# Granulation Techniques and Technologies

Granulation, the process of particle enlargement by agglomeration technique.

Granulation process transforms fine powders into free-flowing, dust free granules that are easy to process compress, packed to use etc.

Or

Decrease the surface area of the sensitive API for further process, transportation, handling, compression etc.

Granules used in the pharmaceutical industry have particle size in the range of:

0.2 - 4.0 mm.

# Granulation Techniques and Technologies

- Granules are produced to enhance the uniformity of the API in the final product.
- Improve flow property and compression characteristics;
- to increase the density of the blend so that it occupies less volume per unit weight for better storage and shipment;
- To facilitate metering or volumetric dispensing
- To reduce dust during granulation process to reduce toxic exposure and process-related hazards
- To improve the appearance of the product.
- To control the rate of drug release

# Granulation Techniques and Technologies

**Characteristics:**

- ❖ Spherical shape for improved flow;
- ❖ narrow particle size distribution for content uniformity;
- ❖ volumetric dispensing;
- ❖ sufficient fines to fill void spaces between granules for better compaction and compression;
- ❖ Adequate moisture and hardness to prevent breaking and dust formation during process.

# Granulation Techniques and Technologies

Properties of the granules depend upon;

- ❖ Particle size of the drug and excipients;
- ❖ the type, concentration, and volume of binder and solvents;
- ❖ granulation time;
- ❖ type of granulator;
- ❖ drying rate (temperature and time), etc.

# Granulation Techniques and Technologies

Mechanism:

- Solid bridges;
- sintering [***process of compacting and forming a solid mass of material by heat or pressure without melting it to the point of liquification***];
- chemical reaction;
- crystallization and
- deposition of colloidal particles.

# Granulation Techniques and Technologies

## Methods:

**Dry granulation**:

Mechanical compression (slugs) or compaction (roller compaction).

**Wet granulation**:

Uses granulation liquid (binder/solvent) to facilitate the agglomeration by formation of wet mass by adhesion.

The type of process selection requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties etc.

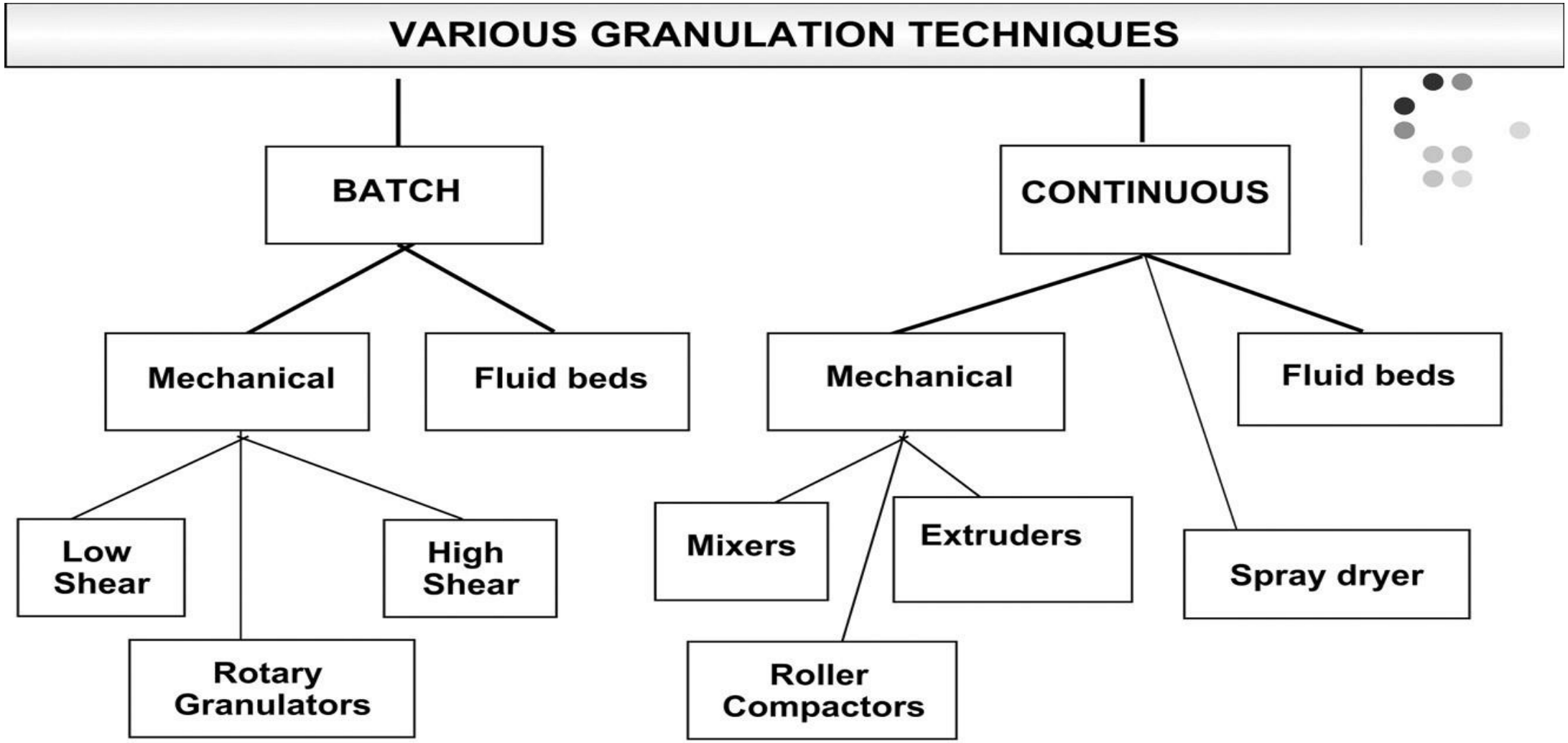
# Granulation Techniques and Technologies

**Granulation technologies:**

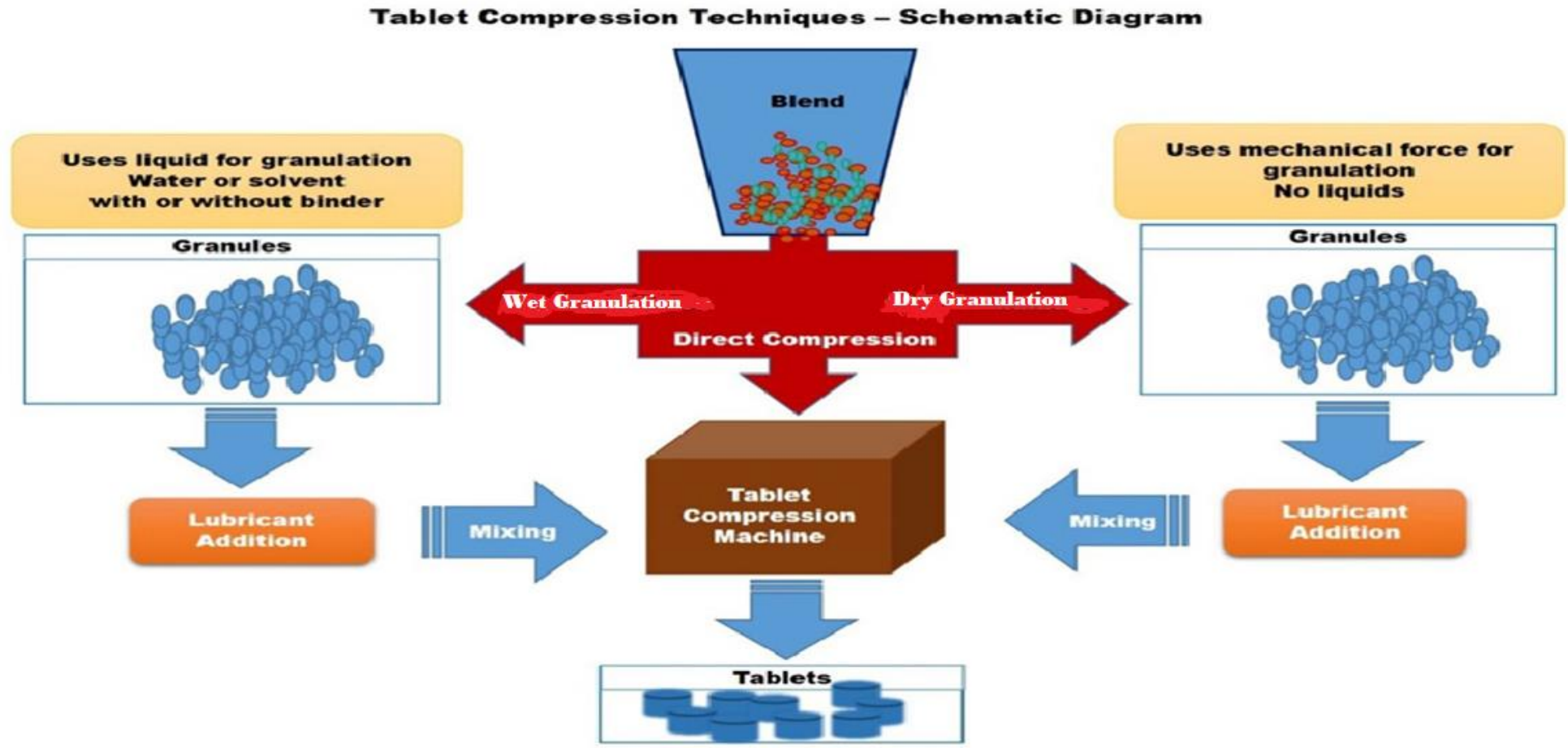
i. Roller compaction,
ii. Extrusion / Spheronization

Other are

i. Spray drying,
ii. Supercritical fluid,
iii. Low / High shear mixing,
iv. Fluid Bed Granulation, etc.
v. Reverse wet granulation
vi. Hotmelt Granulation
vii. Freeze granulation
viii. Foam Granulation


VARIOUS GRANULATION TECHNIQUES
BATCH
CONTINUOUS
Mechanical
Fluid beds
Mechanical
Fluid beds
Low Shear
High Shear
Rotary Granulators
Mixers
Extruders
Roller Compactors
Spray dryer

# Granulation Techniques and Technologies




**Schematic diagram of tablet compression techniques**

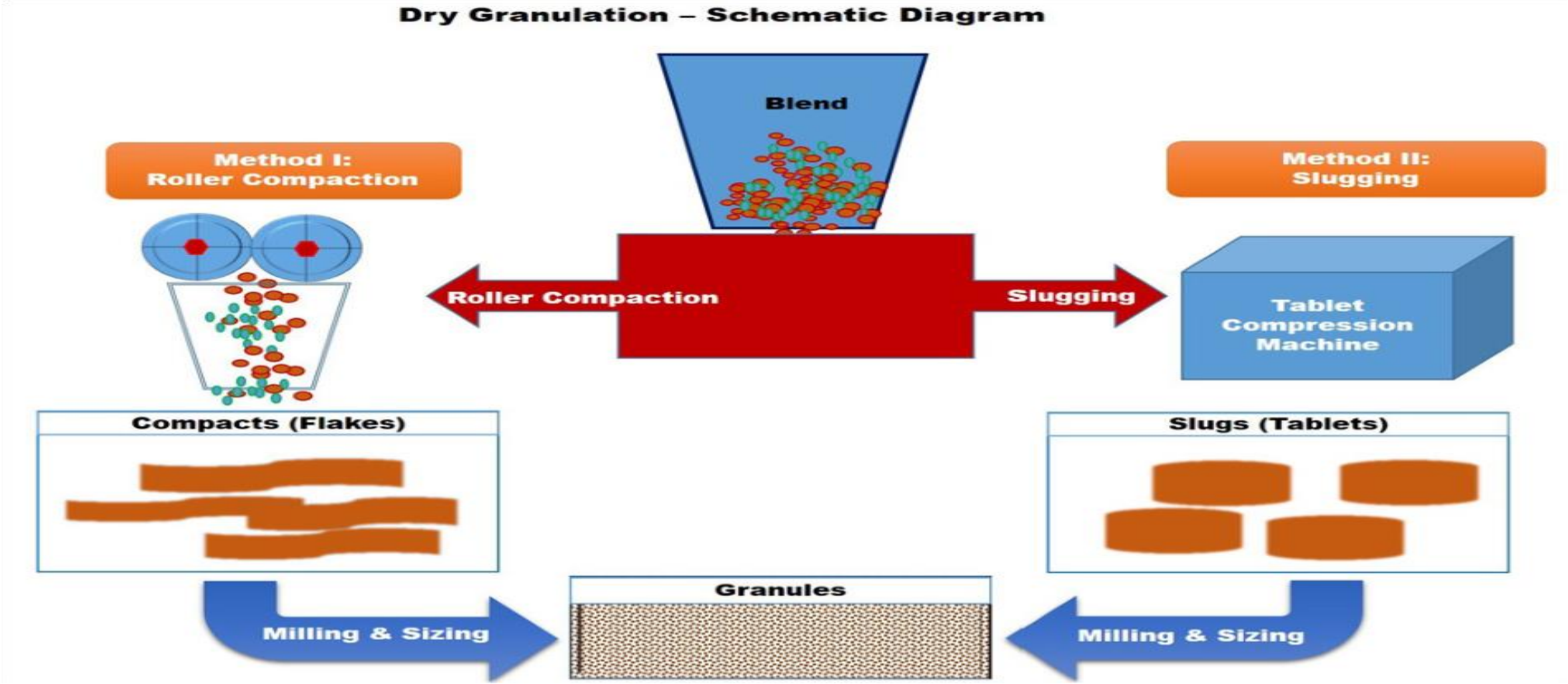
# Granulation Techniques and Technologies

Roller Compaction:
A process to force fine powders between two counter rotating roll and presses the raw material into a solid compact (flakes, sheets, strips). Roll Compacters are also called dry granulations.

This process relies on interparticulate bond formation. Granule bond formation is characterized in different stages, which usually occur in the following order:

1. Particle rearrangement
2. Particle deformation
3. Particle fragmentation
4. Particle bonding.

# Granulation Techniques and Technologies




Schematic diagram of dry granulation and two different techniques. Method I is roller compaction and Method II is slugging.

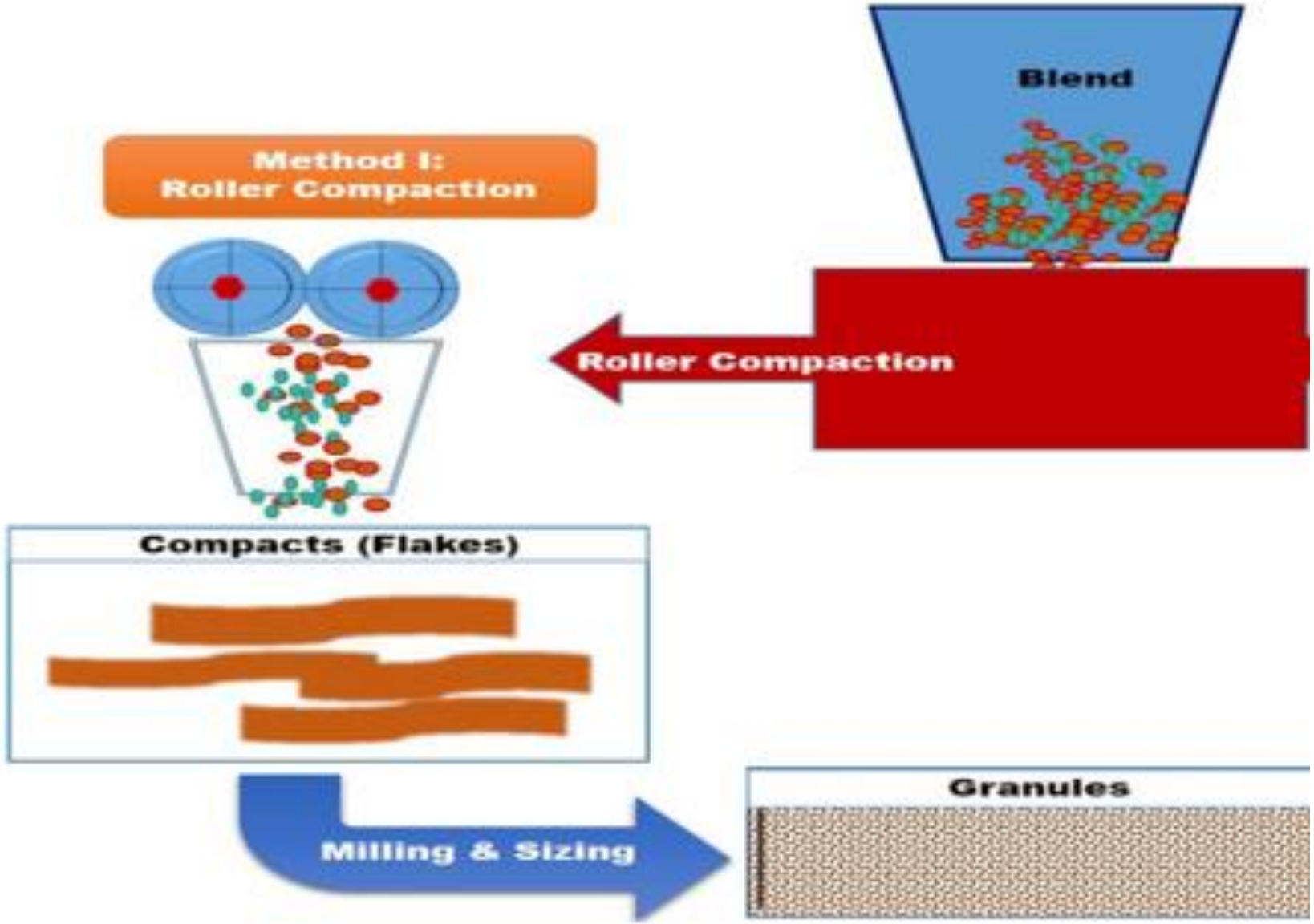
# Granulation Techniques and Technologies

**Principle:** A roller compactor generality consists of three major units;

1) A feeding system, which converts the powder to the compaction area between the rolls;

2) A compaction unit, where powder is compacted between two counter rotating rolls to a ribbon by applying a force; and

3) A size reduction unit, for milling the ribbons to the desired particle ze. The most important parameter in the dry granulation process is the force applied on the powder compacted between two rolls. The applied force is expressed in KN/cm, being the force per cm roll width.


Blend
Method I:
Roller Compaction
Roller Compaction
Compacts (Flakes)
Milling & Sizing
Granules

# Granulation Techniques and Technologies

**Types of Roller Compactors**

Roller compactors can be divided into two categories;

- ❑ Equipped with a fixed gap
- ❑ With a floating gap.

Both consist of the three major units as explained above but differ in the way in which the smallest distance (gap) between the two rolls is realized;

1. When a fixed gap installed, the amount of powder drawn in into the compaction area between the rolls is inconstant which results in different forces applied to the powder bed and will cause large fluctuations in the ribbon and granulate properties.
2. In the floating gap the distance between the rolls change according to the amount of powder feed. The force applied to the powder remains constant. This ensures that property fluctuations in the granules are reduced to a minimum.

# Granulation Techniques and Technologies

**Main Process variables**:

1. Compaction pressure, i.e. compaction force per cm of roll width.
2. Speed of feeding screws.
3. Roll Speed.

# Granulation Techniques and Technologies

Advantages:

1. Due to absence of water or organic solvents attractive for drugs, which are moisture or heat sensitive.
2. Suitable for drugs that either have a low melting point or degrade rapidly during heating.
3. The granules thus formed give porous tablets and allowing water to penetrate more easily into the tablet which improved disintegration time.
4. This process is environmentally friendly and provides an efficient and easily automated process.
5. Low operational cost
6. Roll compaction / dry granulation can be used, if the drug or the excipients have poor flowability.
7. It can also be used for densification of powders prior to encapsulation.

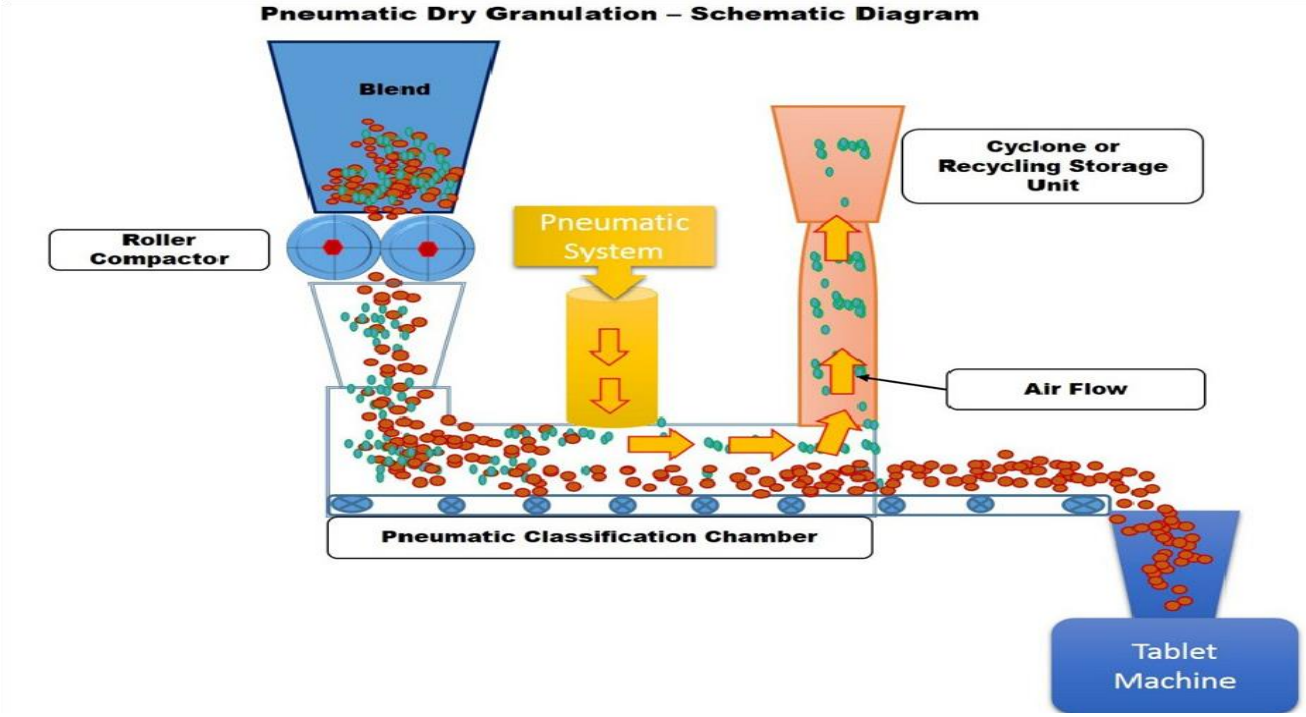
# Advantages of Roller Compaction

| | |
|---|---|
| ❖ Simplifies processing | ❖ Uses less raw materials |
| ❖ Facilitates powder flow | ❖ Eliminates water-induced degradants |
| ❖ Uses minimal energy to operate | ❖ Improves process cycle time |
| ❖ Requires less man-hours to operate | ❖ Prevents particle segregation |
| ❖ Improves drug dosage weight control | ❖ Facilitates continuous manufacturing |
| ❖ Reproduces consistent particle density | ❖ Improves content uniformity |
| ❖ Produces good tablet and capsule disintegration | ❖ Does not require explosion proof room / equipment |
| ❖ Eliminates aqueous and solvent granulating | ❖ Produces a dry product that is process scale able |

# Granulation Techniques and Technologies

## Pneumatic Dry Granulation (PDG)

Pneumatic dry granulation (PDG), an innovative dry granulation technology, utilizes roller compaction together with a proprietary air classification method to produce granules with extraordinary combination of flowability and compressibility.

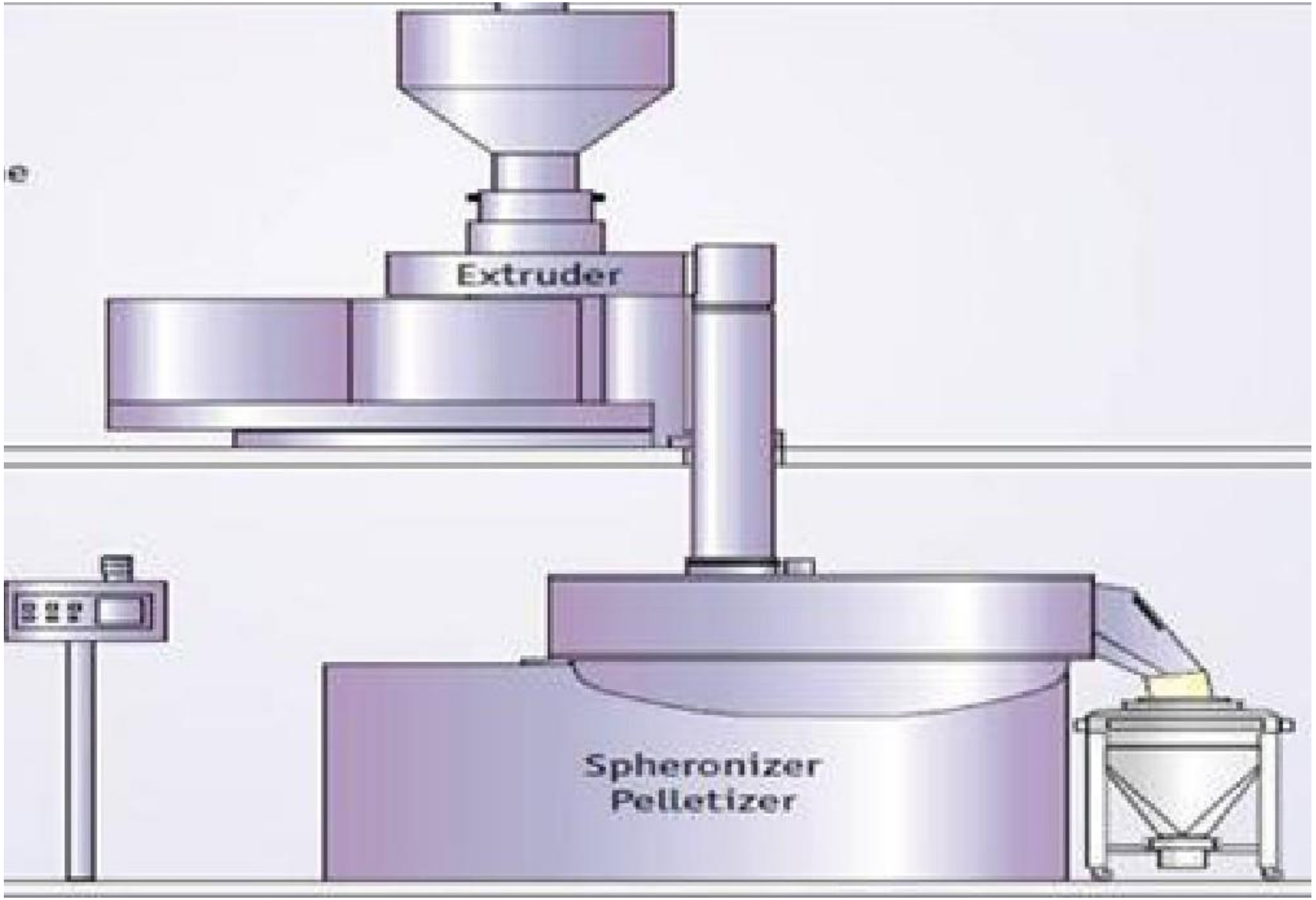



Initially applying mild compaction
Produce a compacted mass comprising a mixture of fine particles and granules.
Fine particles / granules are separated from the intended size granules in a fractioning chamber by entraining in a gas stream (pneumatic system) and be compressed into tablets.
The entrained fine particles / granules separated by cyclone and return to roller compactor for immediate reprocessing.

# Extrusion / Spheronization

**Extrusion is a process used to create objects of a fixed cross-sectional profile. The products of extrusion are generally called "extrudates".**

**Spheronization, or Maramuerization, is a rapid and flexible process where pharmaceutical products are made into small spheres, or spheroids. Spheronized products are relatively dense, of a uniform in size and shape and have defined surface characteristics.**


Extruder
Spheronizer
Pelletizer


a
b
c

1


2

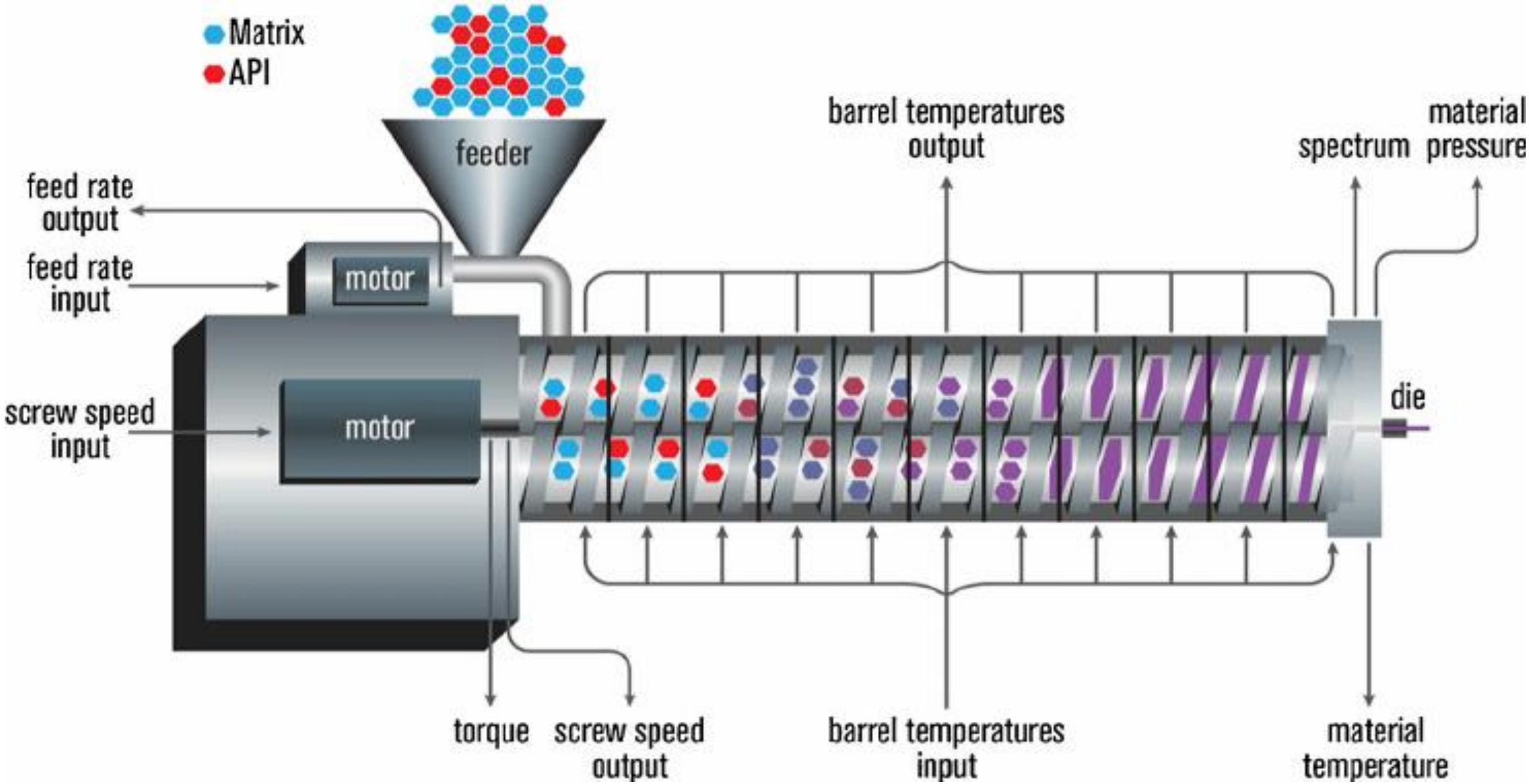

3


4

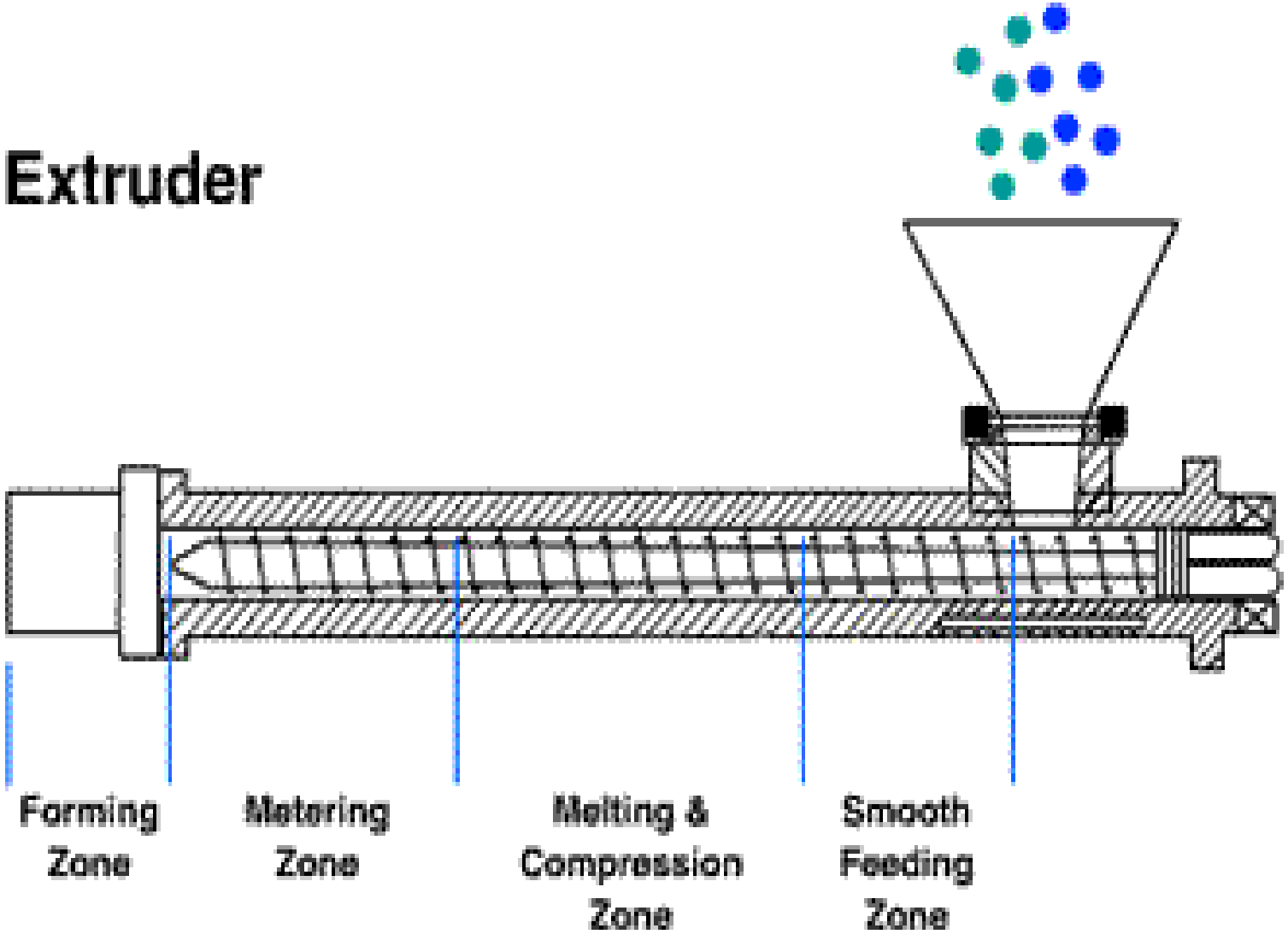
# Extrusion / Spheronization

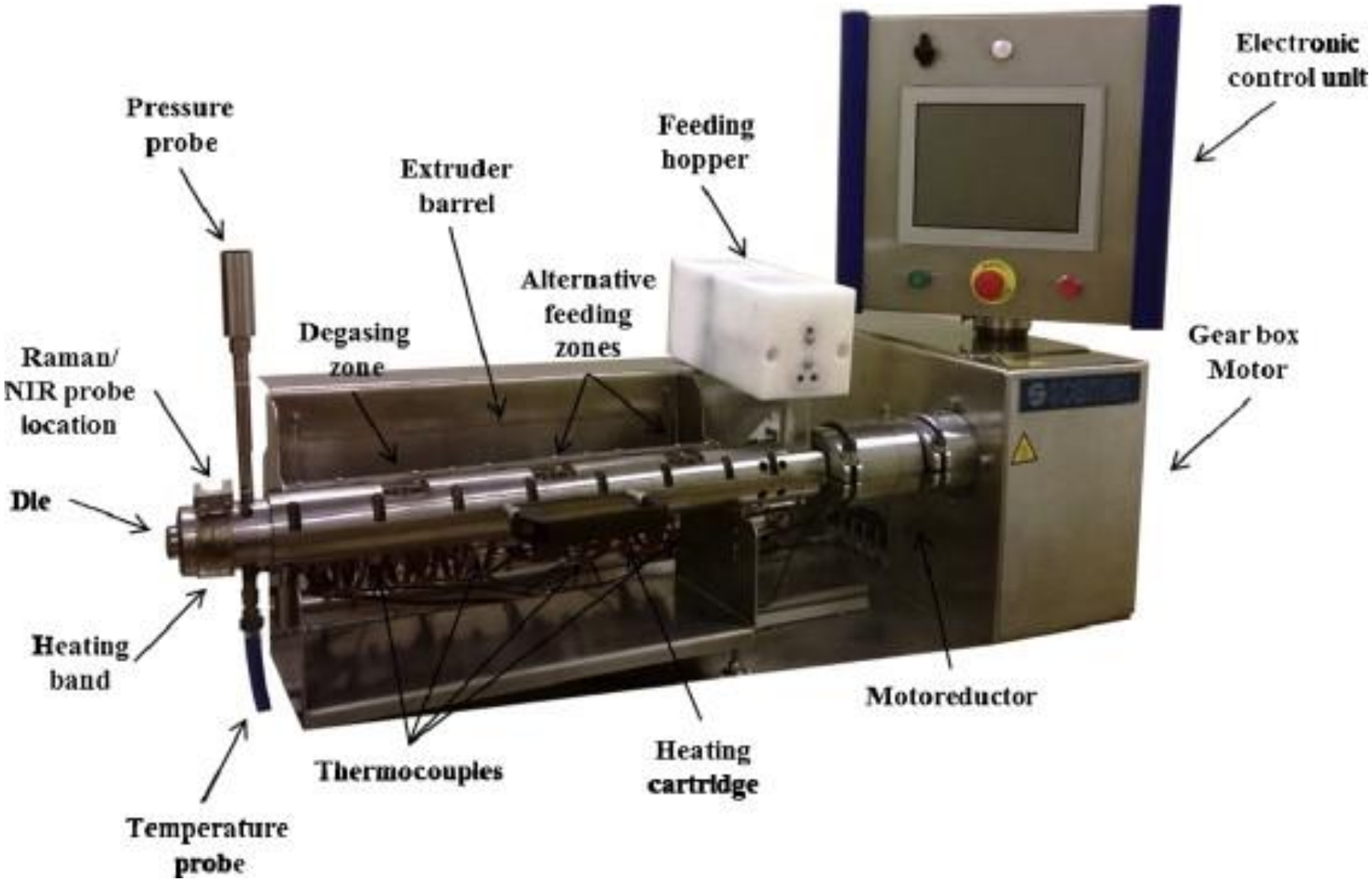
**Extrusion-spheronization a pelletization technique was developed in the early 1960s, and this process is commonly used in the pharmaceutical industry to make uniformly sized spheroids. It is especially useful for making dense granules for controlled-release solid oral dosage forms with a minimum amount of excipients.**

**The spheronization technology was introduced by Nakahara in 1964. Spheronization (or) marumerization, is a rapid and flexible process where pharmaceutical products are made into small spheres, (or) spheroids.**


Matrix
API
feeder
feed rate output
feed rate input
motor
screw speed input
motor
barrel temperatures output
material spectrum
material pressure
die
torque
screw speed output
barrel temperatures input
material temperature

# Smooth Barrel Extruder




Pressure probe
Extruder barrel
Feeding hopper
Electronic control unit
Alternative feeding zones
Degasing zone
Raman/ NIR probe location
Gear box Motor
Die
Heating band
Motoreductor
Thermocouples
Heating cartridge
Temperature probe

# Extrusion / Spheronization

**Advantages of Spheronization**

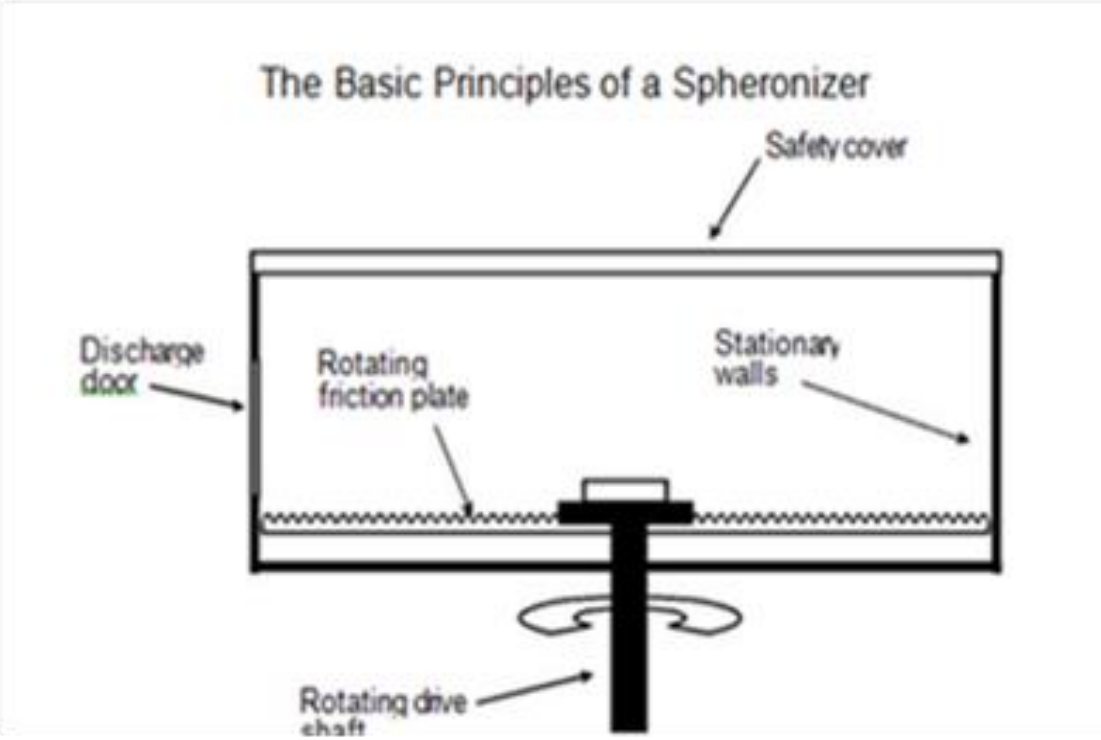
- **Optimum flow and handling characteristics.**
- **More reproducible packing into small containers.**
- **Minimum surface area to volume ratio.**
- **Optimum shape for coating and for controlled release.**
- **Easy mixing of non-compatible products.**
- **Elimination of dust.**
- **Improved hardness and friability.**

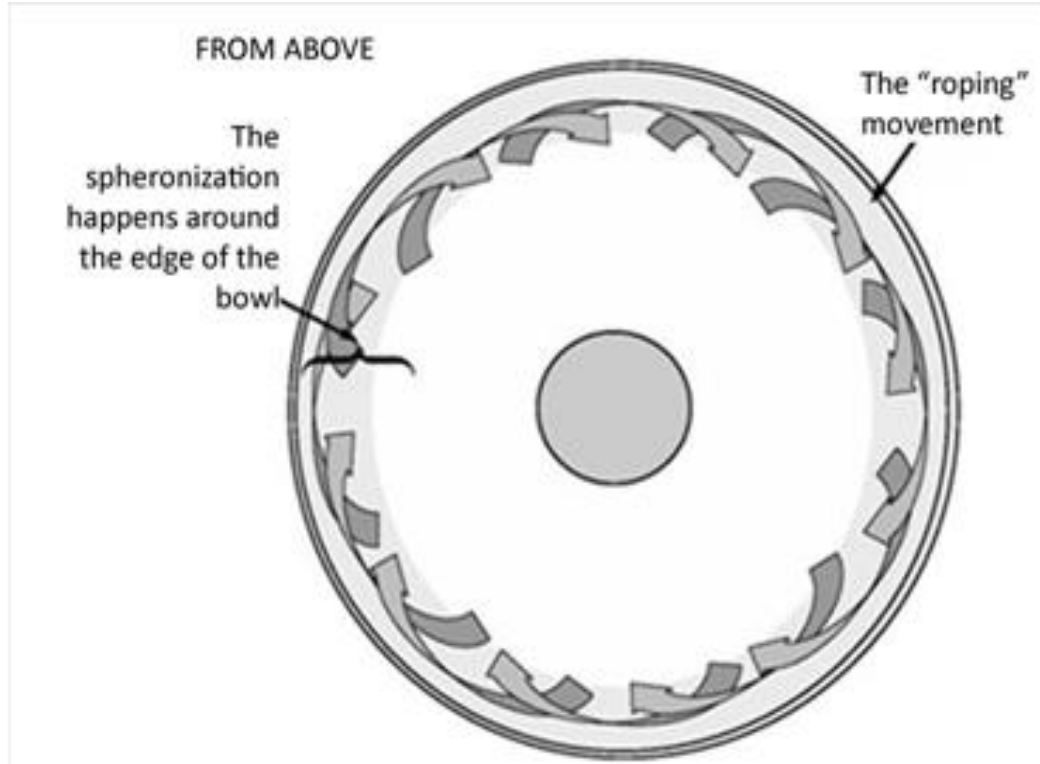
**The process consists of four process steps:**

- **Moistening the powder mixture,**
- **Forming cylinder-shaped agglomerate through extrusion,**
- **Breaking and rounding the extrudate to round pellets through Spheronization, and**
- **Drying the finished product.**

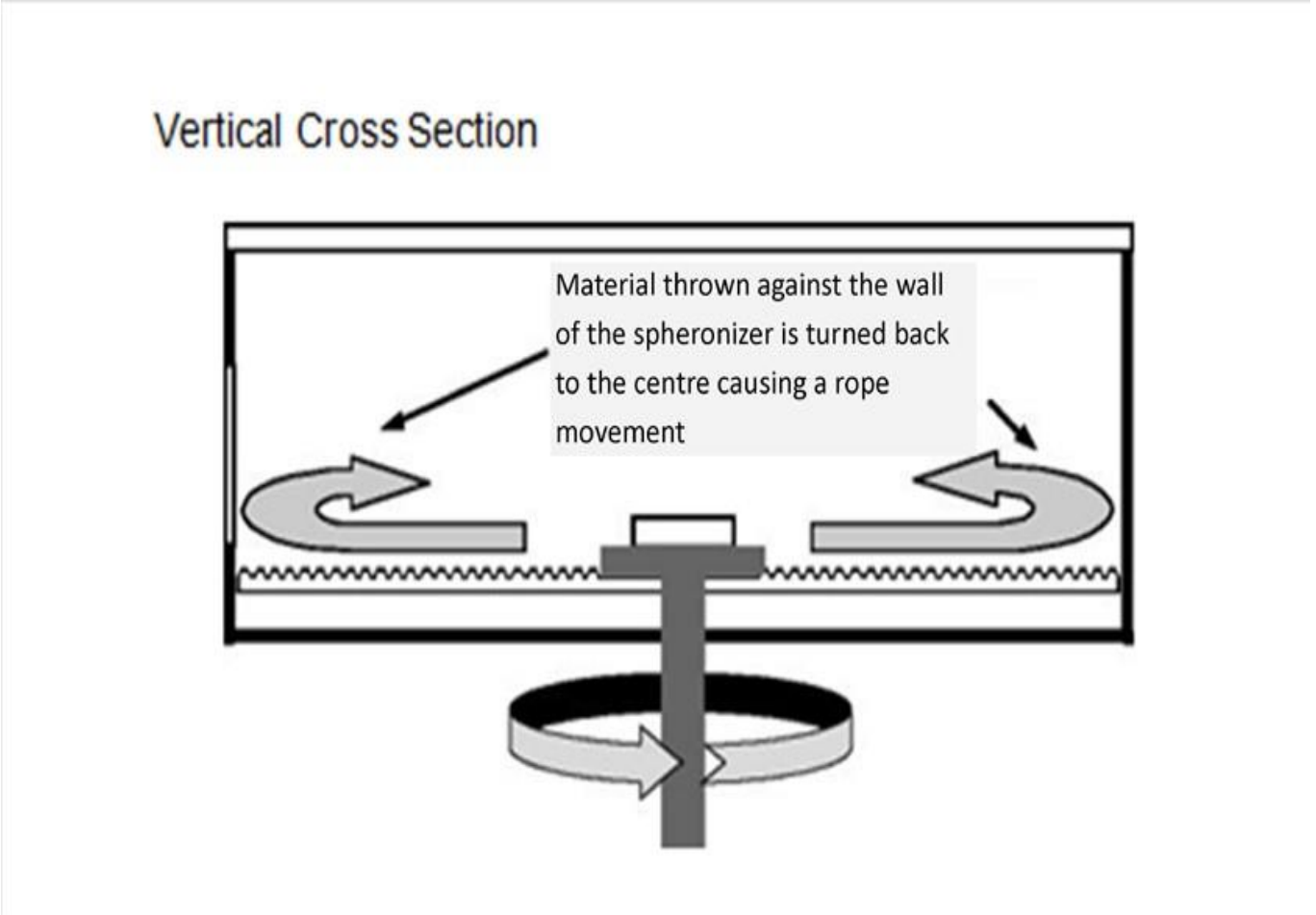
**In principle the basic machine consists of a round disc with rotating drive shaft, spinning at high speed at the bottom of a stationary cylindrical bowl. The spinning friction plate has a carefully designed groove pattern to the base. This is most often cross-hatched, but several sizes and other types are available. These discs are designed to increase the friction with the product.**

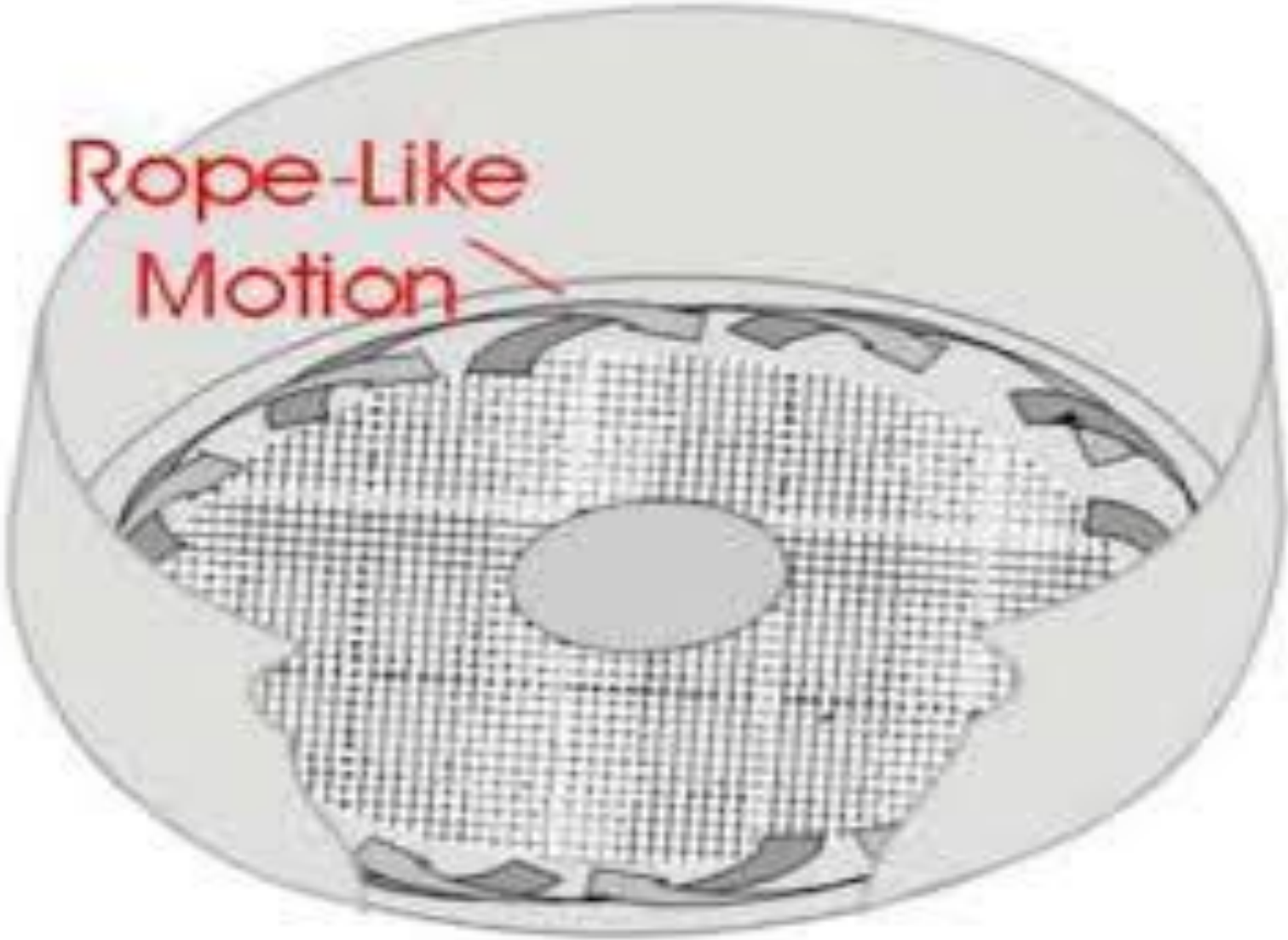
**Extrudates are added to the spheronizer and they fall onto the spinning plate. During the early contacts of the cylindrical granules with the friction plate, the extrudates are cut into segments with a length ranging from 1 to 1.2 times their diameter.**

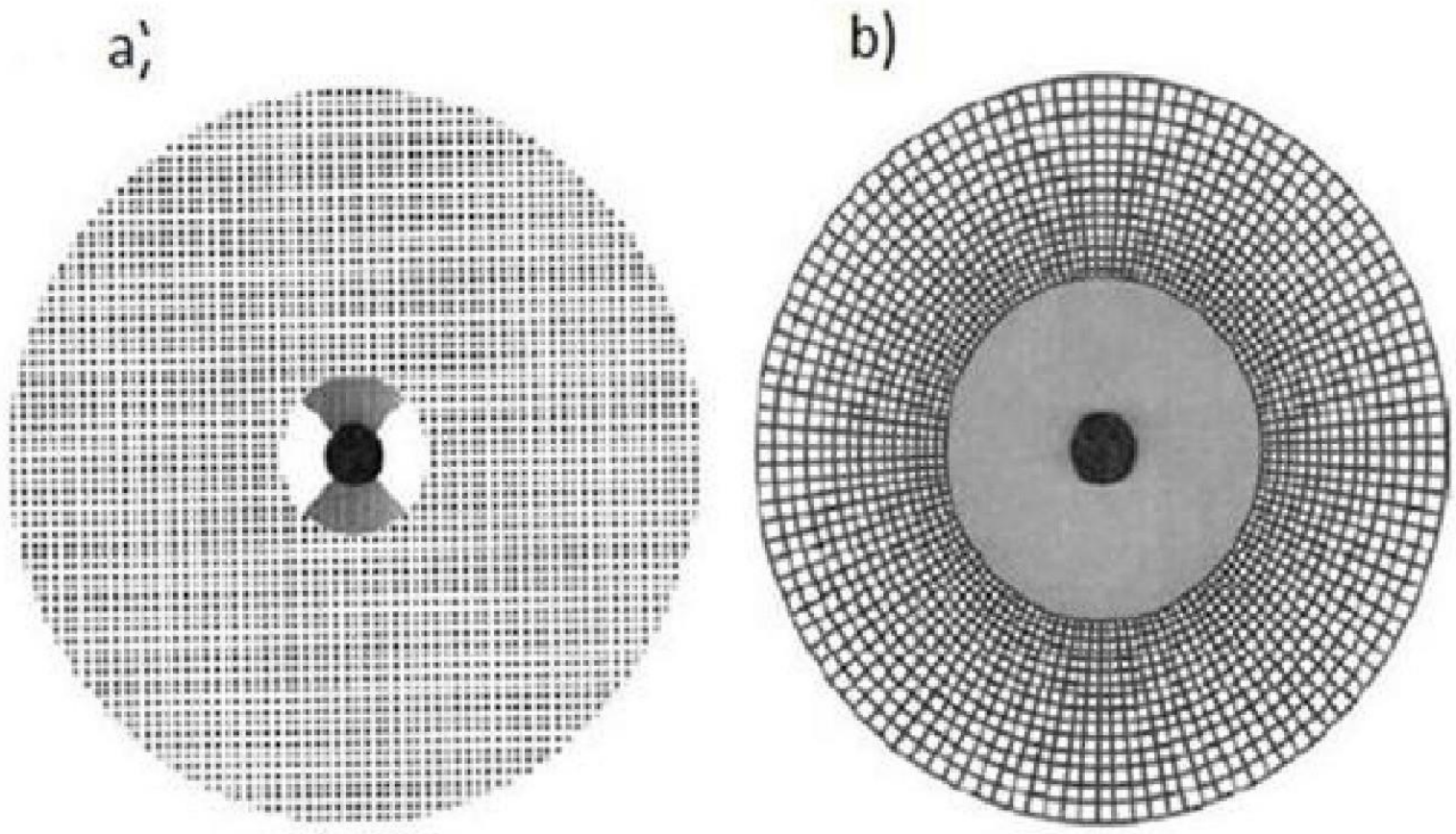


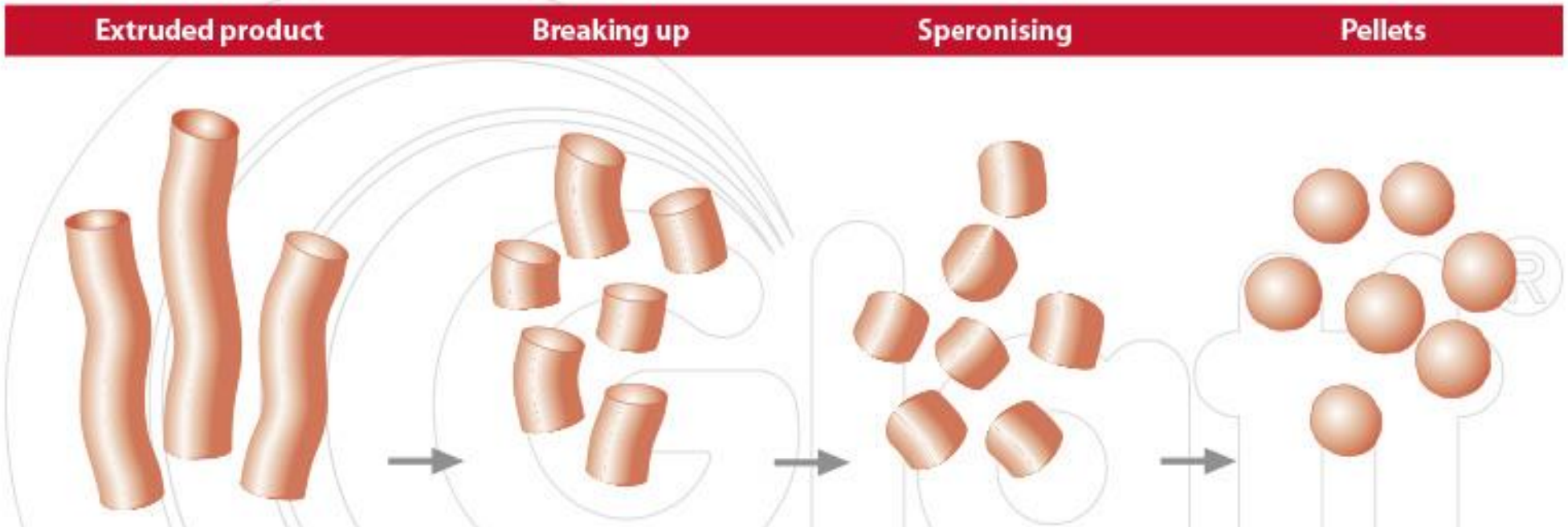
**Centrifugal force sends the material to the outside of the disc. The action of the material being moved causes the extrudate to be broken down into pieces of approximately equal length relative to the diameter of the extrudate. These cylindrical segments are gradually rounded by the collisions with the bowl wall, the plate and each other.**



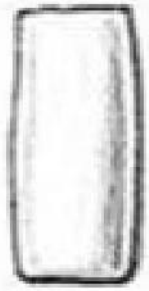

Rope-Like
Motion




Spheronizer disks having two geometric patterns: (a) a cross-hatched pattern with the groves running at right angles to one another, and (b) a radial pattern with the groves running radially from the center.


Extruded product
Breaking up
Speronising
Pellets

1(a)



cylinder

1(b)

rope

1(c)

dumb-bell

1(d)

sphere
with cavity

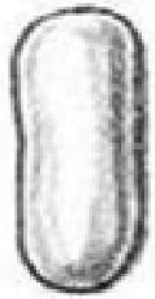
1(e)

sphere

2(a)

cylinder

2(b)



cylinder with
rounded ends

2(c)

dumb-bell

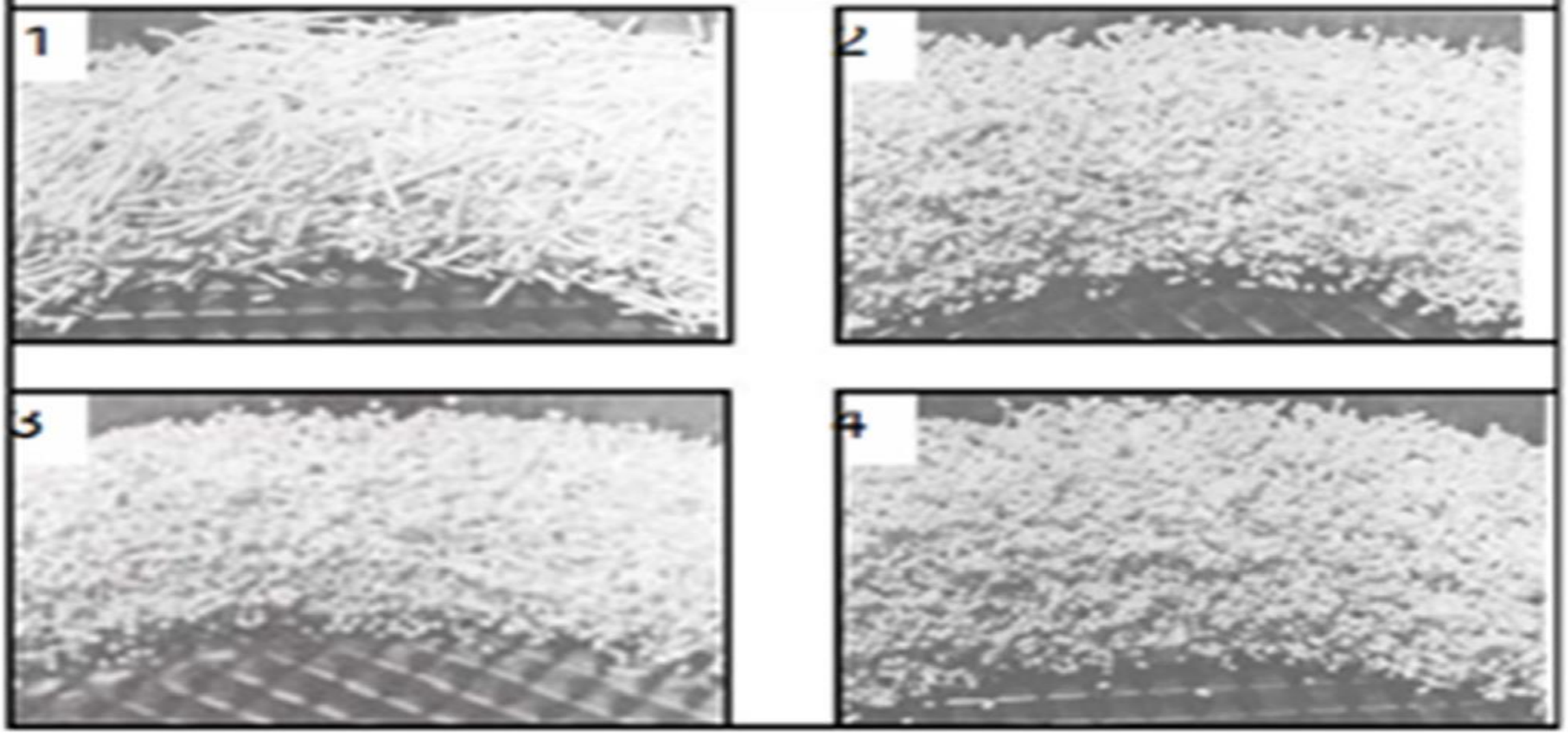
2(d)

ellipsoid

2(e)

sphere

The changing shape of extrudate with increasing time



Spheronizer 500:-

# Spray Dried Granulations

Spray Dried Granulation occurs when a liquid solution containing active ingredient / excipients are rapidly dried in hot air bed or vacuum or drying gas or microwaves.

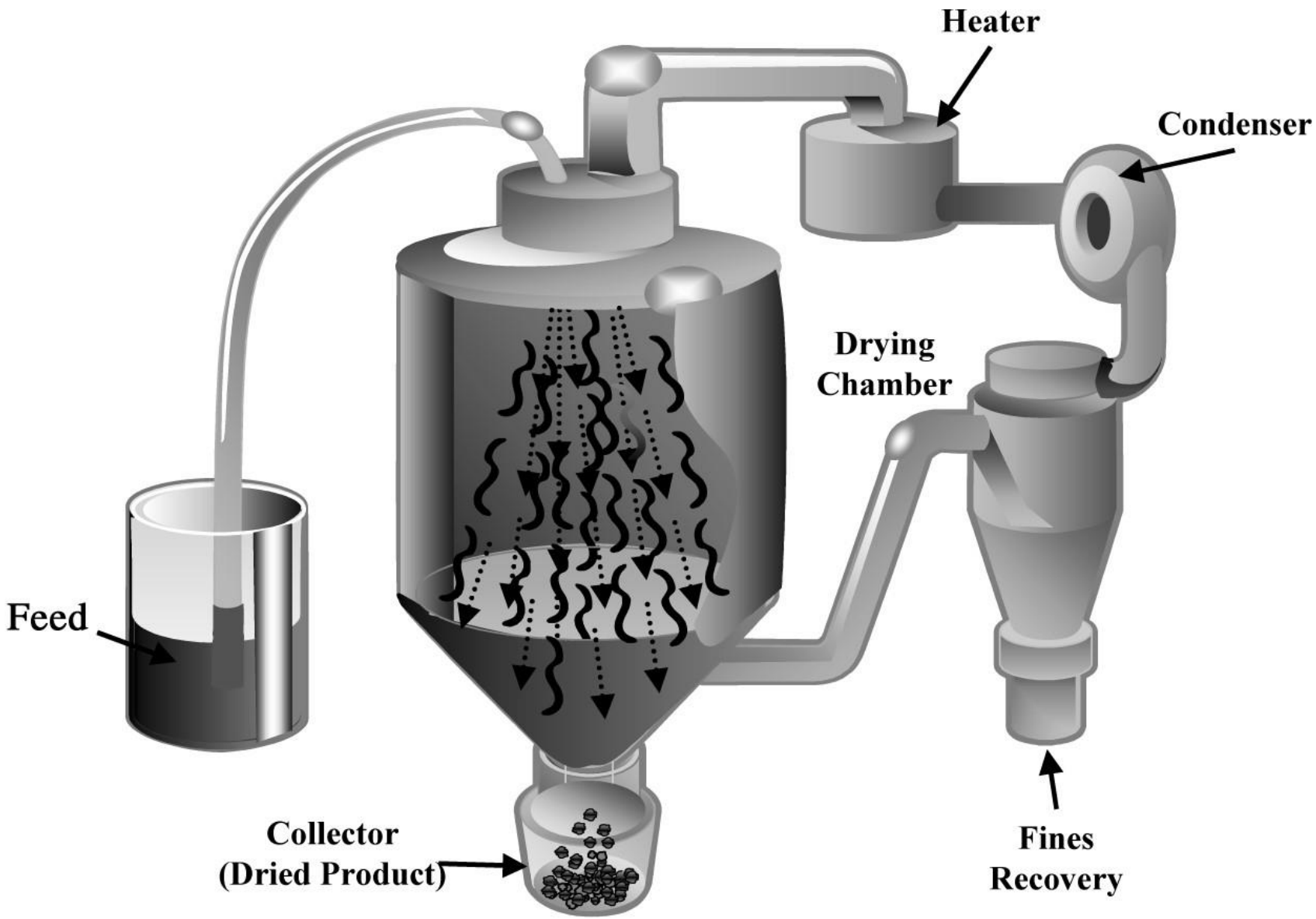
Process;

Particles are conveyed through the inner partition into the expansion chamber by the hot fluidizing air.

Gravity overcomes the force of the fluidized air and the particles fall back into the outer partition.

Pneumatic atomizing nozzle in the bottom center of the chamber introduces the coating solution.

Nozzle sprays upward providing successive applications of coating to the product.


Heater
Condenser
Drying
Chamber
Feed
Collector
(Dried Product)
Fines
Recovery

# Mechanism

## Stages in Spray Granulation:

1. Atomization of granulation liquid
2. Agglomeration of particles

## ATOMIZATION

It is the process by which a liquid is disintegrated into many fine droplets, thereby yielding a high surface/mass ratio.

This is achieved by supplying energy to the liquid in the form of kinetic energy, pressure energy, centrifugal energy etc.

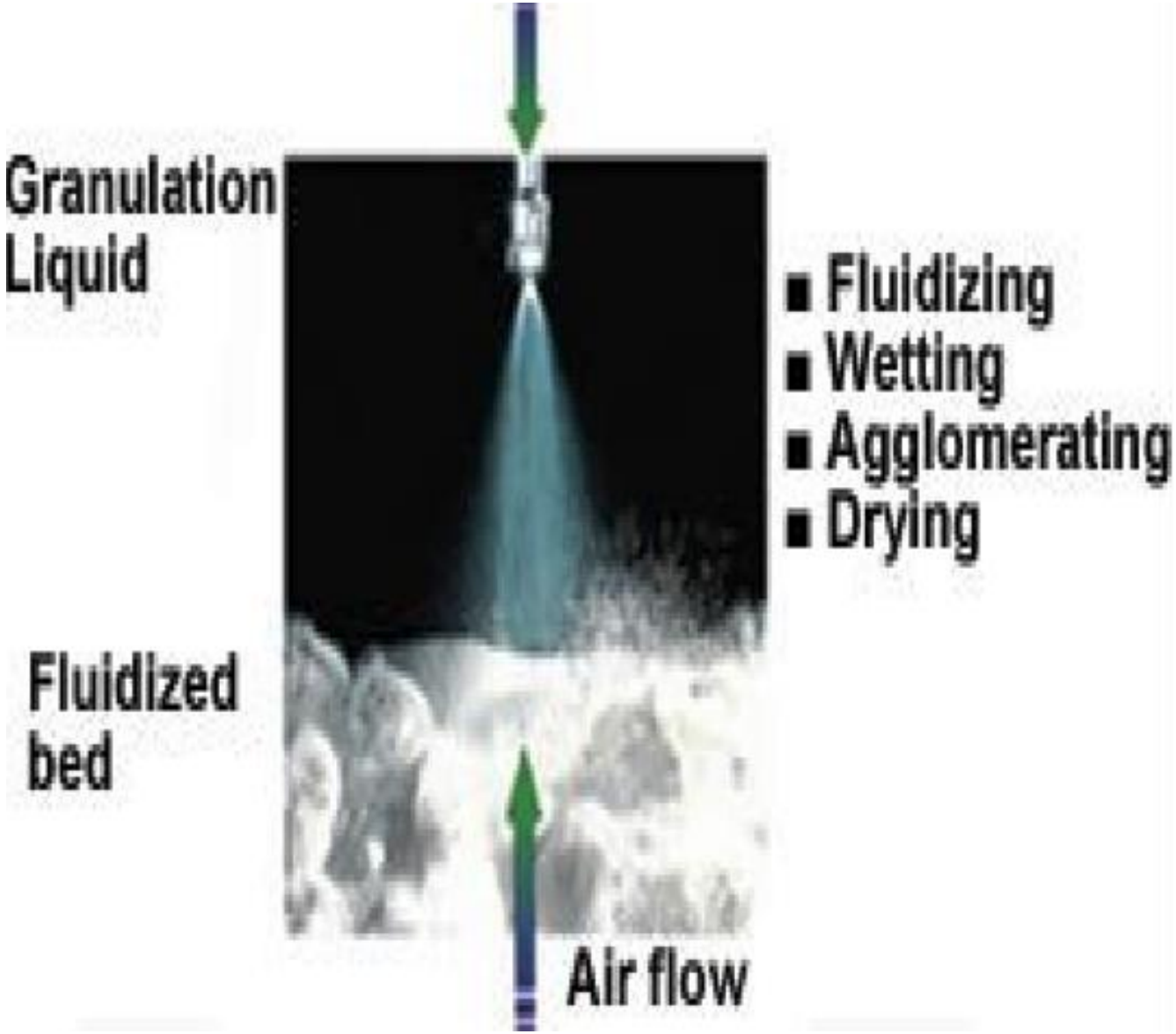
The most common form of atomization is hydraulic PRESSURE NOZZLE ATOMIZATION, CENTRIFUGAL ATOMIZERS, SONIC ENERGY ATOMIZERS.

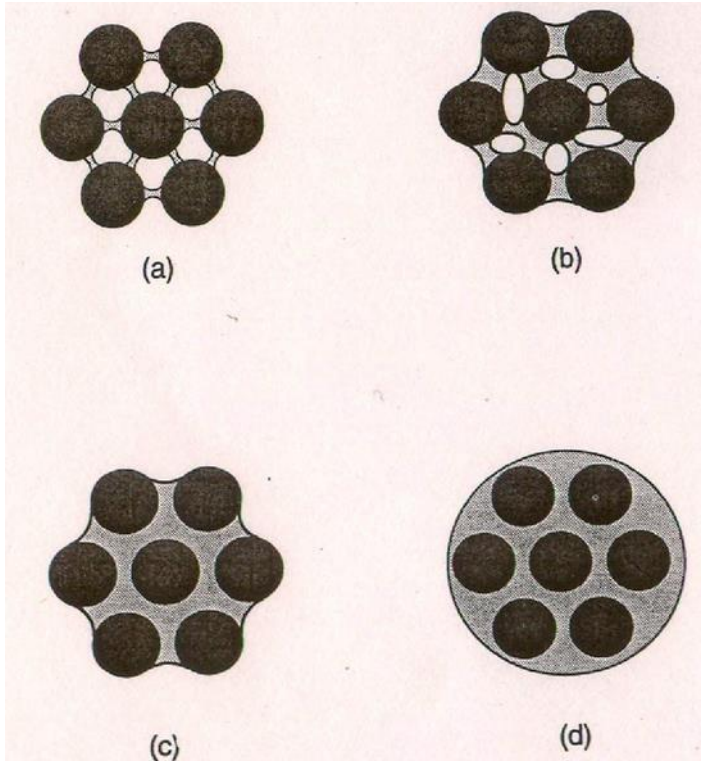
The differential pressure drop across the orifice determines the mean droplet diameter.

## AGGLOMERATION

In this stage, the atomized granulating liquid is sprayed over the particles to facilitate the agglomeration.

At low moisture contents, particles contact each other and adhere due to the formation of liquid bridges. Finally, droplets are formed when the liquid surrounds the granule. The strength of the droplet is dependent on the surface tension of the liquid phase.


Granulation Liquid
Fluidizing
Wetting
Agglomerating
Drying
Fluidized bed
Air flow


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

## DRYING

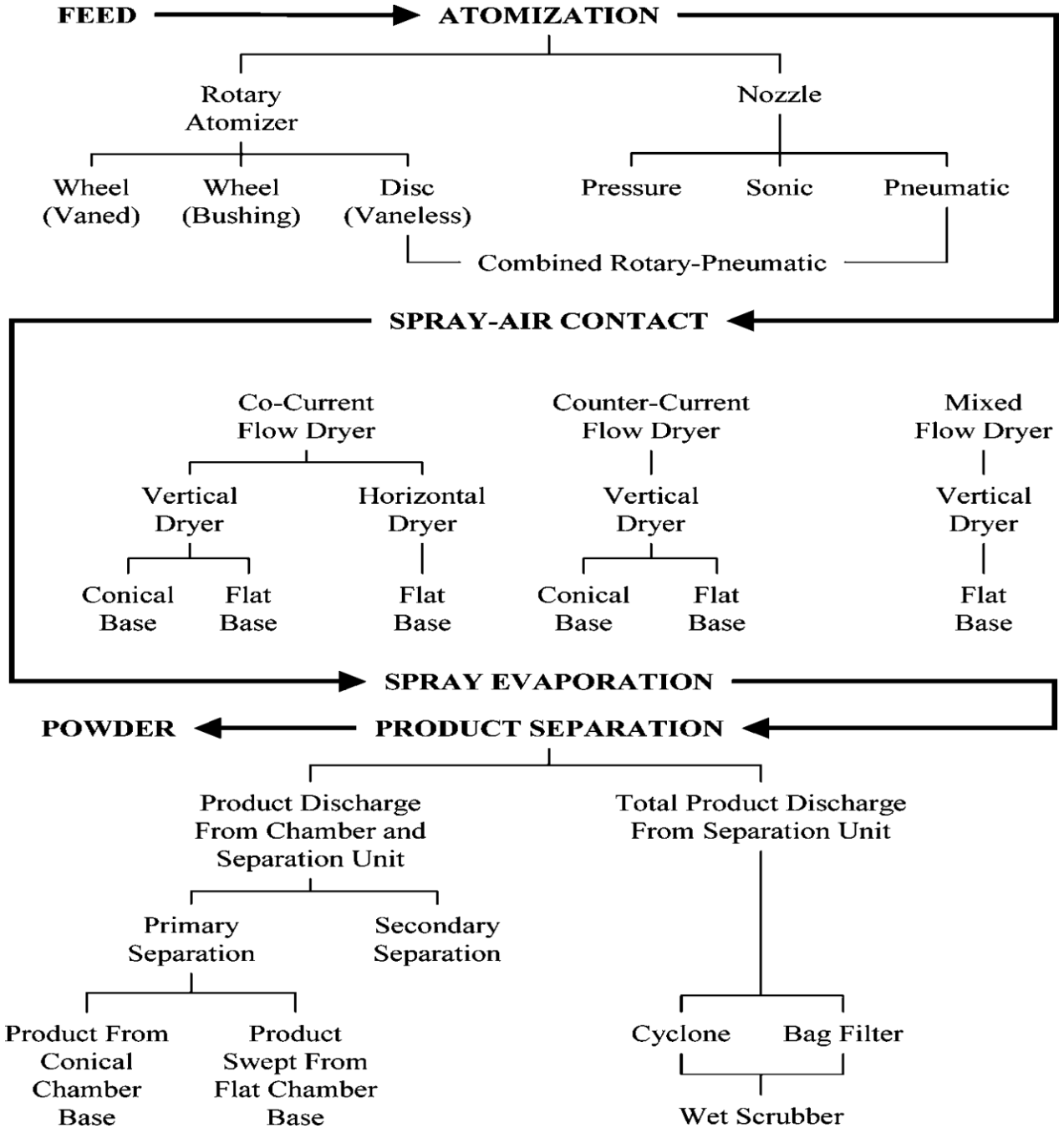
**In this stage, the agglomerated droplets are brought into contact with heated gas for the evaporation to take place equally from the surface of all droplets.**

## Advantages

- ✓ **Dust-free granules**
- ✓ **Spherical pellets**
- ✓ **Free flowing properties**
- ✓ **Good solubility**
- ✓ **Compact structure**
- ✓ **Less hygroscopic**
- ✓ **Less abrasive**
- ✓ **Different types of granulators**

**Limitations.**

- ❑ **Not typically well suited for producing granules with mean particle size >200 mm.**
- ❑ **Has poor thermal efficiency at lower inlet temperatures and the exhaust air stream contains heat, which often requires sophisticated heat exchange equipment for removal.**




**Schematic of spray-drying process shown in stages:**
**stage I: atomization;**
**stage II: spray–air contact and evaporation;**
**stage III: product separation**

## Particle formation in fluidized bed granulation is influenced by numerous parameters

- Moisture content in solids
- Liquid spray flow rate
- Airflow rates
- Atomization pressure
- Batch fluid bed

Rotary atomizers are utilized to produce a fine to medium-coarse product with a mean size of 20 – 150 mm though larger spray-dried particles can also be obtained if a very large drying chamber is used.

Nozzle atomizers are used to produce spray-dried product with a coarse mean particle size of 150 – 300 mm.

For a given spray-drying application, the selection between rotary and nozzle atomizers involves the following considerations:

- The feed capacity range of the atomizer for which complete atomization is attained
- Atomization efficiency
- The droplet-size distribution at identical feed rates
- Spray homogeneity
- Operational flexibility
- The suitability of dryer chamber design for atomizer operation
- Feed properties
- The atomizer experience available for the product in question.

# SPRAY DRYING APPLICATIONS

**Granulation**

**As it produce free flowing and spherical granules so it is suitable process for the production of directly compressible excipients such as lactose, microcrystalline cellulose, and mannitol.**

**Modification of Solid-State Properties**

**The hollow structure of the spray-dried particles increases the solubility and subsequent dissolution rate of the drugs by several folds. For example;**

- **The dissolution rate of poorly water-soluble salicylic acid was found to be almost instantaneous and 60 times faster when spray dried as compared to that of the original powder;**
- **Spray drying of the poorly soluble drug with 50% PVP resulted in enhanced dissolution when compared to a physical mixture of micronized drug with PVP.**
- **A physically stable amorphous form of ibuprofen, which has a low melting point, was obtained when spray dried in the presence of 50 – 75 % PVP.**

# SPRAY DRYING APPLICATIONS

## MICROENCAPSULATION

**The preparation of microcapsules involves the coating of particles or liquid droplets with a biodegradable polymer. Applications for microspheres in the pharmaceutical industry include controlled release, particle coating, flavor stabilization, taste masking, and physical or chemical stabilization.**

## OTHER USES (under consideration)

- ❑ **Inhalation Dosage Forms**
- ❑ **Nanoparticles**
- ❑ **Peptides and Proteins**
- ❑ **Dry Elixirs and Emulsions**
- ❑ **Effervescent Products**

# Single-Pot Processing

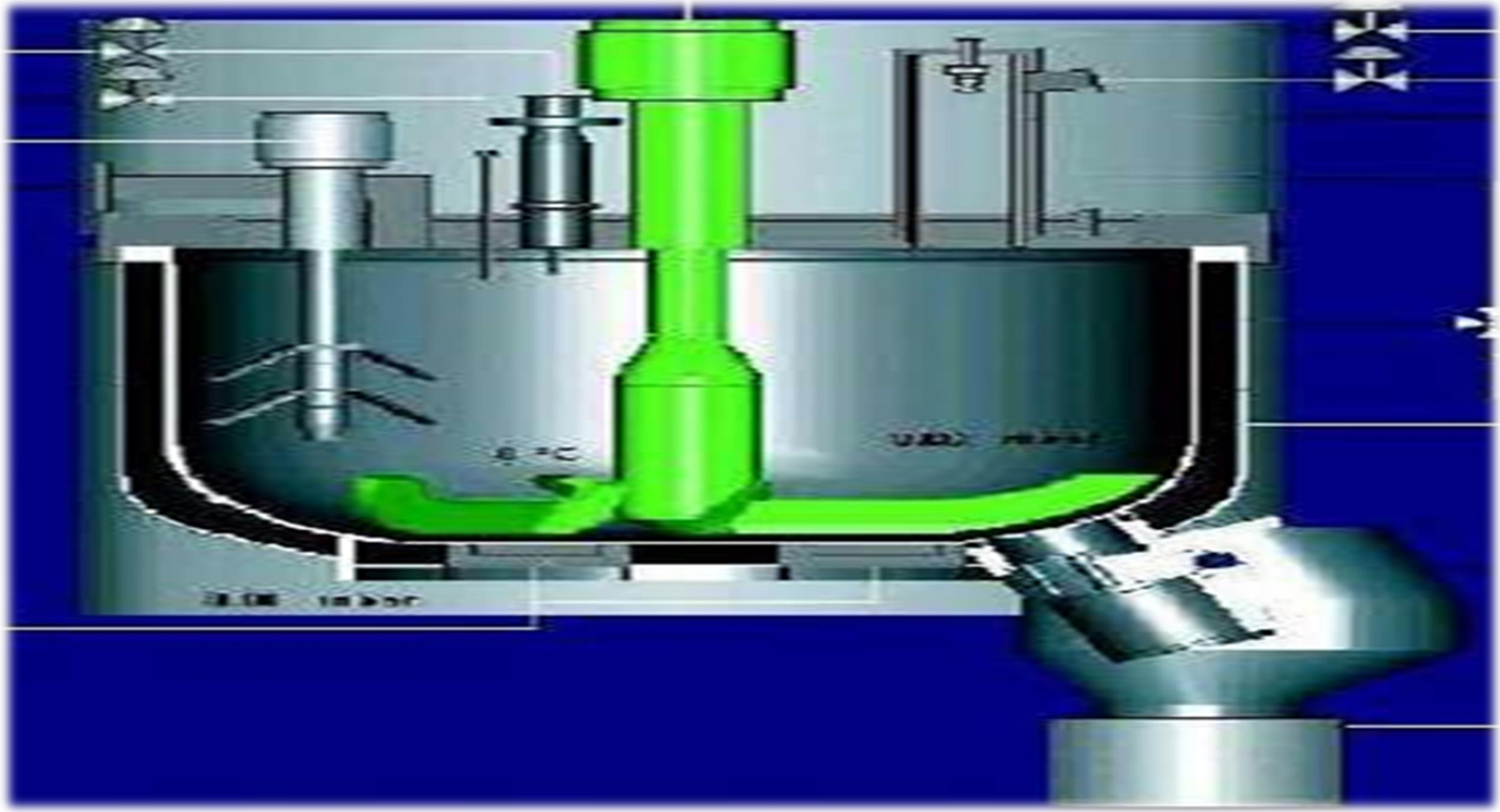
**That provide the means for mixing, granulating, drying, and blending pharmaceutical granulations in a single apparatus.**

**The processors consists of a high- or low-shear mixer granulator (similar to conventional granulators) and outfitted with a variety of drying options.**

**Initially, vacuum was combined with a heat-jacketed bowl to provide the means for drying in the single pot. Now a days, processors are available that provide vacuum drying with microwaves or that percolate gas under low pressure into the vacuum chamber (i.e., processing bowl).**

**Thus, single pot processing (SPP) is the production of pharmaceutical granules using a wet granulation process in which dry mixing, liquid addition, wet granulation, drying and sizing of the granules is done in one machine.**


VAGUMA



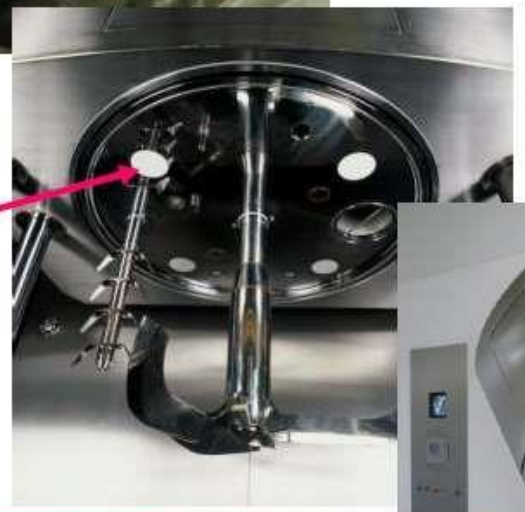
➔A range of high-shear granulation systems for MIXING, GRANULATING and **DRYING**

**UNIQUE CONCEPT**

All available vacuum drying techniques are integrated :

- **VACUUM**
- **TRANSFLO™**
- **MICROWAVES**

and be combined with:
**SWINGING BOWL**



# TYPICAL SINGLE-POT PROCESS

- Dry Mixing
- Addition of Binder Solution
- Wet Massing
- Drying
  - Conductive Drying
  - Vacuum Drying
  - Gas-Assisted Vacuum Drying
- Sizing and Lubrication

# Advantages

- By integrating granulating and drying capabilities into a single unit, capital investment in equipment and good manufacturing practice floor space may be lower than the other alternatives.
- The number of material-handling steps is decreased; consequently, the total processing time may be shorter while maintaining a high yield and keeping production support to a minimum.
- Environmental variables, such as humidity, are eliminated from the manufacturing process, which may offer advantages for processing moisture-sensitive formulations.
- State of the art is to outfit a single-pot processor with clean-in-place systems, thereby enhancing operator safety by minimizing exposure to the product both during manufacturing and during cleaning
- The processors can be used as mixer–blenders for direct compression formulations, or as mixer–granulators to prepare wet granulations for fluid-bed drying or utilized for their full range of capabilities as a single-processing unit for all the steps required for granulation preparation. Some vendors offer the option of upgrading their small-scale processors.

| TECHNIQUES / TECHNOLOGIES | DESCRIPTION | GRANULE CHARACTERISTICS | MERITS | LIMITATIONS | EQUIPMENT |
|---|---|---|---|---|---|
| Pneumatic Dry, Granulation | Dry granulation, Mild Compaction and Pneumatic classification | Porus, highly compressible, Taste making, Fast disintegration, Release time modification. | Drug loading, Thermolabile and moisture sensitive drugs. Product stability, Cost and waste | Recycled granule quality, Segregation potential, Friability. | Roller compaction with air steam or vacuum. |
| Reverse Wet, Granulation | Wet granulation, Water or solvent is granulating liquid | Uniform wetting, Uniform erosion. | Particle size, Spherical shape, Poorly water-soluble drugs | Larger particle size, Lower porosity, Many problems similar to conventional wet granulation. | High speed mixer. |
| Steam, Granulation | Wet granulation, Steam is granulating liquid. | Diffusionate, Uniform distribution. Surface area, Spherical shape. | Eco-friendly, sterility process time, No solvent use, No health hazards. | local over heating / wetting, High energy inputs, Thermolabile drugs., Limited binders | High speed mixer with steam, generator regulator. |
| Moist-Activated Dry, Granulation | Wet granulation, 1-4% water is granulating liquid and moisture absorbing material | Uniform size, Flowability, Compressibility. | Less energy input, No drying process *Wide applicability Continuous processing, Shorter process time, Process variables | Moisture sensitive drugs, Impossible high drug loading, Limited absorbents. | High-shear mixer coupled with a sprayer. |
| Thermal, adhesion, Granulation | Wet granulation. Low water solvet is granulating liquid and heating at 30-130$^0$C | Flowability, Friability, Tensile Strength. | Drug loading, No drying process dust | High energy inputs, Thermolabile and moisture sensitive drugs, Limited binders | Tumble blender or similar equipment coupled with heating system. |
| Melt, Granulation | Wet granulation, Meltable binder as granulating liquid, heating at 50-90$^0$C | Possible modified release, Dissolution. | No water or solvent, No drying process Energy input, Cost and process time water sensitive drugs. | Tehermolabile drugs, Limited binders | High shear mixer. *Fluidized be |
| Freeze, Granulation | Wet granulation, Spray freezing and subsequent freeze drying for slurry or suspension. | Uniform size, Flowability, Spherical shape. | Granule homogenecity, Thermolabile drugs, Granule density control *Material waste | limited solvent medium, Only suitable for conversion of liquid slurry or suspension to granules. | Spray freezer coupled with freeze dryer. |
| Foam, Granulation | Wet granulation, Foam a, granulating liquid. | Uniform binder distribution, No over wetting. | water requirement, No spray nozzle use *Low water required, Cost & process time, Water sensitive drugs. | Moisture sensitive drugs, Limited binders. | High shear mixer or fluidized bed, granulator coupled with foam, generator regulator. |