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presents

FINE MILLING OF THE PHARMACEUTICAL COMPOUNDS: AN OVERVIEW ABOUT DIFFERENT TECHNOLOGIES AND APPLICATIONS

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MAIN TOPICS

- What is a pharmaceutical powder? (definition and characteristics)
- Why particle size reduction?
- How to obtain the suitable solid form? (different methods)
- Different milling technology – an overview

WHAT IS A PHARMACEUTICAL POWDER?

In the pharmaceutical field "powder" can be intended as a set of solid particles, dry, having different shape and dimensions, and is the basis of different preparations like granulate, tablets, capsules, is part of the compounds of various pharmaceutical form like:

- **suspensions,**
- **suppositories,**
- **semisolid preparation for topical use,**

It may also represent a pharmaceutical form in itself; in this case we speak of powder for internal use or dispersions for external use.

CLASSIFICATION OF THE PHARMACEUTICAL POWDERS

Kind of powder	Size in µm	Sub-divisions	Size in µm	Application
Granulates	600-4000			direct administration, compressing
Pharmaceutical powders	0.5-1000	coarse	500-1000	for maceration and percolation (vegetal drugs), compressing
		fine	100-600	direct administration (powder,capsule, pod)
		very fine	20-100	suspensions, dispersions, direct administration
		micronized	0,5-20	suspensions, adsorption powder, direct administration

WHY PARTICLE SIZE REDUCTION?

Particle size reduction is useful or necessary for technical as well therapeutic purposes, i.e.:

- **improve tolerability of ophthalmic preparations containing particles in suspension,**
- **obtain a most efficient delivery to the lungs in the inhalation therapy,**
- **improve the stability of the suspensions, increase the homogeneity of a formulation,**
- **increase the specific surface of the ingredient,**
- **increase the bioavailability of a poorly soluble drug**

PARTICLE SIZE REDUCTION: THE MAIN METHODS

Suitable powder can be obtained through two different approaches:

- **A physical and chemical approach (molecular aggregation)**
- **A mechanical approach (reduction of a coarse material in small particles)**

PARTICLE SIZE REDUCTION: THE MOLECULAR AGGREGATION

The molecular aggregation's techniques involve the aggregation of ions or molecules in crystals or amorphous particles:

sublimation
crystallization (from temperature or solvent change)
precipitation
spray-drying (drying from spray)

In the precipitation and crystallization it is possible to affect the particle size varying the speed of some parameters, typically:

temperature change
addition of solvent
mixing of reagents

Through the techniques of molecular aggregation it is possible to obtain very fine powder and regular particles the disadvantage may be represented y the loss of material

PARTICLE SIZE REDUCTION: MILLING, THE «MECHANICAL APPROACH»

Generally speaking milling means mechanical reduction of a coarse material in small particles

Depending on the size of the raw material and on the obtained final particle size distribution we speak of:

1. crushing: a raw material is reduced in coarse pieces (some mm)

2. milling: the final particle size range is from a few hundred to a few tens of µm

3. micronization: final particle size less than 20µm

For each of these operations there are appropriate equipment

PARTICLE SIZE REDUCTION: RAW MATERIAL CHARACTERISTICS

MATERIAL'S PROPERTY WHICH CAN AFFECT THE MILLING PROCESS:

HARDNESS: according to the MOHS scale

ADHESION: adhesives materials are milled with difficulty; the milled particles tend to agglomerate, we can proceed suggest a co-milling with excipients.

SOFTENING TEMPERATURE: heat released in milling can soften certain substances, i.e. fats, in such cases we can operate at low temperature.

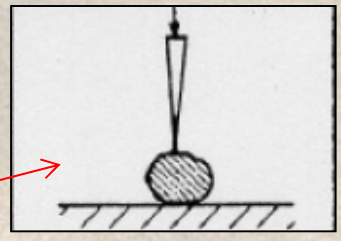
MOISTURE CONTENT: for substances with high humidity content it is recommended a pre-drying.

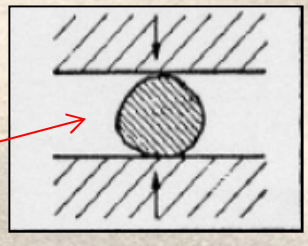
PLASTICITY: substances with high degree of plasticity are difficult to be milled; it is suggested a cryo-milling or dissolving the powder in a solvent and then evaporating it.

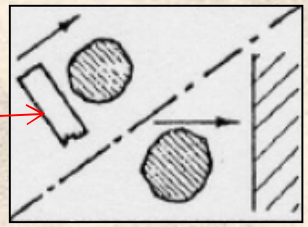
PARTICLE SIZE REDUCTION: MILLING PRINCIPLES

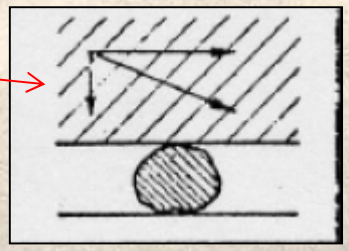
MILLING PRINCIPLES

The milling process takes place following 4 main mechanisms:









1. cutting
2. compression
3. impact
4. friction

The various types of mill differ according to the type of the applied force and may also combine different mechanisms

PARTICLE SIZE REDUCTION: MILLING PRINCIPLES

MILLING PRINCIPLES

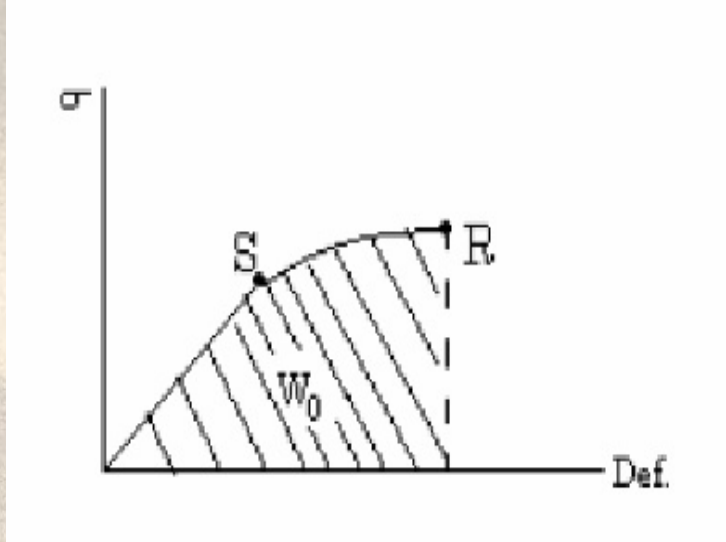
Within a certain level there is a proportion between the applied force and the obtained deformation of the particle;

we speak of elastic deformation

Over this limit the deformation is no more reversible,

we speak in this case of plastic deformation

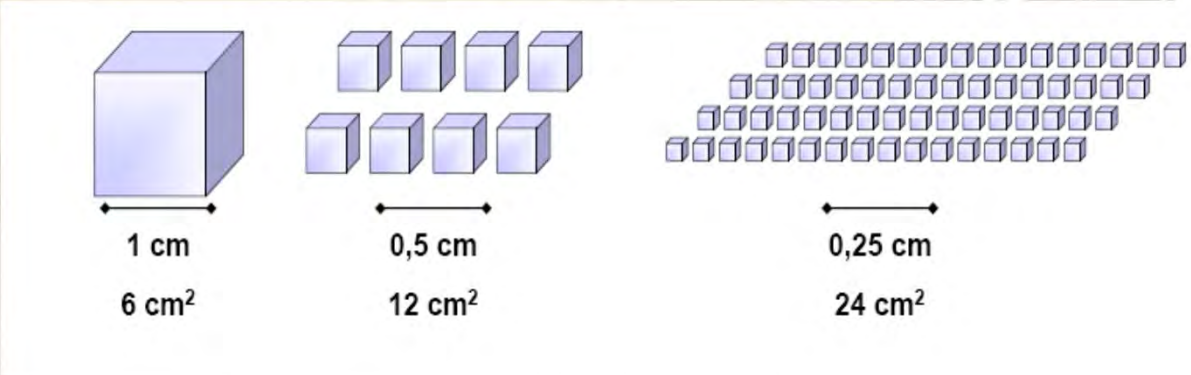
After this stage further increasing the applied force we obtain the particle breaking



DIFFERENT MILLING TECHNOLOGIES: MICRONIZERS

The micronization is a pioneering technique that allows to reduce the particle size of a substance in powder form down to micro-meter size (<0,5-20 µm) using high pressurized gas.

The benefit of a micronized powder is related to the increased product surface: an higher exposed surface allows for an higher availability of the molecule in the relevant process/use



In the pharmaceutical industry the micronization is normally used to increase the bioavailability of a poorly soluble drug, where for bioavailability of a drug means the fraction of the administered dose that reaches the systemic circulation of a living organism and the speed with which this process occurs.

DIFFERENT MILLING TECHNOLOGIES: MICRONIZERS

WORKING PRINCIPLE:

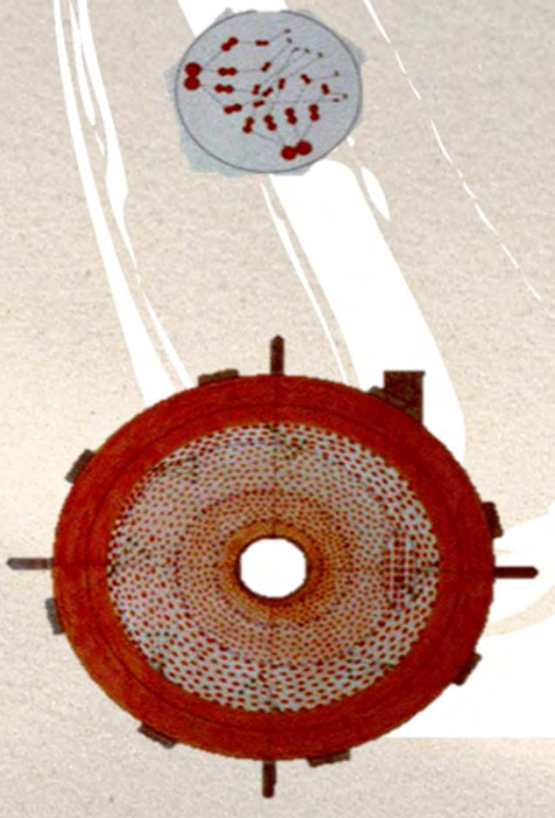
Product particles are fed into the milling chamber through a Venturi injector.

High-velocity air is introduced into the mill through jet nozzles placed around the circular chamber of the mill.

Particles are consequently accelerated inside the milling chamber and dragged in a spiral movement causing them to collide repeatedly.

They break up into progressively small particles until the accumulated energy is reduced to negligible values.

The exhausted air carries micronized particles into a suitable dedusting unit.



DIFFERENT MILLING TECHNOLOGIES: MICRONIZERS

ADVANTAGES:

among the different milling systems know at the present, the spiral jet mill is, without doubt, the most suitable for the micronizing of the chemical and pharmaceutical products.

Thanks to its well established and particular working principle is able to meet numerous demand of fineness until to obtain

micronized particles up to the 100% below 5 microns.

This is result that cannot be achieved by more conventional mills having different conception.

DIFFERENT MILLING TECHNOLOGIES: MICRONIZERS

ADVANTAGES:

- **Easy Cleaning for Validation (to avoid cross contamination)**
- **No mechanical parts in movement (no lubrication, strong reduction of metallic contamination)**
- **No Heat Generation (Joule-Thompson effect)**
- **Constant Temperature (useful to avoid polymorphism)**

DIFFERENT MILLING TECHNOLOGIES: HAMMER MILLS

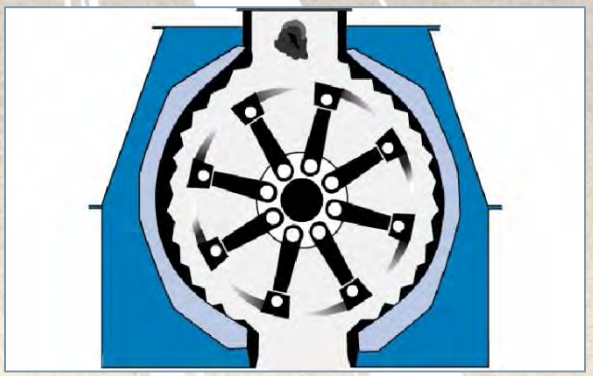
The hammer mill is the optimum solution for the fine milling and pulverization of hard, crystalline and fibrous products.

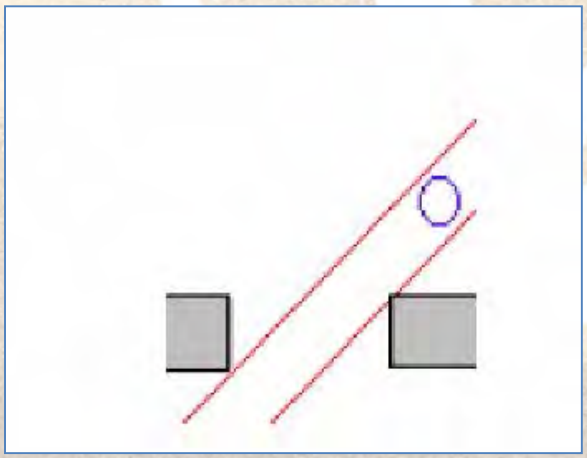
WORKING PRINCIPLES:

The operating principle is widely experienced:

inside the grinding chamber the rotor is provided with double profile hammers which, due to the centrifugal force repeatedly collide with the product to be treated up to reduce it to the size defined by the calibration screen and avoiding any metal to metal contact.

The particles reach the calibration screen sideway and not vertically, in this manner the exit dimension of the particles is smaller than the diameter of the screen's holes.





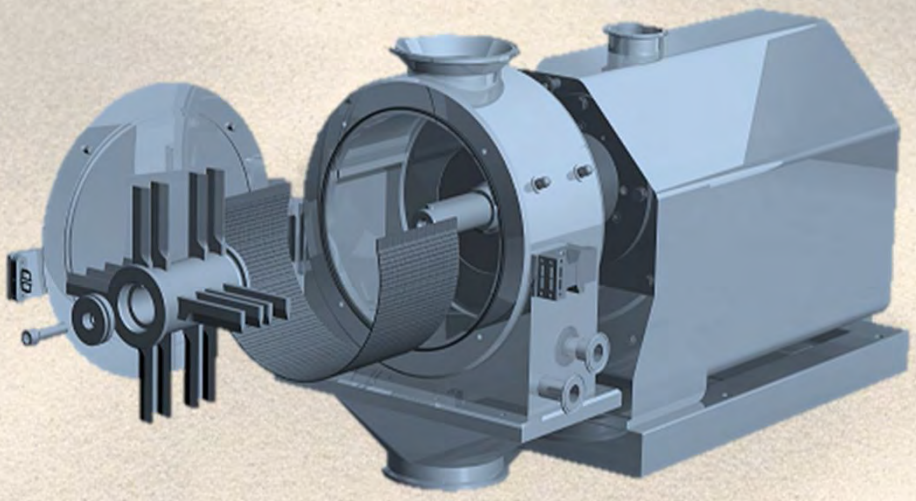
DIFFERENT MILLING TECHNOLOGIES:
HAMMER MILLS

The hammer mill is available in different models, suitable for treatment of batches from 0,1 kg/h up to 2000kg/h and more, reaching fineness lower than 100 microns upon a feeding size of few cm.

This mill stands out for easiness in radical cleaning and disassembly.

The mill can be supplied complete with devices able to grant automatic charge/discharge but it can be installed in pre-existing plants too.

DIFFERENT MILLING TECHNOLOGIES: HAMMER MILLS

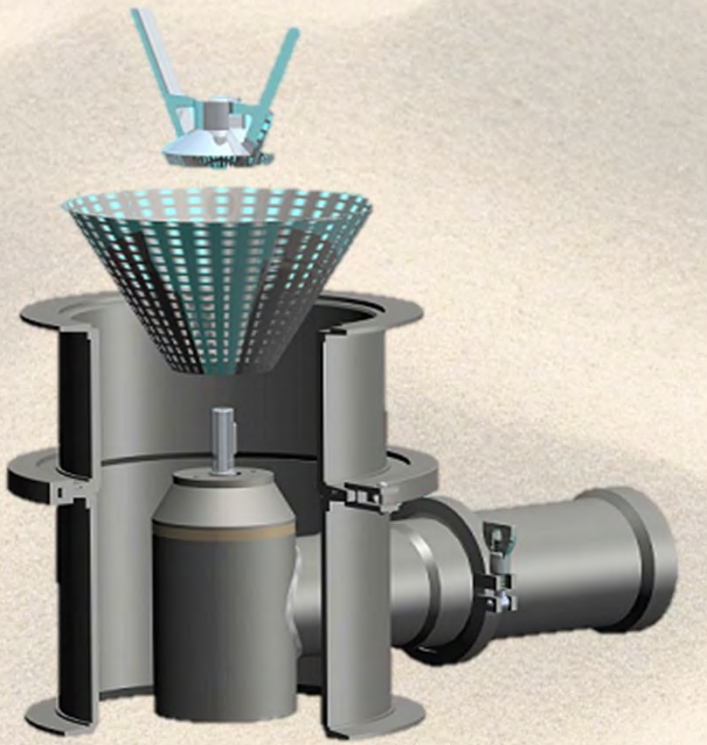


PROCESS VARIABLES:

The productivity and the final particle size are principally influenced by:

- **The tip speed of the rotor**
- **The shape of the milling tools (hammer-knife)**
- **The hole's diameter and number**
- **The holes shape**

DIFFERENT MILLING TECHNOLOGIES:
CONE MILLS

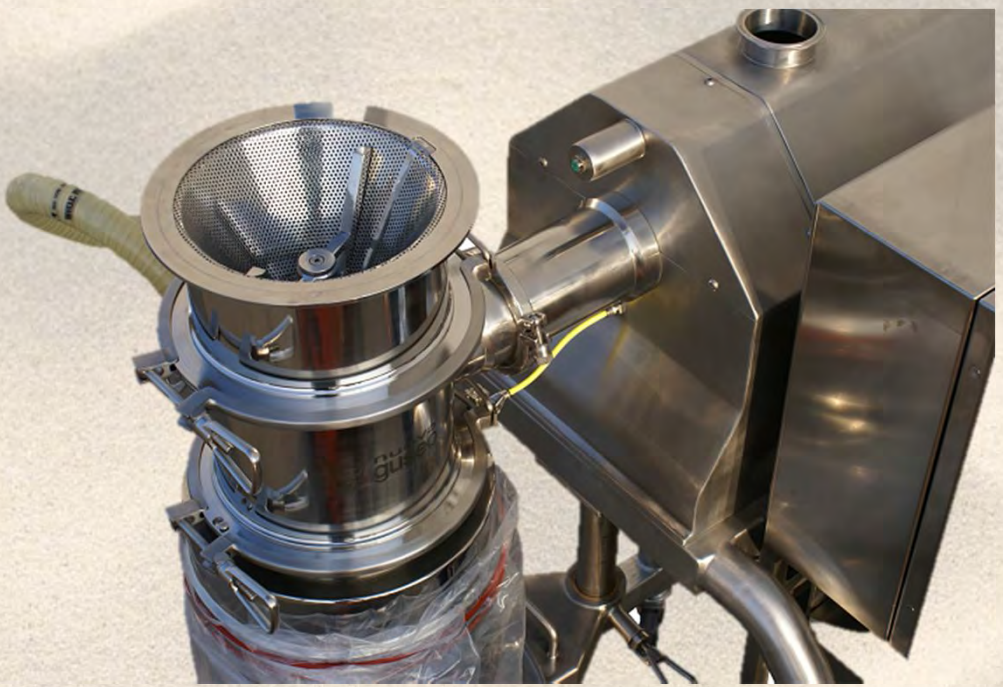


The cone mill is mainly suitable for de-lumping and sizing of products, in medium batch, having heterogeneous particle size to a fines between 100 and 200 microns

Working principle is simple:

the product, when fed into the calibrating chamber, is forced by a rotating impeller outward to the conical screen surface and once the product has passed through the screen, it falls into the receptacle beneath.

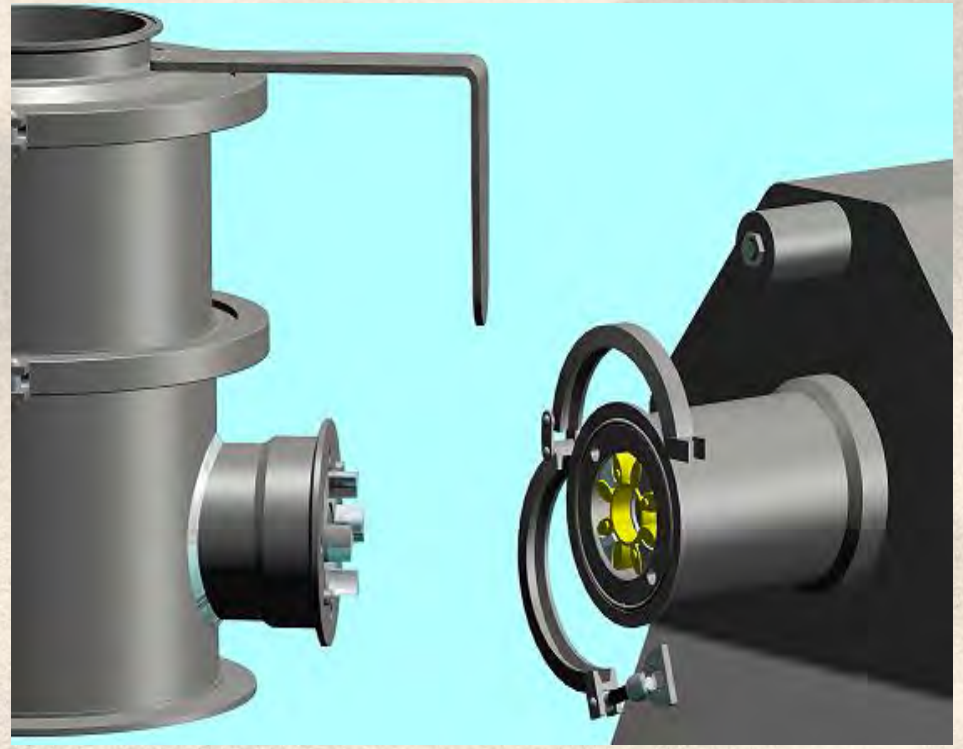
DIFFERENT MILLING TECHNOLOGIES:
CONE MILLS



The cone mill can be used to process, with high-performance, several kind of materials even wet, fragile, gummy etc. and is ideal to satisfy production requirements of the following industries:

- **Pharmaceutical**
- **Chemical**
- **Foodstuff**

THE DIFFERENT MILLING TECHNOLOGIES:
CONE MILLS



The cone mill are available in different configurations: for use in the industrial field and/or specific developed for the pharmaceutical field.

This latter, realized in strict compliance with cGMP's, differs for the accuracy of details and the surfaces finishing degree.

In this version is possible to separate the mill from the relevant motor; this peculiarity enables to install the mill in working area and the motor in technical one granting the possibility, when necessary, to detach the mill for cleaning operations.

DIFFERENT MILLING TECHNOLOGIES:
CONE MILLS

PROCESS VARIABLES:

The productivity and the final particle size are principally influenced by:

- **The impeller's speed**
- **The distance between impeller and screen**
- **The hole's diameter and number**
- **The holes shape**

Thank you very much for your attention!

You are more than wellcome at our booth
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