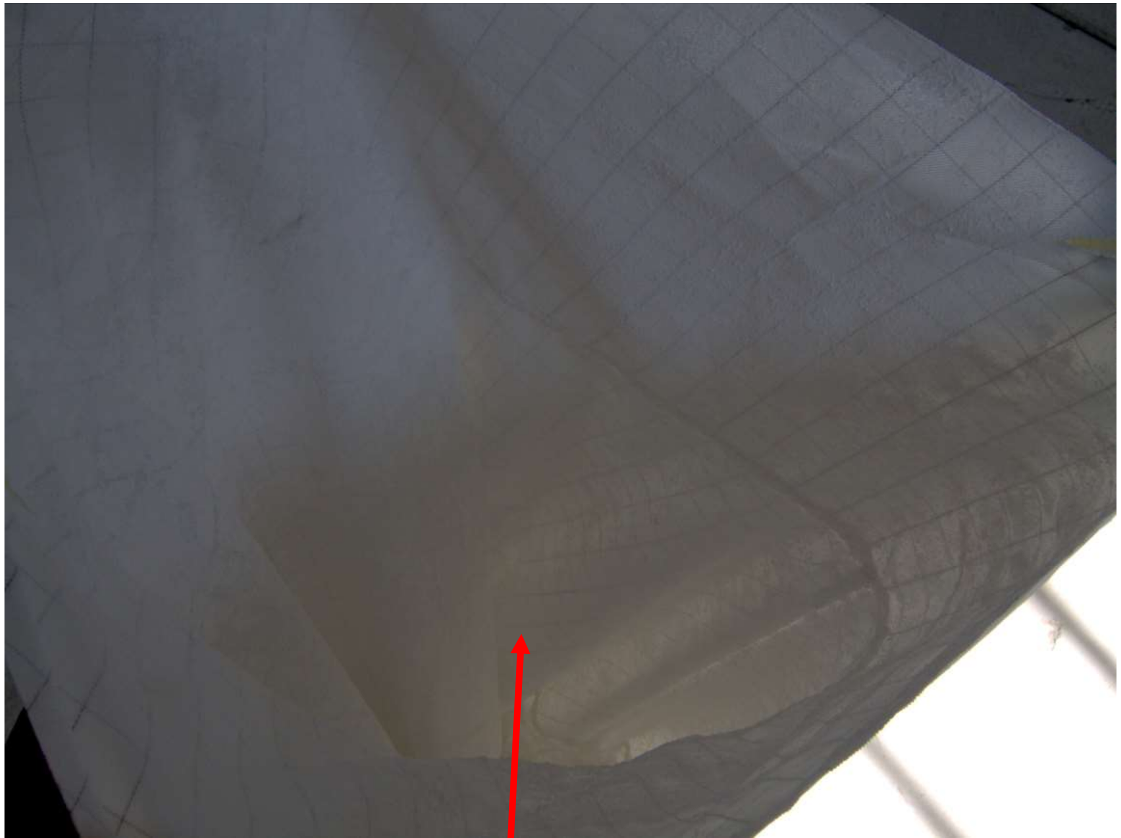
- ***No build-up***
- ***High recovery yield (>95 %)***
- ***Suitable for sticky material***

Sleeve Filter

Particle size reduction:

Milled product recovery_Sleeve filter « Octopus »

Post milling

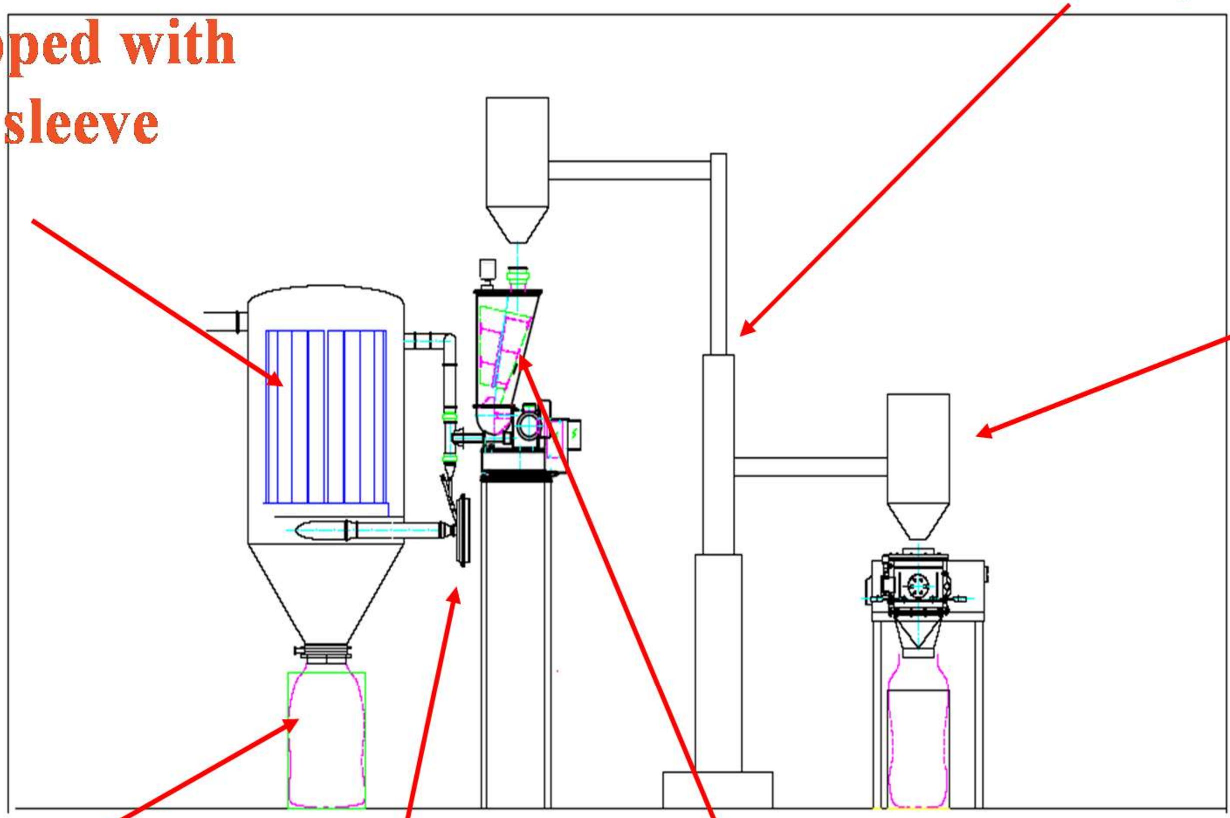


Inside of the cyclone

Inside of the filter

Particle size reduction:

Example of gloabl installation



Particle size reduction:

Selection of jet mill material

Particle size reduction:

Selection of jet mill material

- ***Adhesion between powders and surfaces plays an important role in the handling and processing of pharmaceutical materials.***
- ***Different mechanisms that cause adhesion can be Van der Waal's forces, electrostatic forces, liquid bridges or contact melting***

Particle size reduction:

Selection of jet mill material

- *It is already known that small particle size and needle-like morphology can lead to issue like bad flowability and adhesion to surface of jet mill piping and filters which may results on bad jet milling yield and a possible failure of the final quality attributes*
- *To manage this processing risk, the flow functions of the unmilled API and jet milled need to be carried out as function of jet mill material*

Particle size reduction:

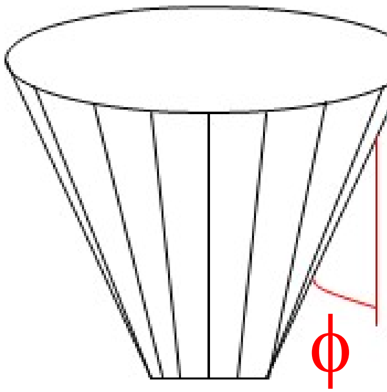
Selection of jet mill material_Hopper Indicizer®

A Hopper Index (HI) representing the hopper angle required to initiate movement along the walls of the hopper is then calculated. A Chute Index (CI) could also be determined with this equipment and this index recommends the chute angle necessary to prevent material build up on the solids

Particle size reduction:

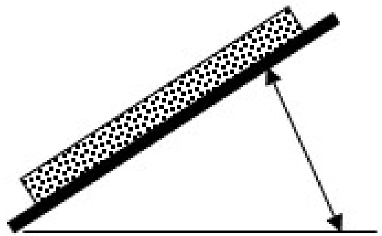
Selection of jet mill material_Hopper Indicizer®

Conical hopper with free flowing



Hopper Index HI

HI = 42 - φ'



Chute Index

CI

degre

Particle size reduction:

Selection of jet mill material_Hopper Indicizer®

	Delumped API		Jet milled API	
	Hopper index	Chute index	Hopper index	Chute index
Stainless steel 316L mirror polished	Higher than 90	0	Higher than 90	0
stainless steel 316L electro-polished	Higher than 90	0	Higher than 90	0
steel 316L mechanical polishing	Higher than 90	0	Higher than 90	0
Polyethylene terephthalate (PET)	86	0	Higher than 90	0
Polyoxymethylene (POM-C)	Higher than 90	0	87	8
polyethylene UHMW (PE 1000)	89	0	Higher than 90	0
Polytetrafluoroethylene (PTFE)	81	6	46	18

lower hoper index (HI) and the higher chute index (CI) were obtained when using Polytetrafluoroethylene (PTFE) for both quality of API

Particle size reduction:

Caracterization methods

Particles size reduction:

impact on the different powder properties

- **Particles size distribution (or Specific surface area) : always monitored as a target or specification.**
- **Particles morphology**
  - Generally , the particles size reduction process leads to an isotropic shape.
  - Will never be a key parameter for the technology selection.
- **Flowability**
  - Could have a significant impact on the drug product process
  - The particles size reduction process could enhance some times the flowability (unmilled product in needles shape) or depredate in general the flowability
- **Plymorphic transformation**
  - The particles size reduction process could leads to polymorphisme change (Hydrate → anhydrous or Crystal to amorphous)
  - Monitoring to be done before and after particles size reduction process

Particle size reduction:

Characterization methods

Characterization

Particle size

- •SEM
- •Laser diffraction
- Optical microscopy

Specific surface area

- •BET surface
- •Blaine Fischer

Crystal lattice

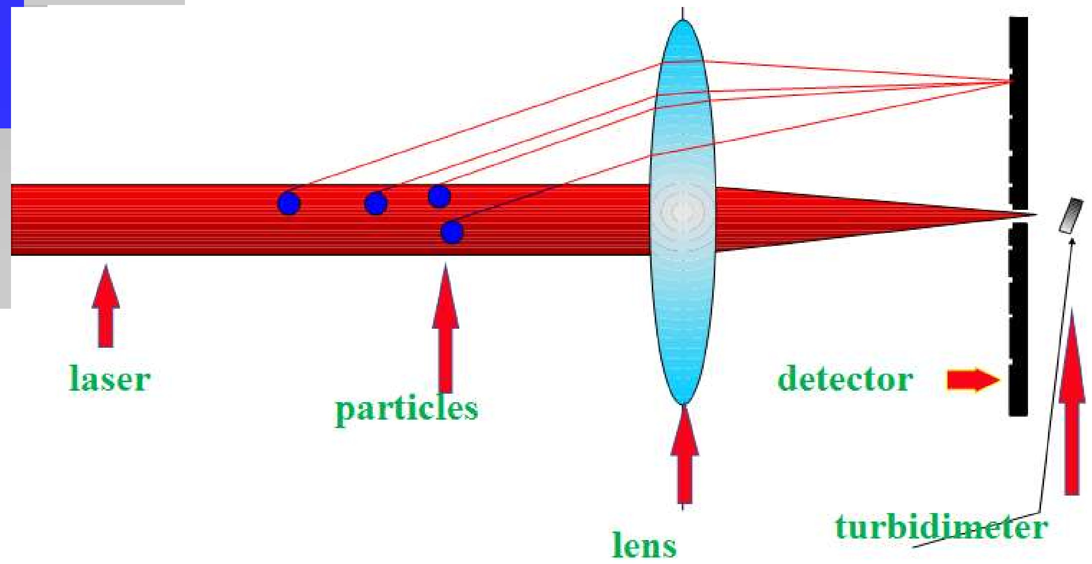
- • X ray diffraction
- • Differential scanning calorimetry

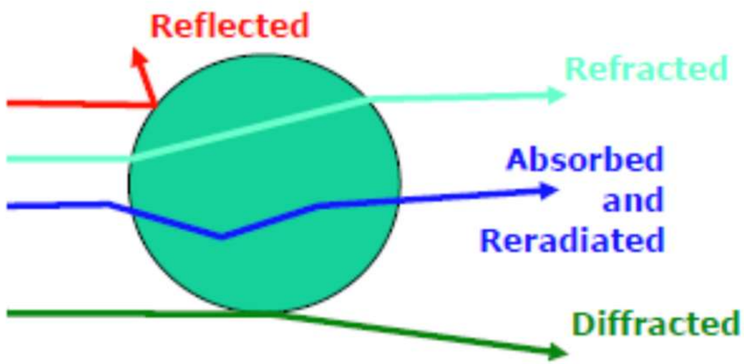
Bulk properties

Particle size reduction:

Particle size reduction

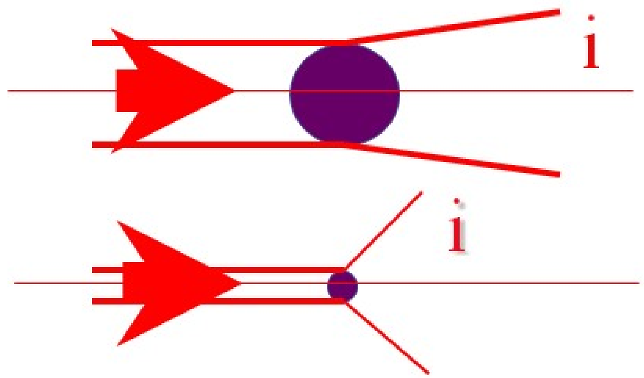
- ***Particles size distribution***
  - *Particles interact with light. Exploitation of diffraction or scattering data gives valuable information on particle size*
  - *When a Light beam Strikes a Particle*





Particle size reduction:

Particle size reduction

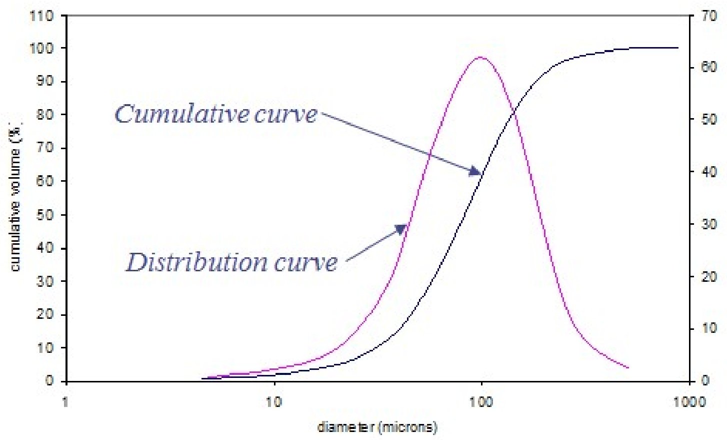


- ***Large particle scatter intensly at narrow angle***
- ***Samll particle scatter weakly at wide angle***
- ***Laser diffraction analyzers capture the diffraction***
- ***pattern produced by this scattering and then use an optical model to derive the size distribution of the particles that produced it.***

Particle size reduction:

Particle size reduction

- *to get particle size data from scattered light optical model with the mathematical transformations is required: Fraunhofer or Mie*
- *Fraunhofer is an approximation of the Mie theory*



Particle size reduction:

Particle size reduction

- ***Fraunhofer vs Mie***

Fraunhofer

- The particles being measured are opaque discs.
- Light is scattered only at narrow angles.
- Particles of all sizes scatter light with the same efficiency.
- The refractive index difference between the particle and surrounding medium is infinite.

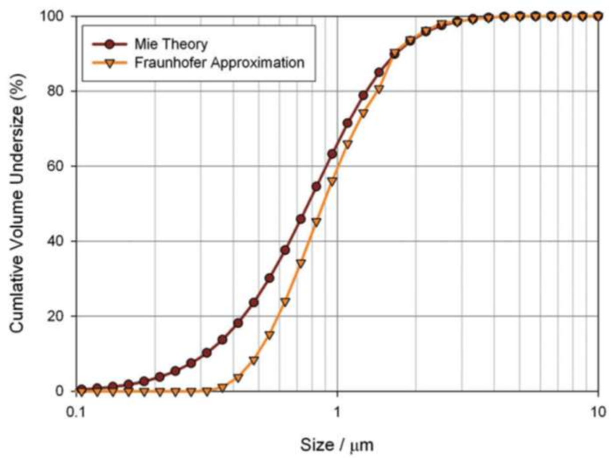
Mie

- The particles being measured are spherical.
- The suspension is dilute, so that light is scattered by one particle and detected before it interacts with other particles.
- The optical properties of the particles, and the medium surrounding them, are known.
- The particles are homogeneous.

Particle size reduction:

Particle size reduction

- *Fraunhofer is particularly inaccurate below 2µm and also fails to properly characterize systems containing transparent particles.*
- *When the refractive index difference between the particles and the surrounding medium is low, inaccuracies also tend to increase.*
- *Fraunhofer may inaccurately predict the size of particles or the amount of material within a given size range*
- *ISO13320, recognises the fundamental superiority of Mie for measurement range (0.1 to 3000 µm).*



Mie theory correctly interprets the low intensity scattering

Particle size reduction:

Particle size reduction

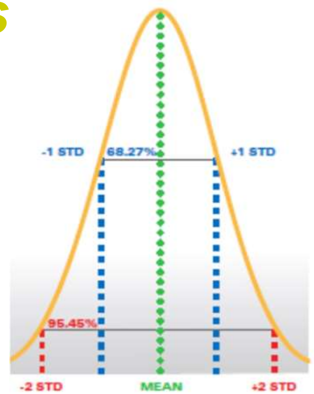
❖ Particles size distribution

- *Laser diffraction using Fraunhofer or Mie theory*
- *Extract characteristic diameters of particle size distribution d10, d50, d90*
- *Calculate Span : (d90-d10)/(2*d50)*
- *Calculate the narrowing index*

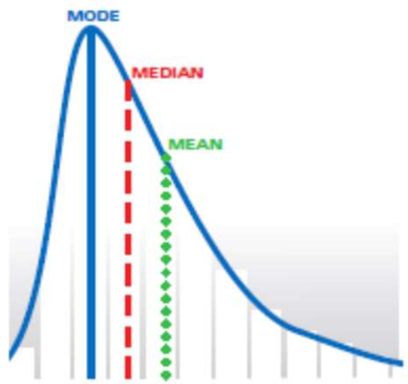
$$P.I = \ln\left(\frac{d_{10} * d_{90}}{d_{50}^2}\right)$$

  - *P.I = 0 for log-normal distribution*
  - *P.I < 0 for dissymmetric distribution towards small diameters d50/d10 > d90/d50*
  - *P.I > 0 for dissymmetric distribution towards large diameters*

log-normal distribution ➡



Dissymetric distribution ➡

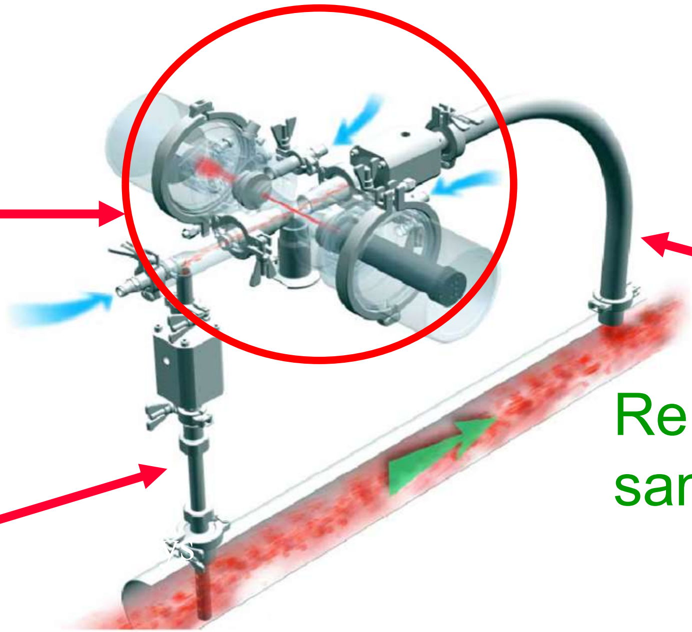


Particle size reduction:

On-line PSD probe

❖ ***On-line monitoring with Malvern Insitec or equivalent probe :***

Better understanding of the process
Improvement of productivity and yield (IPC)
Better control of the physical quality



Measurement of the PSD

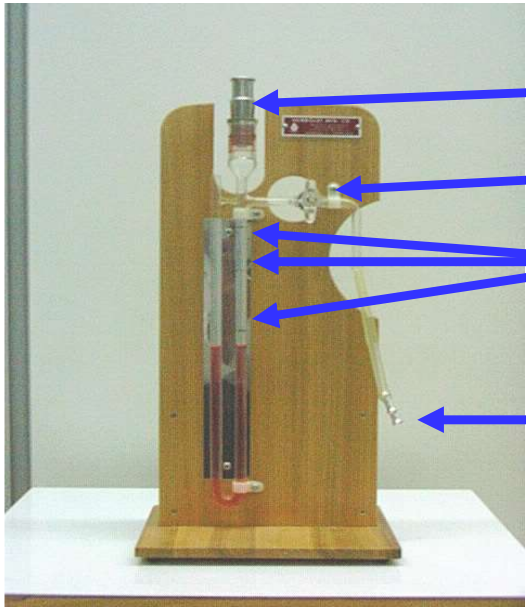
Isokinetic sampling

Reintroduction of the sample, no losses.

Particle size reduction:

Surface specific area_Permeametry_Blaine

Flow of a fluid through packed bed is function of bed thickness, porosity and surface area.



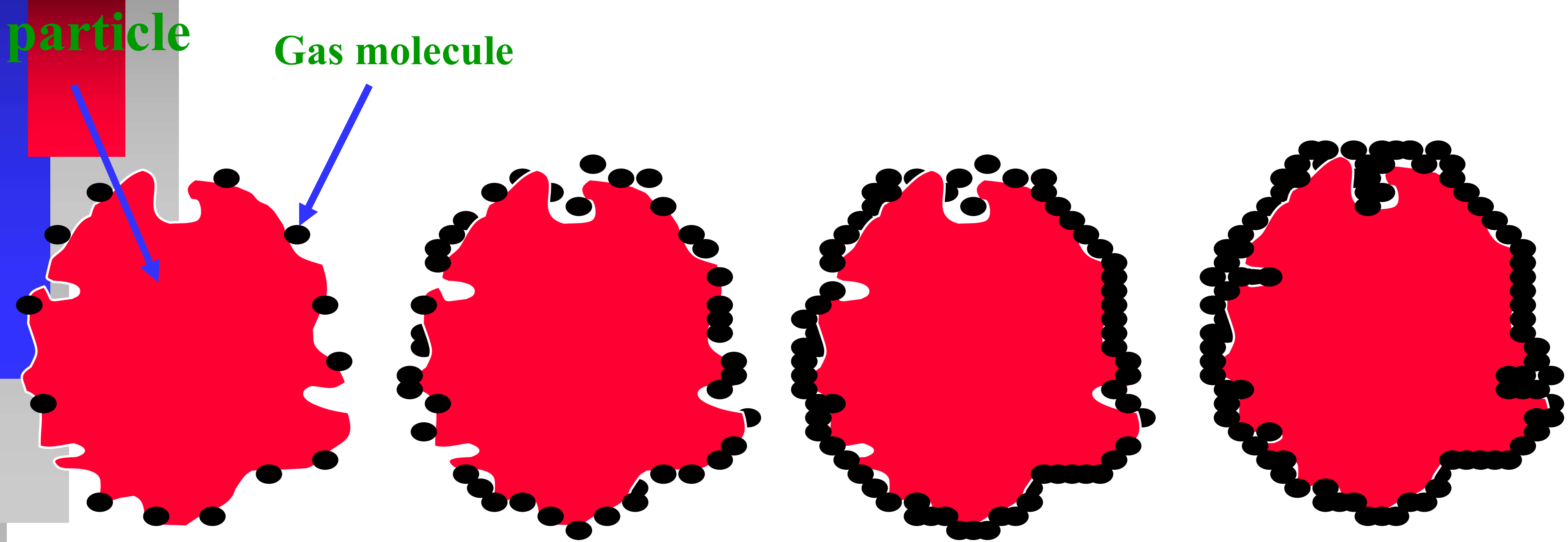
k : apparatus constant
L : powder bed length
ε : powder bed porosity
t : time for liquid to fall between two levels
ρ_s : solid density

$$S = \sqrt{\left[\frac{kt\varepsilon^3}{\rho_s^2 L(1-\varepsilon)^2}\right]}$$

Kozeny-Carman

Particle size reduction:

Surface specific area_Gas sorption



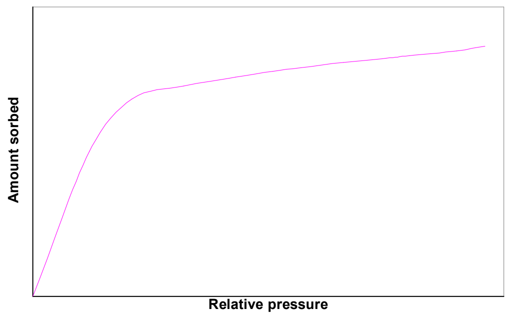
Gas adsorption with relative pressure increase

Commonly used gas : nitrogen, krypton at liquid nitrogen temperature

Particle size reduction:

Surface specific area_Gas sorption_ BET (Brunauer, Emmett, Teller)

The first part of adsorption curve, up to 0.3 relative pressure, is used to determine specific surface area. equation is commonly applied.



$$\frac{P}{V(P_0 - P)} = \frac{1}{V_m c} + \frac{c-1}{V_m c}\frac{P}{P_0}$$

Vm : monolayer volume per gram of solid
P : partial pressure
P_0 : saturation pressure at analysis temperature
c : gas dependant constant

Plot of P/V(P0-P) against P/P0 yields a straight line of slope (c-1)/Vmc and intercept 1/Vmc. Surface area is obtained from Vm.

$$S = \frac{N\sigma V_m}{M_v}$$

N : Avogadro number
σ : area occupied by one adsorbate molecule
Mv : gram molecular volume

Particle size reduction:

Flowability

- ❖ Powder flow is a key requirement for pharmaceutical manufacturing process

  Tablets are often manufactured on a rotary multi-station tablet press by filling the tablet die with powders or granules based on volume:

  - Flow of powder from the hopper into the dies often determines weight, hardness, and content uniformity of tablet

- ❖ For capsules manufacturing, similar volume filling of powders or granules is widely used

- ❖ Understanding of powder flow is also crucial during mixing, and transportation.

Particle size reduction:

Flowability

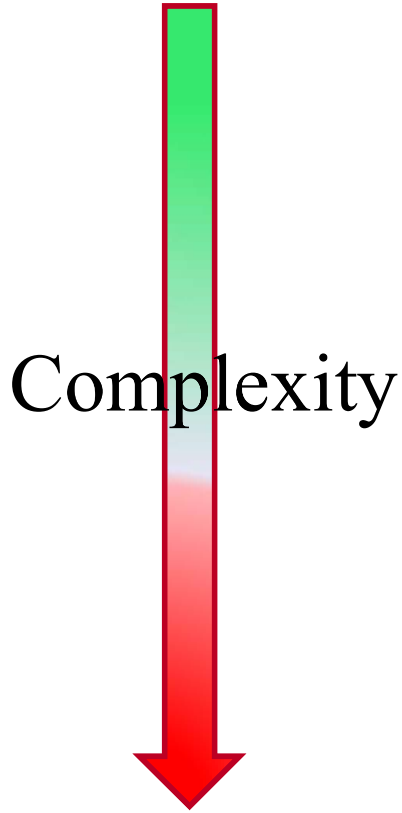
❖ ***Measurement of the flowability Index***

Volumetry (1965):

- ***Carr Index (CI)***
- ***Hausner index***

Johanson cell (1990)

Jenicke Cell (1961)



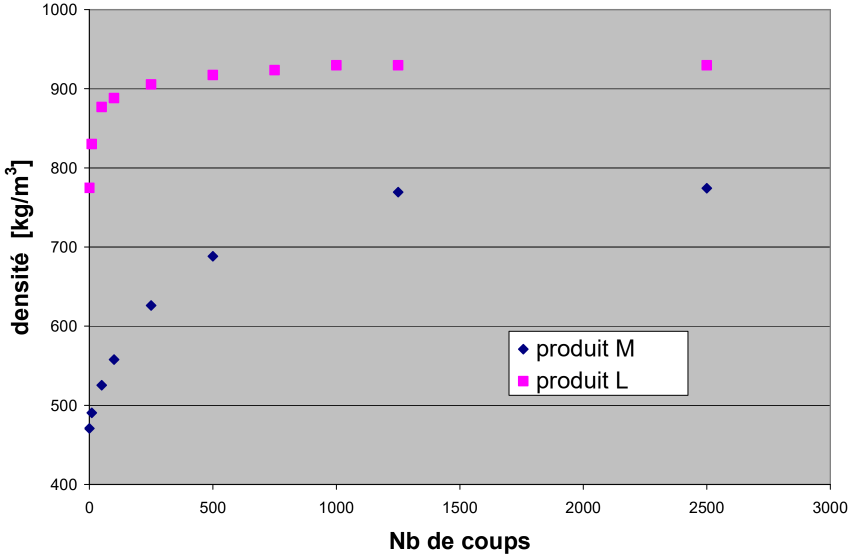
Particle size reduction:

Flowability_volumetry

- **Volumenometry :**

  Measurement of powder bed densities

  Settlement curves



$$I_{carr} = \frac{(\rho_{tapped} - \rho_{untapped})}{\rho_{tapped}}$$

$$HR = \frac{\rho_{tapped}}{\rho_{untapped}}$$

Carr classification

Particle size reduction:

Flowability_volumetry

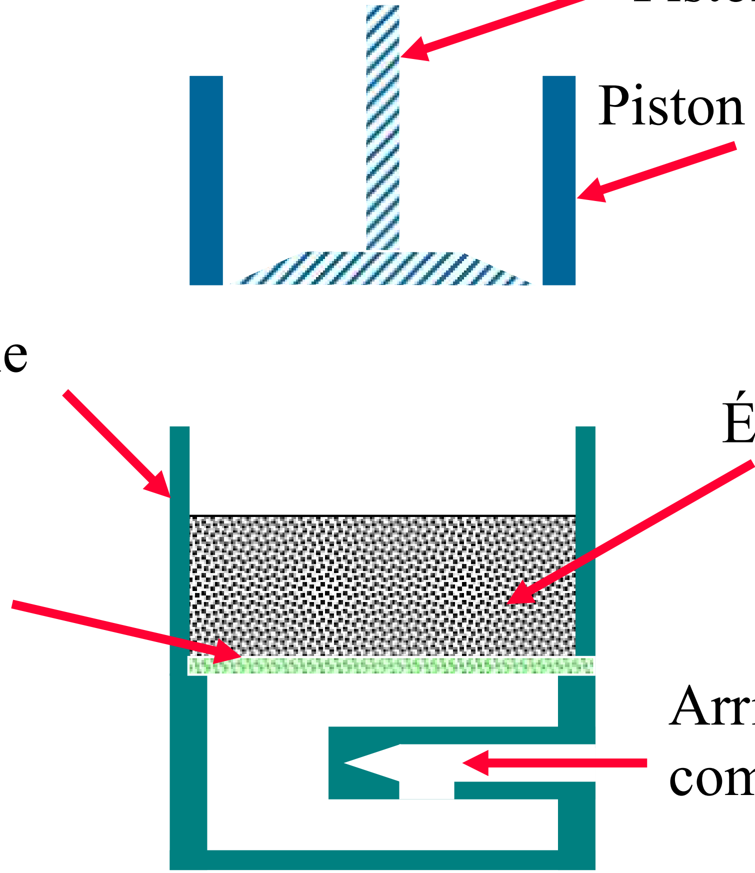
Carr classification

Carr's Index	
% Compressibility	**Relative flowability**
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair
23 – 28	Slightly poor
28 – 35	Poor
35 – 38	Very poor
> 40	Extremely poor

Particle size reduction:

Flowability_Johanson cell

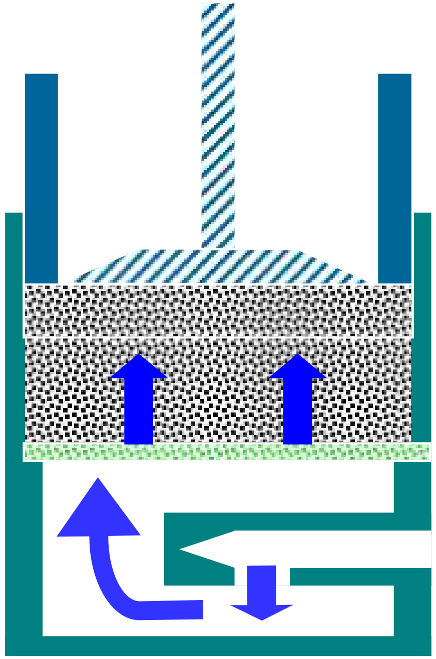
❖ ***Air permeability***



Particle size reduction:

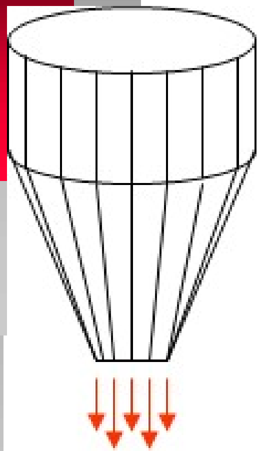
Flowability_Johanson cell

- **Measurement**
  - Perméabilité
  - Feed Density Index
  - Bin Density Index
  - SpringBack Index
  - Flow Rate Index



Particle size reduction:

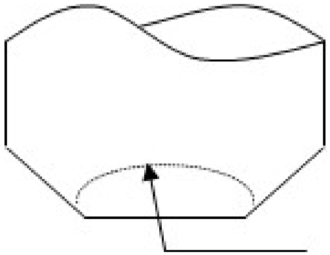
Flowability_Johanson cell



Flow Rate Index **FRI**

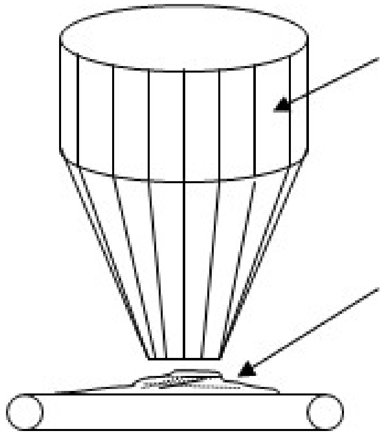
(mass/time

Solid flow rate



Springback Index **SBI**

Density indices (mass/volume)



Bin Density Index **BDI**

Feed Density Index **FDI**

COM = (BDI/FDI)-1

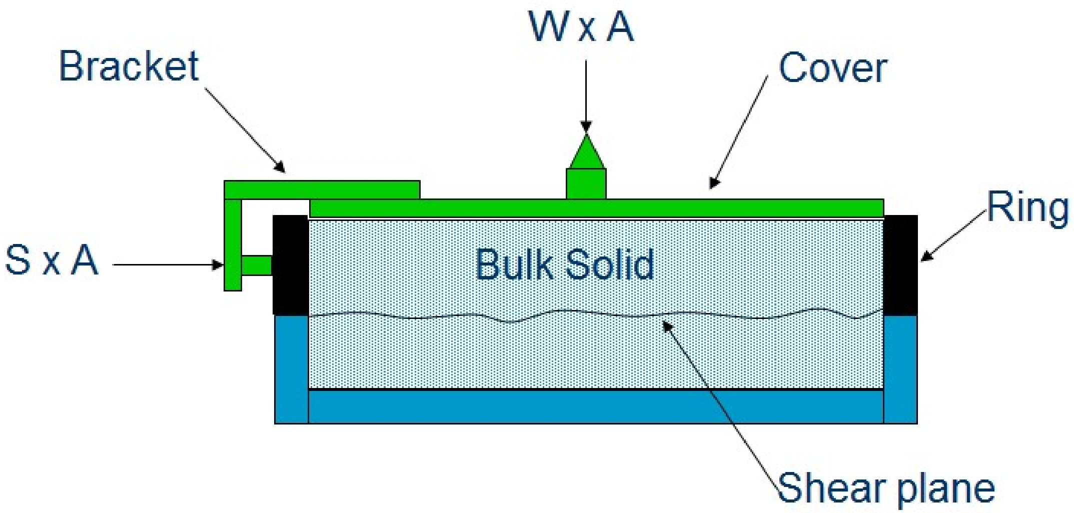
Jenike Shear Tester

Wall Friction: Jenike Shear Tester

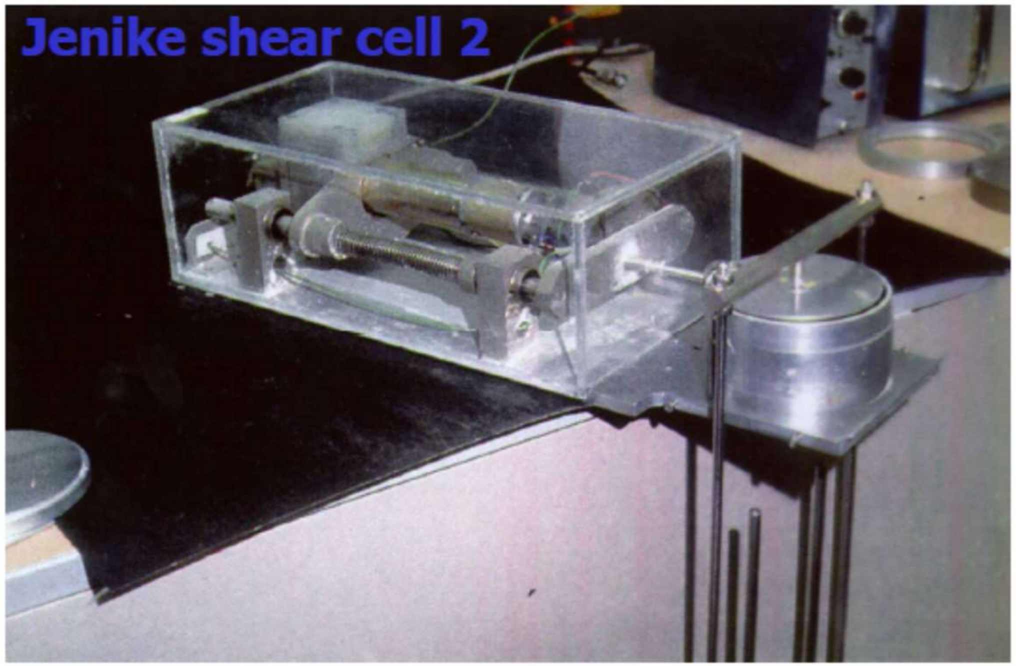
- ***The standard method to characterize flow properties of solid materials is the shear testing which provides the information for the yield locus of the solid***
  - ***Yield locus is an important tool in determining the flow properties of bulk materials.***
    - *angle of internal friction, cohesion, flow function, kinematic angle of wall friction, etc. are obtained from yield loci*
  - ***Shear testing is based on the information of shear stress values against normal stress values and these are obtained by sliding the material inside itself under defined load values.***

Jenike Shear Tester

Wall Friction: Jenike Shear Tester



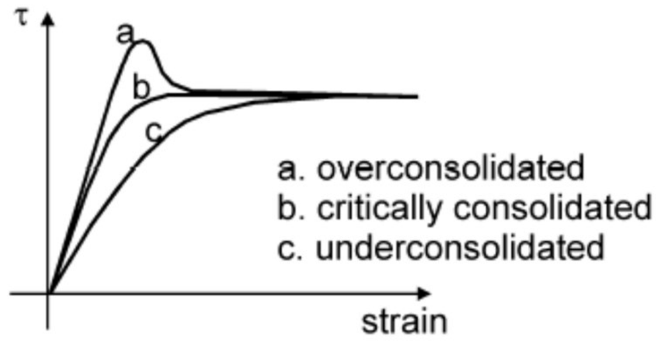
A. Serkan et.al



Jenike Shear Tester

Wall Friction: Jenike Shear Tester

- **The shear test generally consists of two steps.**
  - *The first step is the consolidation (pre-shear) step in which a criticially consolidated sample prepared*
  - *The second step is the attainment of steady state flow in the shear cell which is called as shear step.*
  - *Shear points on yield locus with failure point (require for material to flow) shear stress values were obtained for a defined shear normal stress at a selected pre-shear normal stress.*



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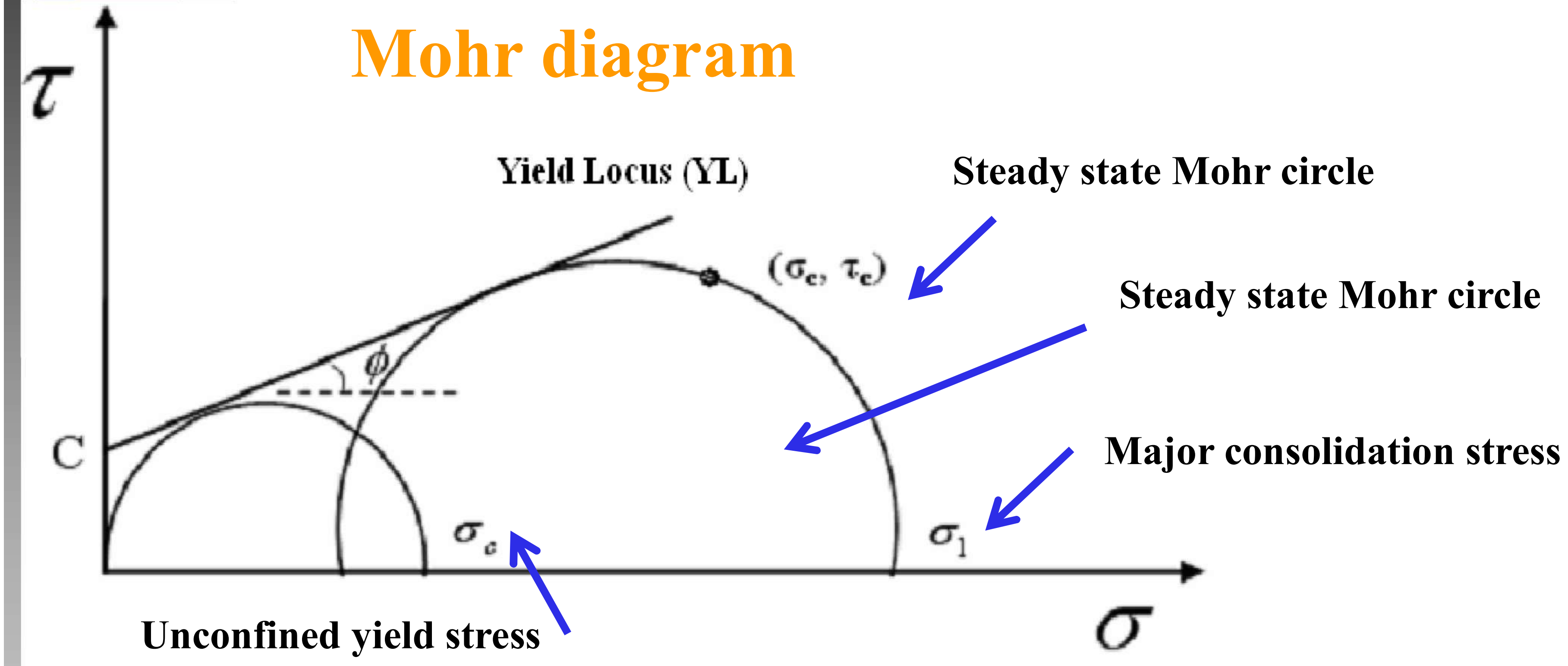
Wall Friction: Jenike Shear Tester



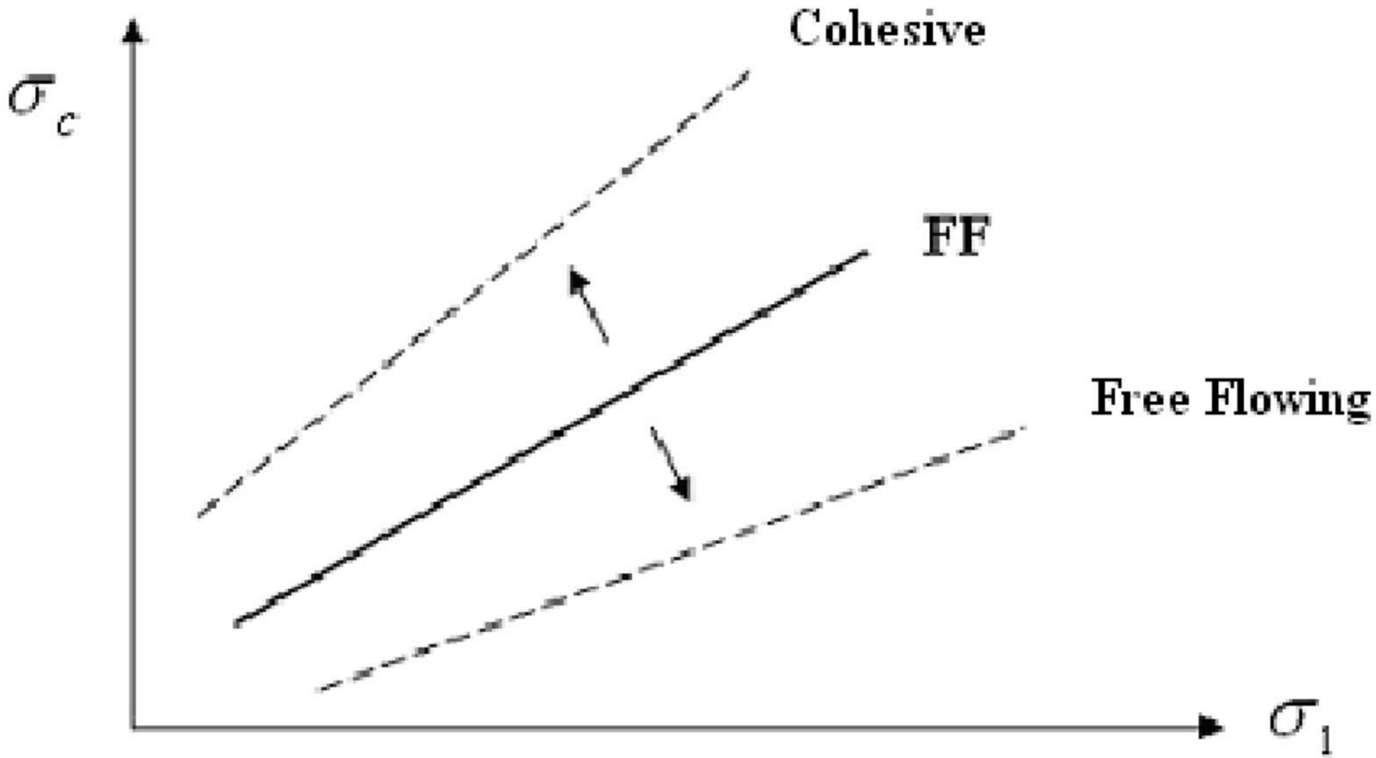
the maximum normal stress value which a solid having a free and stressless surface flows or deforms.

$\sigma_c = f(\sigma_1)$ → the material flow function

A straight line approach can be made for most material's flow function

Jenike Shear Tester

Wall Friction: Jenike Shear Tester



Material cohesiveness shows increase with inreasing slope values regarding flow function graph,

$1/Slope_{FF} = ff_c =$ flow index

Flowability	Hardened	Very cohesive	Cohesive	Easy flowing	Free flowing
Flow index (ff_c)	< 1	< 2	< 4	< 10	> 10

Particle size reduction:

DVS : Dynamic Vapor Sorption

- Exposing a sample to a series of progressive changes in relative humidity and control the variation of sample mass as a function of time. Gravimetric equilibrium expected with each new moisture step before moving to the next level of humidity.

  Technique used to characterize the species in equilibrium depending on the relative humidity.

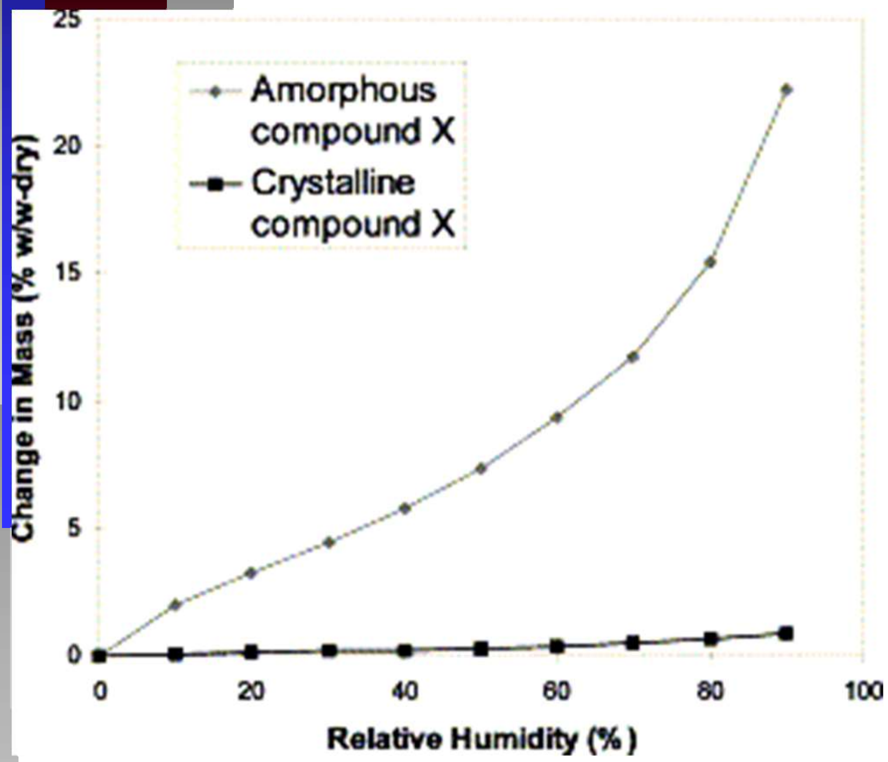
  Presence or absence of hydrate

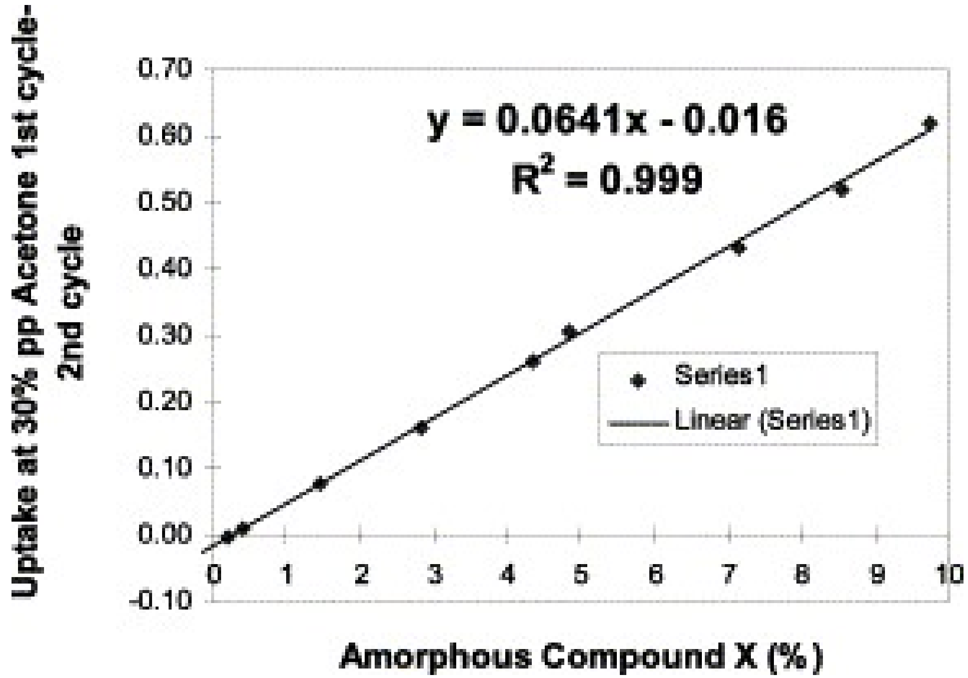
  Amorphization or not

  Special packaging to implement

Particle size reduction:

DVS : Dynamic Vapor Sorption





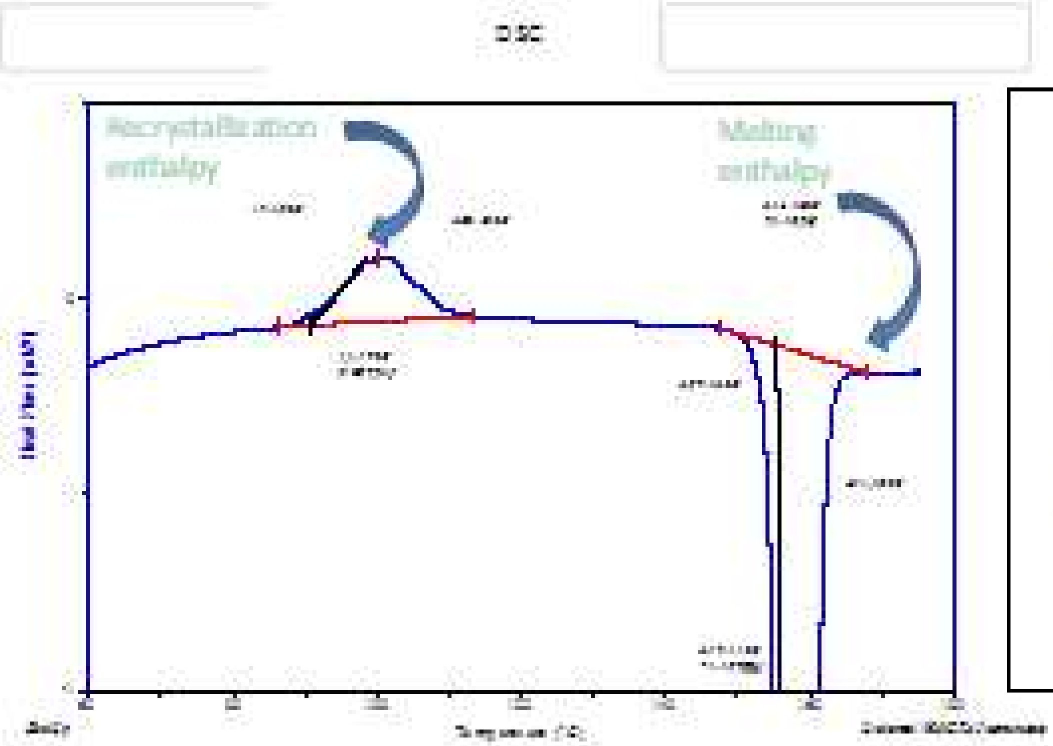
Amorphous/Crystal

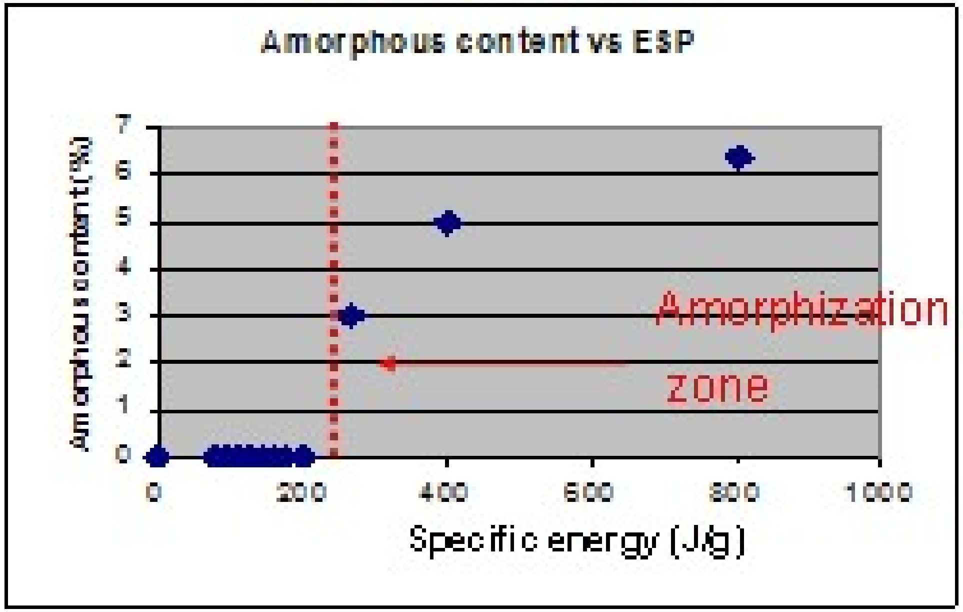
Sorption isotherm

Calibration

Particle size reduction:

Impact of the milling on the crystal structure





- *over 200 kj/Kg partial amorphization is observed*
- *Amorphous material is not thermodynamicaly stable, can be converted in crystal form*
- *Particle size can grow-up during storage*

Particle size reduction:

Stability study

Particle size reduction:

Technical stability study

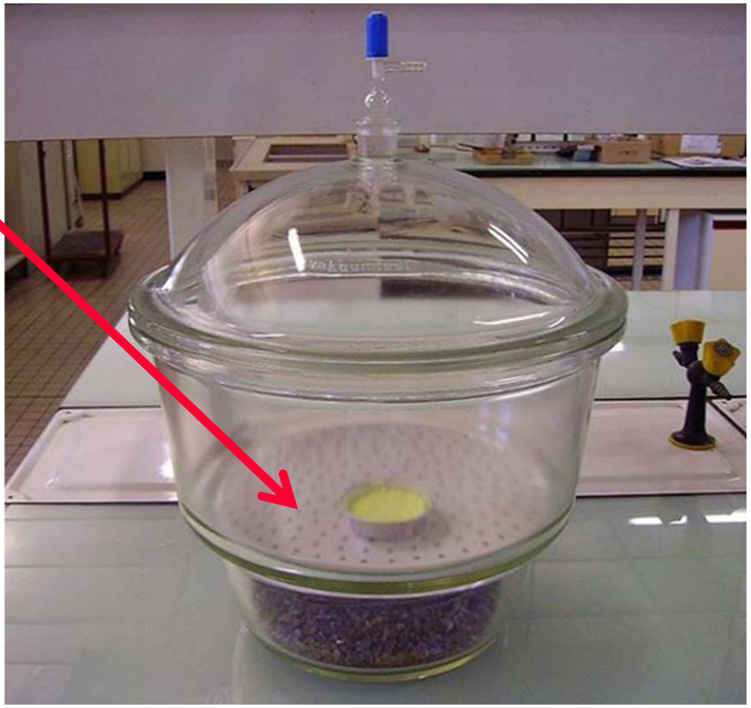
- Purpose : to be confident about the proposed specifications
- How to : follow vs. time in accelerated conditions the physical stability of milled or micronized products
- Storage of one or many samples in selected conditions and monitoring of the PSD or SSA vs time (reagglomeration)
- Conditions
  - Temperature
  - Relative humidity

Particle size reduction:

Technical stability study

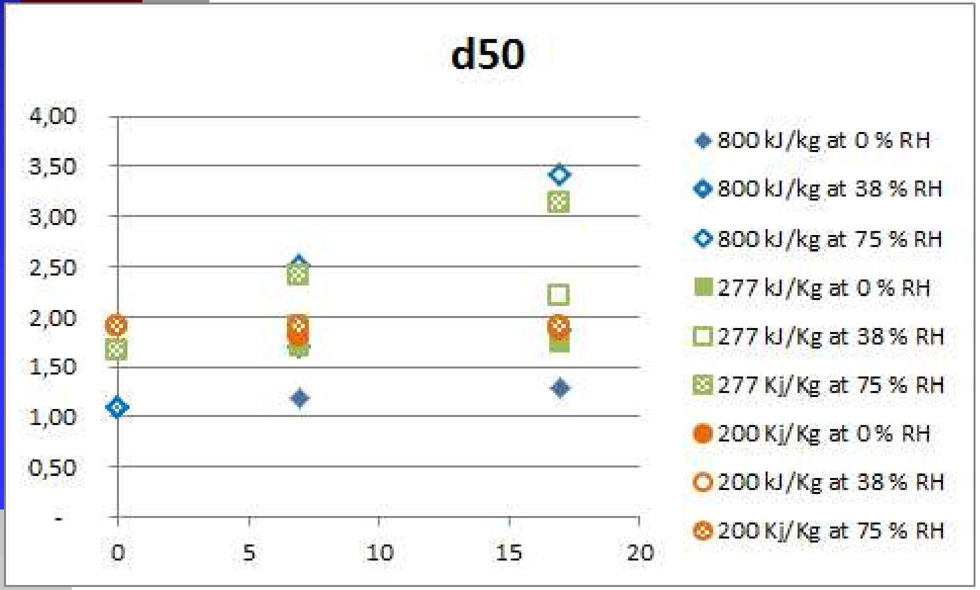
- **Temperature**
  - *Laboratory, Tray dryer or constant climate chambers*
- **Relative humidity**
  - *Saturated salt solution, examples*

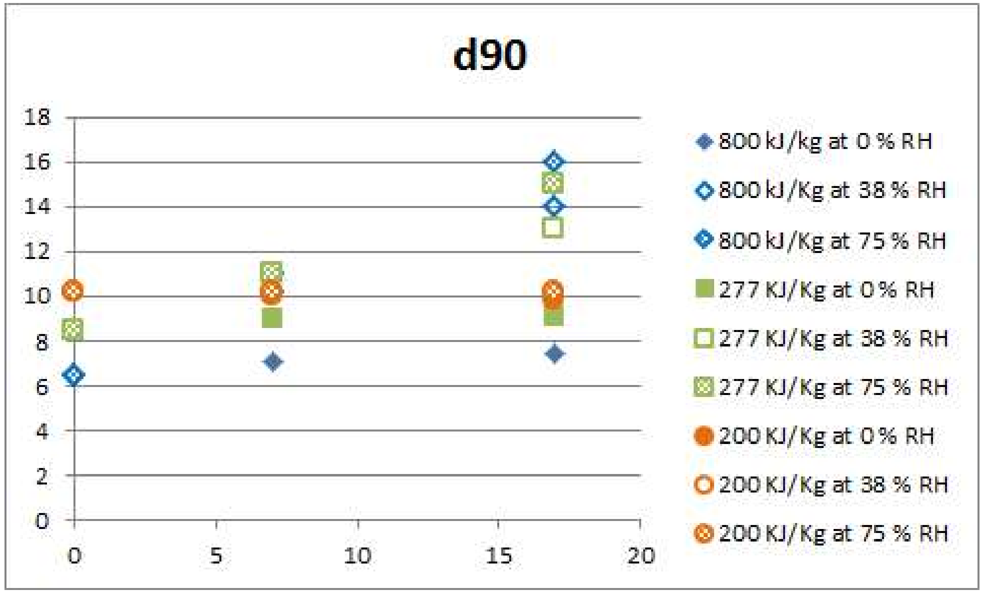
	HR en %		
	5°C	20°C	40°C
silicagel bleu sec; Co	0	0	0
KOH		5	
LiCl	16	12	11
KOAc,1,5 H_2O	25	23	23
$MgCl_2$, 6 H_2O	33	33	31
$Zn(NO_3)_2$, 6 H_2O	43	38	19
K_2CO_3, 2 H_2O		44	40
NaBr, 2 H_2O	59	57	57
NaCl	76	75	75
$(NH_4)_2$ SO_4	81	79	79
K_2SO_4	98	97	94
$CuSO_4$		98	



Particle size reduction:

Technical stability study





$$S(t) - S_\infty = (S_0 - S_\infty)e^{k_{T,\%HR}t}$$

S_∞ = final SSA

S_0 = initial SSA

$k_{T,\%HR}$ = agglomeration cste

Particle size reduction:

Equipment cleaning

Particle size reduction:

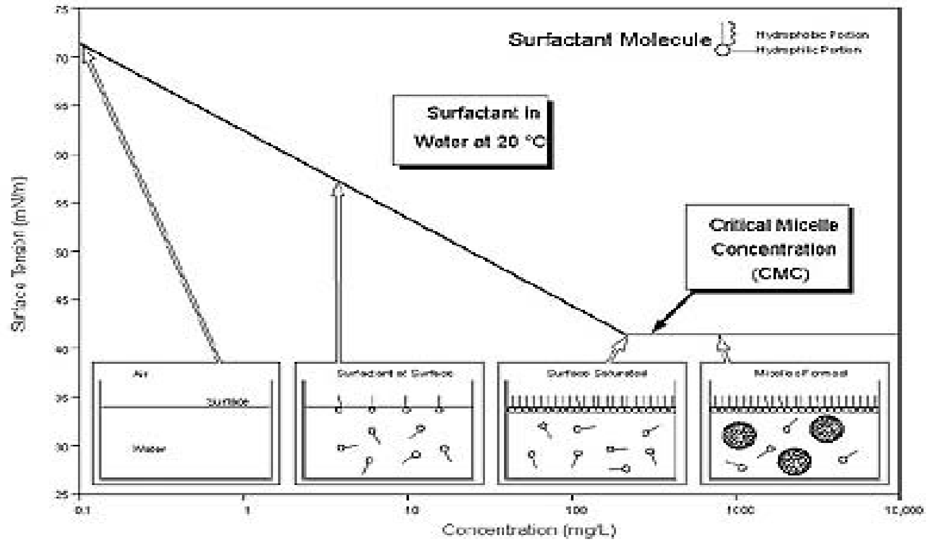
Equipment cleaning_surfactant selection

- *The cleaning of pharmaceutical equipments is required in order to avoid the cross contamination*
- *The cleaning method has to be validated*
- *In order to make the cleaning easier, the use of surfactant is required*
- *Methodology:*
  - *Surfactant screening based on Data base acquisition:*
    - *Surface tension*
    - *Critical micelles concentration (CMC)*
    - *Evaluation of wetability*
      - *Sinking time*
      - *Contact angle*

Particle size reduction:

Equipment cleaning_surfactant selection

- **Data base acquisition**



- ***CMC: The concentration at which there is micelles formation. For surfactant efficiency , it is required to fix concentration higher than the CMC value.***

- *Results:*

Surfactant	CMC (g/l)	Recommended concentration by the supllier (g/l)
X	0,08	2 à 3
Y	10	10 à 20

Particle size reduction:

Equipment cleaning_surfactant selection

❖ *Wettability test*

- *Powder incorporation test*

Contact angle measurement

Results:

tensioactif	concentration (g/l)	contact angle°
Water		90 °
X	2 g/l	39,6 °
Y	15	45,7 °

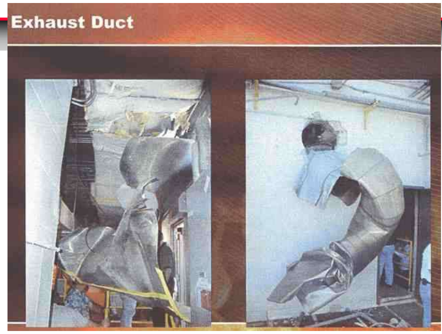
Particle size reduction:

Safety aspect

Particle size reduction:

Safety aspect





- *Mastering the micronisation/milling process has to be a permanent priority*
- *Set up earlier a method for risk evaluation*
- *Acquisition of data base on the product to be processed*
- *Set up a suitable safety barrier for each equipment*
- *Periodic review of risk evaluation*

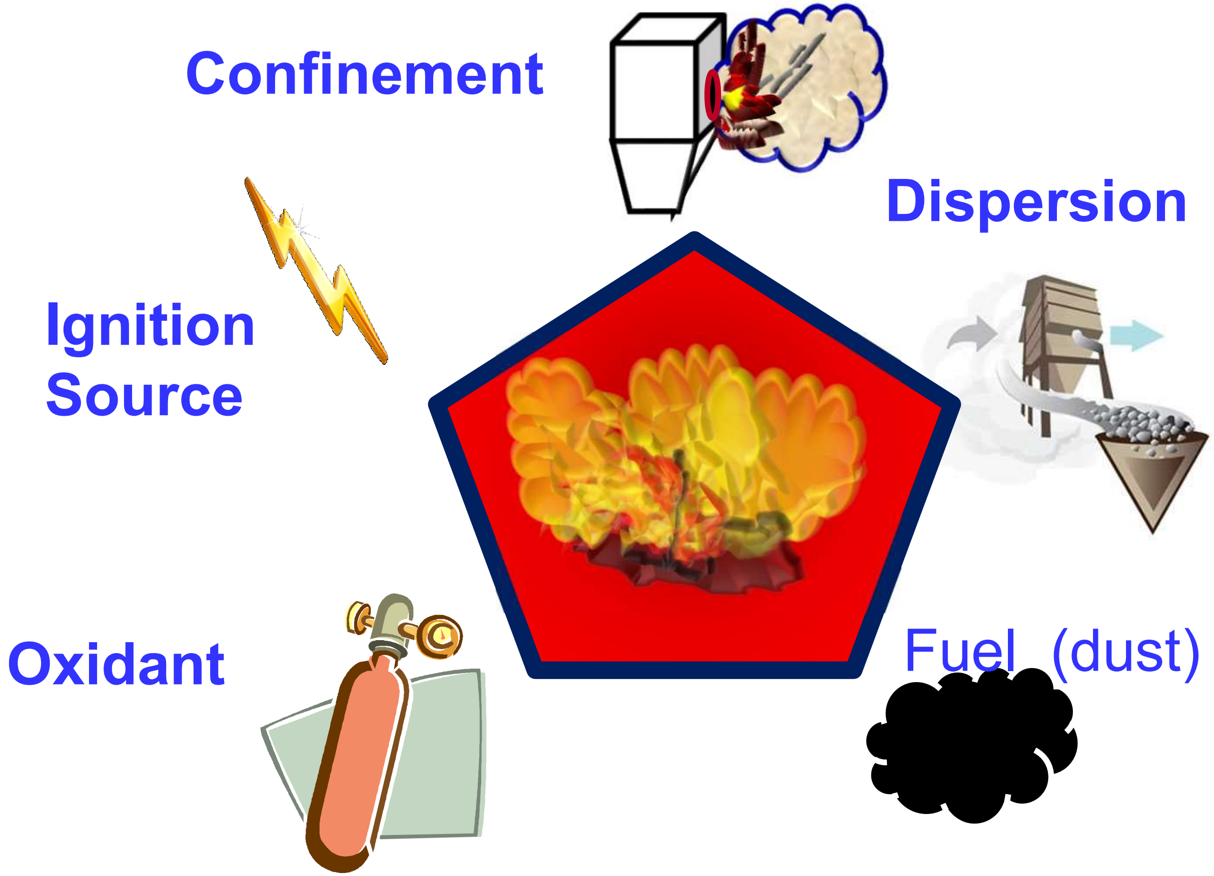
Particle size reduction:

Safety aspect_the well known triangle

Particle size reduction:

Safety aspect_Explosion of combustible dust

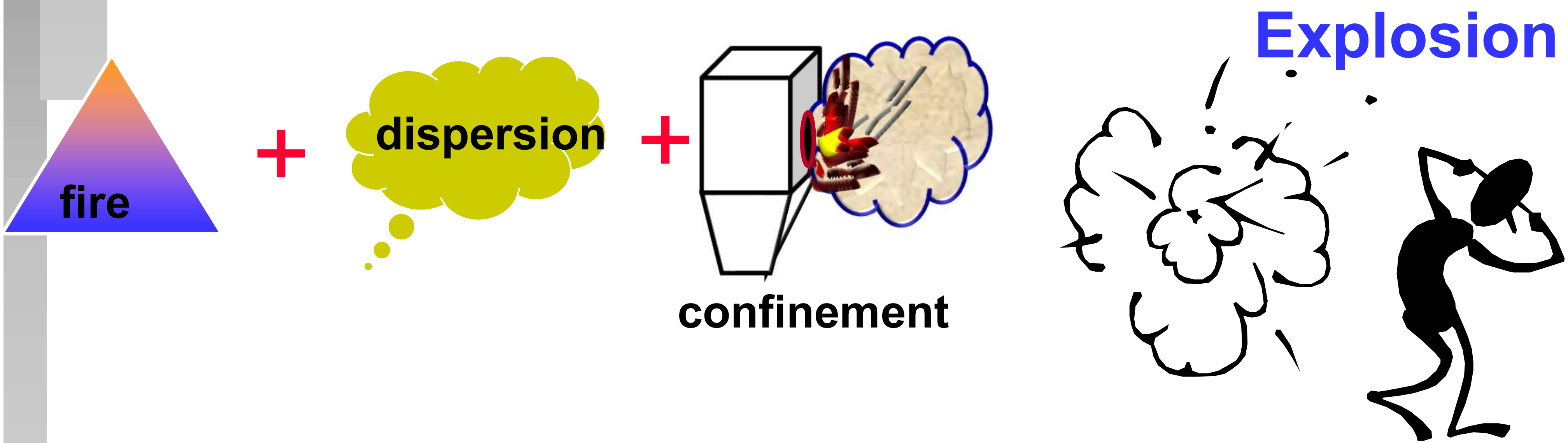
- ***For a combustible dust explosion to happen, it requires the presence of all these factors***



Particle size reduction:
Safety aspect_Explosion

❖ ***Results from the combination of these factors:***

- *fire*
- *dispersion of solid particulate material*
- *in a more or less enclosed space*



Particle size reduction:

Safety aspect_Risks evaluation

Identification of explosion risks

→ Safety technical data

Estimation of risks

- Explosive atmosphere

- Ignition source

- consequences of explosion

Evaluation of risks

Scoring

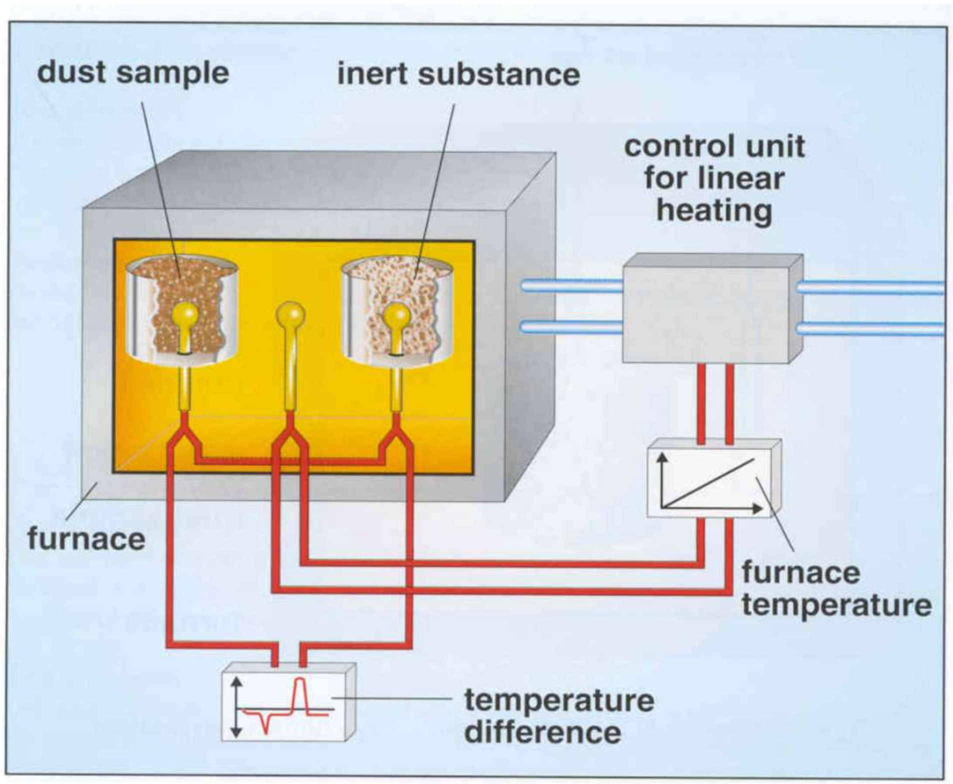
Lowering risks

prevention and mitigation plan

Particle size reduction:

Safety aspect

- ***Identification of explosion risks***
  - ***Basic data acquisition***
    - *Thermal decomposition enthalpy (DSC)*



Test under air or pur O_2

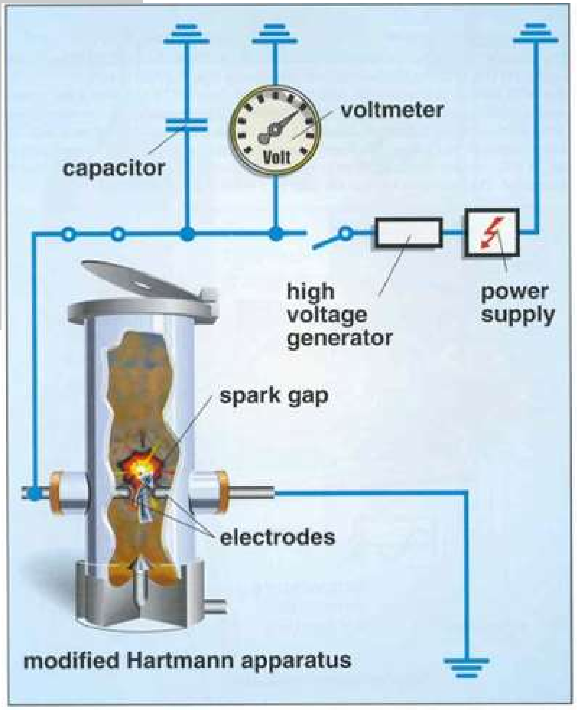
Particle size reduction:

Safety aspect

❖ ***Identification of explosion risks***

- ***Basic data acquisition***
  - *Minimal ignition energy*

Hartmann apparatus



It consists of 1.2 litre vertical tube in which dust was dispersed by air blast.
Two electrodes made of Brass or Stainless Steel (SS) of grade AISI 304 was kept inside the glass tube at some distance apart.
Electrodes were connected with spark ignitor and serves as ignition source.
Spark ignition system was supplied by high voltage DC power
Flame propagation is observed as a function of dust particle size, dust concentration, DC voltage, etc.

Particle size reduction:

Safety aspect

- ***Identification of explosion risks***
  - ***Basic data acquisition***
    - *Minimal ignition energy*

The lower the MIE, the more sensitive a powder is to small sources of ignition

≥ 10 mJ → flammable product

Mastering ignition sources as the only barrier is possible

3 mJ ≤ MIE < 10 mJ → very flammable product

Mastering ignition sources as the only barrier is not possible

< 3mJ extremely flammable product

Mastering ignition sources as the only barrier is possible

Particle size reduction:

Safety aspect

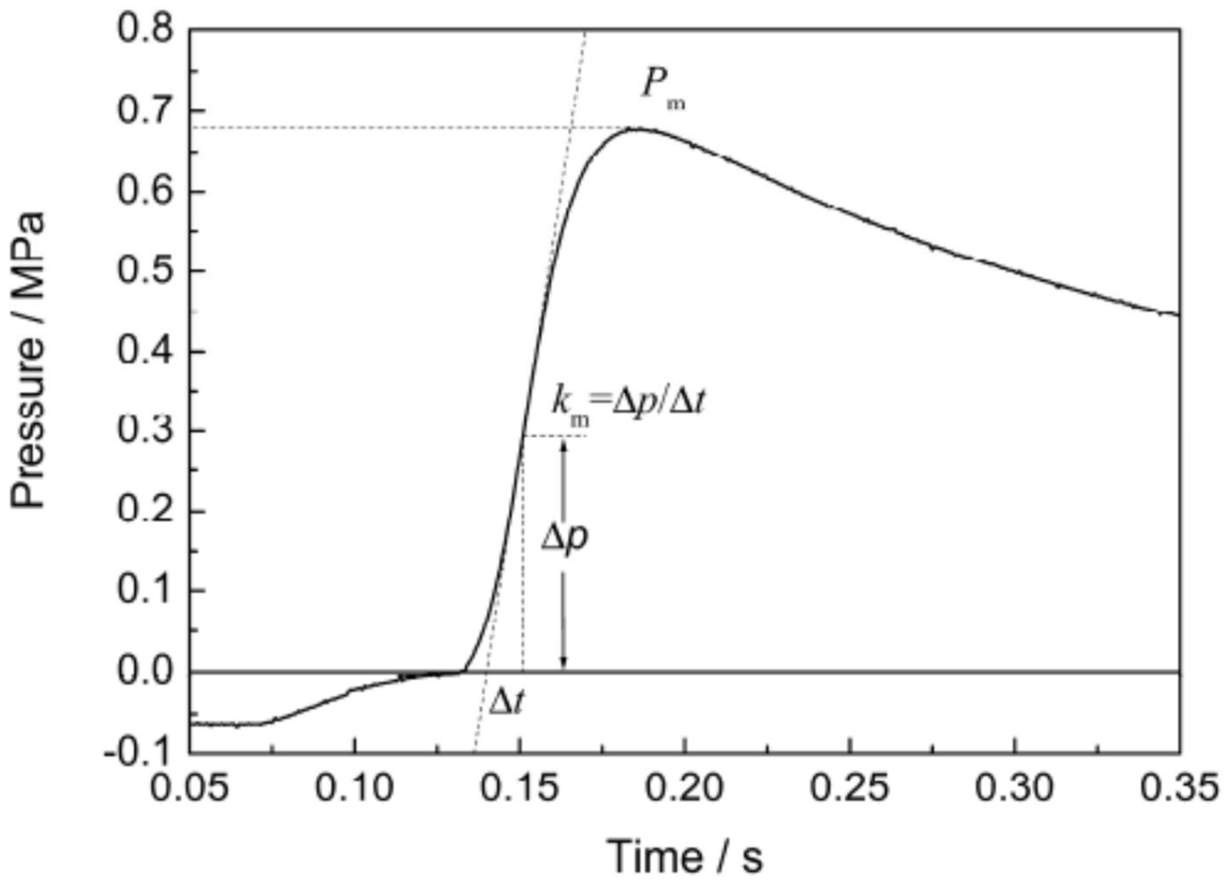
- **Identification of explosion risks**
  - **Basic data acquisition**
    - *Explosion violence*

1) Dust cloud is formed in a closed combustion chamber by dispersion of the dust with compressed air.
2) Ignition of this dust/air mixture is then attempted after a specified delay time by an ignition source located at the center of the chamber.
3) The pressure during the dispersion and explosion is measured by a pressure transducer and recorded by data acquisition system.

Particle size reduction:

Safety aspect

- ❖ Typical time curve



maximum pressure P_m and maximum rate of pressure rise $(dP / dt)_m$ can be obtained.

Particle size reduction:

Safety aspect

Rate of Pressure Rise (dP/dT) – K_{st} Test (generated when dust is tested in a confined enclosure)

K_{st} is the Deflagration Index for dusts,
Kst test results provide an indication of the severity of a dust explosion. The larger the value for Kst, the more severe is the explosion.

Particle size reduction:

Safety aspect_the well known triangle

$$Kst = (dP/dt)max \ V^{1/3}$$

K_{st} Calculation

where:

$(dP/dt)_{max}$ = the maximum rate of pressure rise

V = the volume of the testing chamber:

Dust explosion class	Kst (bar.m/s)	Characteristic
St 0	0	No explosion
St 1	>0 and <=200	Weak explosion
St 2	>200 and <=300	Strong explosion
St 3	>300	Very strong explosion

Estimate – Anticipated Behavior

Particle size reduction:

Safety aspect

- **Identification of explosion risks**
  - **Basic data acquisition**
    - *API powder resistivity and dissipated charges*

Resistivity: ability of powder to conduct electricity
Essential and critical with respect to powder behavior
Powder are resistant when resistivity is > 10^{13} Ωm and are suited for long charge retention
The most method for resistivity measurement is the bulk resistivity cell
The cell should be made from an insulating material
The powder is subjected to steady state DC potential
The current I is measured
Powder resistance can be calculated from Ohm's Law (R= V/I)
Specific resistance is measured using the equation (ρ = (VA/Id)
A and d are the electrode area and electrode separation distance

Powder electrostatic theory: Hosokawa documentation

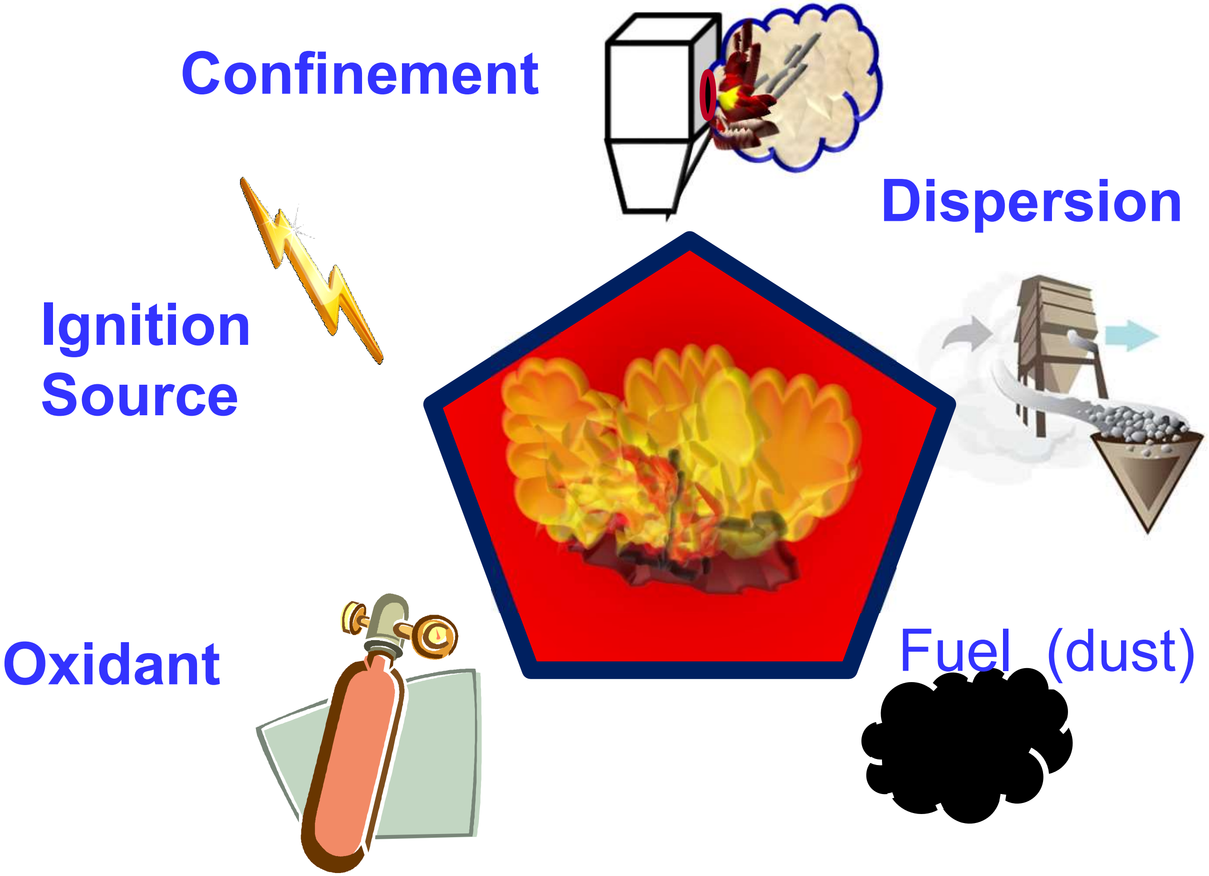
Particle size reduction:

Safety aspect_the well known triangle

- **Static Electricity Discharges**
  - *Static electricity is thee fourth largest cause of ignition sources in dust explosions.*
  - *Handling solids often leads to the accumulation of static electricity. This accumulation can lead to a spark that then serves as an ignition source.*
  - *One method to prevent static electricity is to prevent the accumulation of charge.*
  - *Charge Accumulation:*
    - *Contact and Frictional*
    - *Double layer*
    - *Induction*
    - *Transport*

Particle size reduction:
Mitigation plan

During particle size reduction try to eliminate or reduce one or more of the element that can contribute to explosion.



Particle size reduction:

Safety aspect_Mitigation plan

- Reduce oxygen below minimum oxygen concentration → milling using Nitrogen
- Implementation of Explosion suppression
  - Flap valve. https://youtu.be/6D8mouYaZSo
- Implementation of flameless venting devices that combine the techniques of explosion venting and flame arresting.

https://youtu.be/yqn09qucMmQ

- flushing https://youtu.be/cjf5JPY64nI

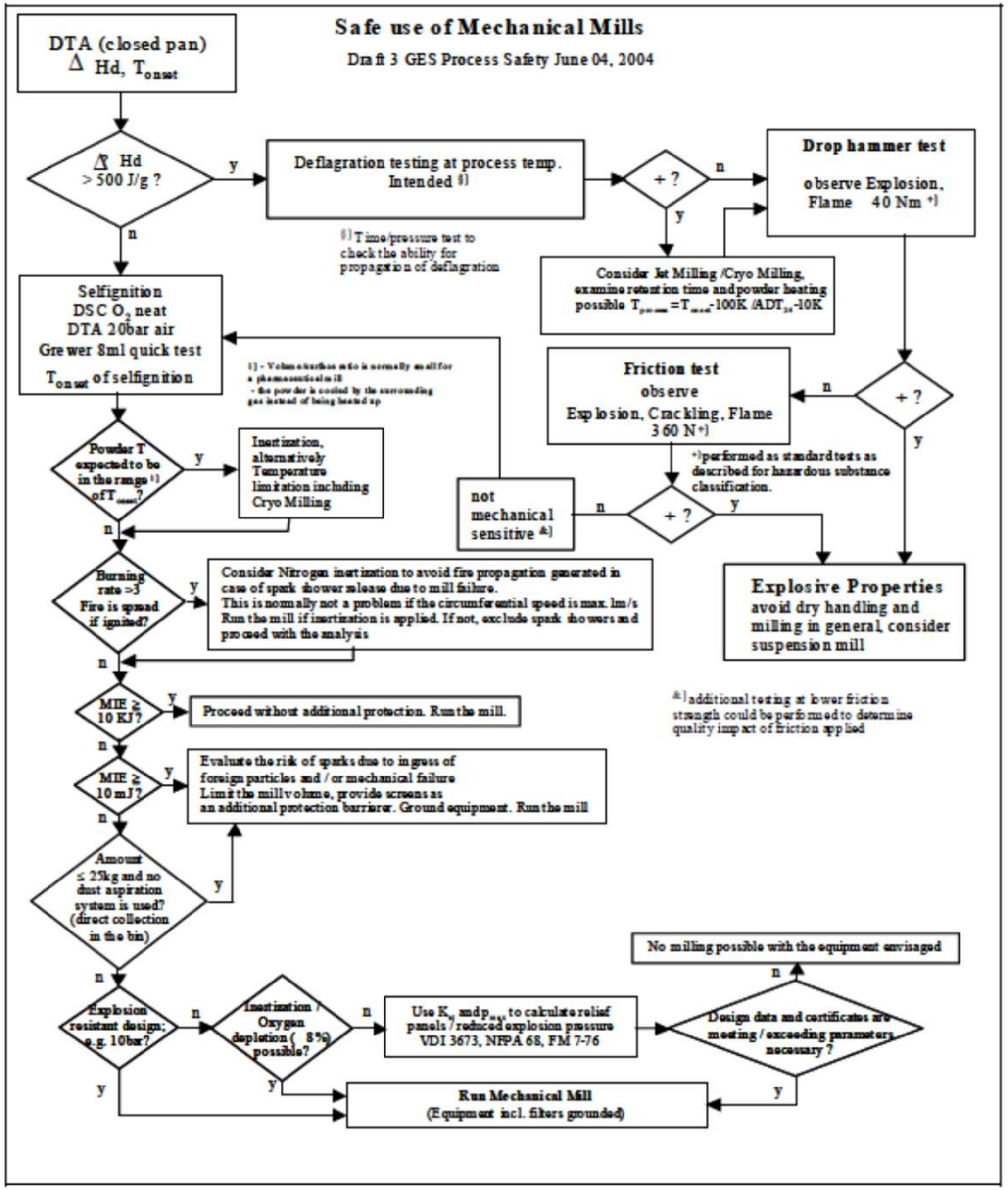
Particle size reduction:

Safety aspect_mitigation plan

- **Prevent accumulation of electrical charges**
  - ***We can eliminate sparks if we ensure that all parts of the system are connected with a conductor***
  - ***The problem comes when pipes or jet mill are Teflon lined or made from polymers or connected with non-conducting gaskets***
- **Grounding**
  - ***Is the connection of a conducting wire between a charged object and the ground.***
  - ***Any charge accumulated in the system is drained off to ground.***

Particle size reduction:

Safety aspect_Decision tree



Particle size reduction:

Safety aspect_mitigation plan

Usual solutions for sensitive powders

Technology	Advantages	Drawbacks
Nitrogen blanketing	• Low adaptation costs • Multiproduct • No product loss	• Safety (anoxia) • Cost of Nitrogen
Explosion proof construction (typically 10 bar overpressure)		• Cost • Mono-product • Each disassembling requires tests • Product loss
Explosion venting system		
Explosion suppression system		

Particle size reduction:

Safety aspect

- Risk of toxicity for the operators (inhalation)
- Explosion Risk
  - Fine particles: possibility to form dust cloud
    - Minimal ignition energy o to be measured
    - Nitrogen blanketing will be required
- Burning risk due the cryogenic conditions
- Anoxia risk
  - Oxygen probe is required
  - Complete suit with breathable air

Particle size reduction:
Safety aspect_Operators protection

Ventilated hood
Containment level : 100 µg/m³ (8h TWA)

Hood with breathable air
Containment level : 100 µg/m³ (8h TWA)
Use of N2

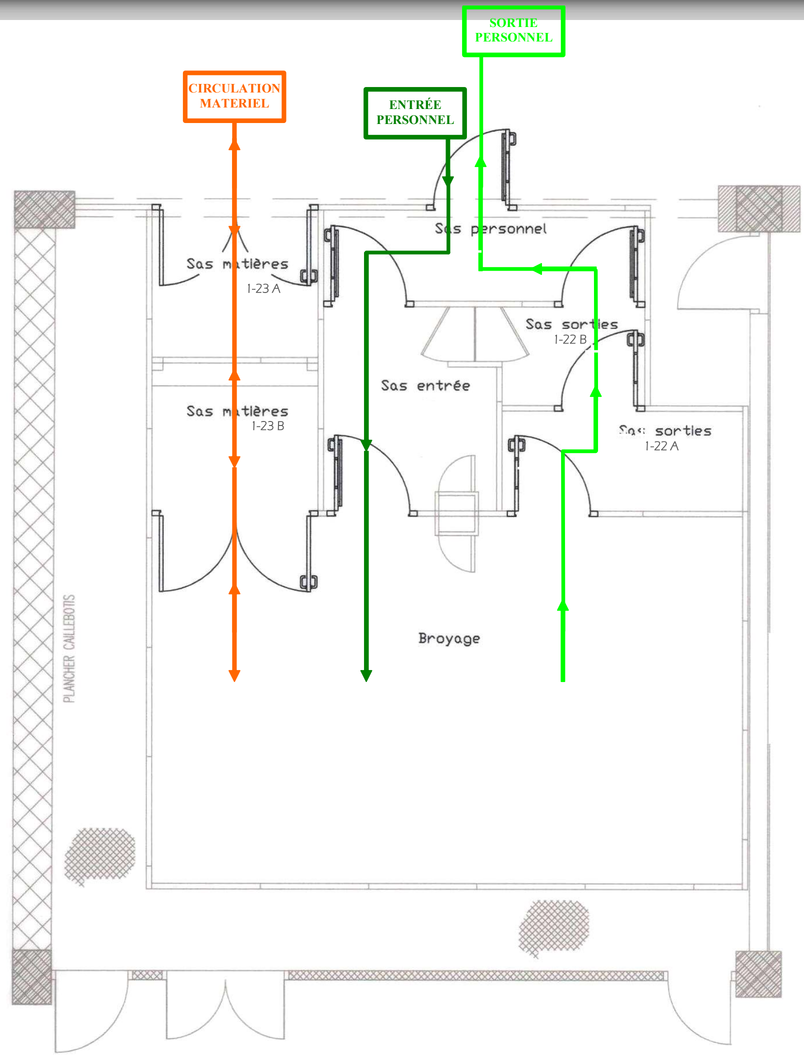
Complete suit with ventilated hood
Containment level : 100 µg/m³ (8h TWA)
Use of N2

Containment level : 10 µg/m³ (8h TWA)
Complete sute equipped with breatable air

Particle size reduction:

Safety aspect_Hygiene

- Exposure to the powder during loading , unloading, cleaning
- According to the OEB product classification, protection measures adapted
- To avoid contamination to outside: classified work rooms, depression, mandatory decontamination before exit of operators by air-lock
  - Example: circulation plan for a typical milling room.



Particle size reduction:

Safety aspect_Operators protection: high containement level

- ***Barrier isolator equipment designed to be used in conjunction with milling equipment***
- ***Isolator designed to have high containment level : 0.1 µg/m3 (8h TWA)***
- ***Isolator and process equipment nitrogen blanketed***
- ***CIP to clean isolator***

Microsoft
owerPoint Slide Sho

Particle size reduction:

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Thank you