Factors of the technological impact of the main processes and devices on the bioavailability of drugs.

Technological process

Technological (production) processes are methods that consist of certain technological methods and operations.

Until the 60s. 20th century The method of preparation of drugs as a factor that affects the effectiveness of the drug, did not betray significant importance.For a long time, the science of manufacturing medicines was considered as a branch of general commodity science.

Technological process

- Biopharmaceutical research has made it possible to give a scientific explanation of the role of technological processes, methods of obtaining drugs in the development of a therapeutic effect.
- The method of obtaining a medicinal product largely determines the stability of the medicinal substance, the rate of its release from the dosage form, the intensity of absorption and, ultimately, its therapeutic efficacy.

Technological process

- Technological methods: grinding, dissolving, drying, filtering, sterilization, freezing, etc.

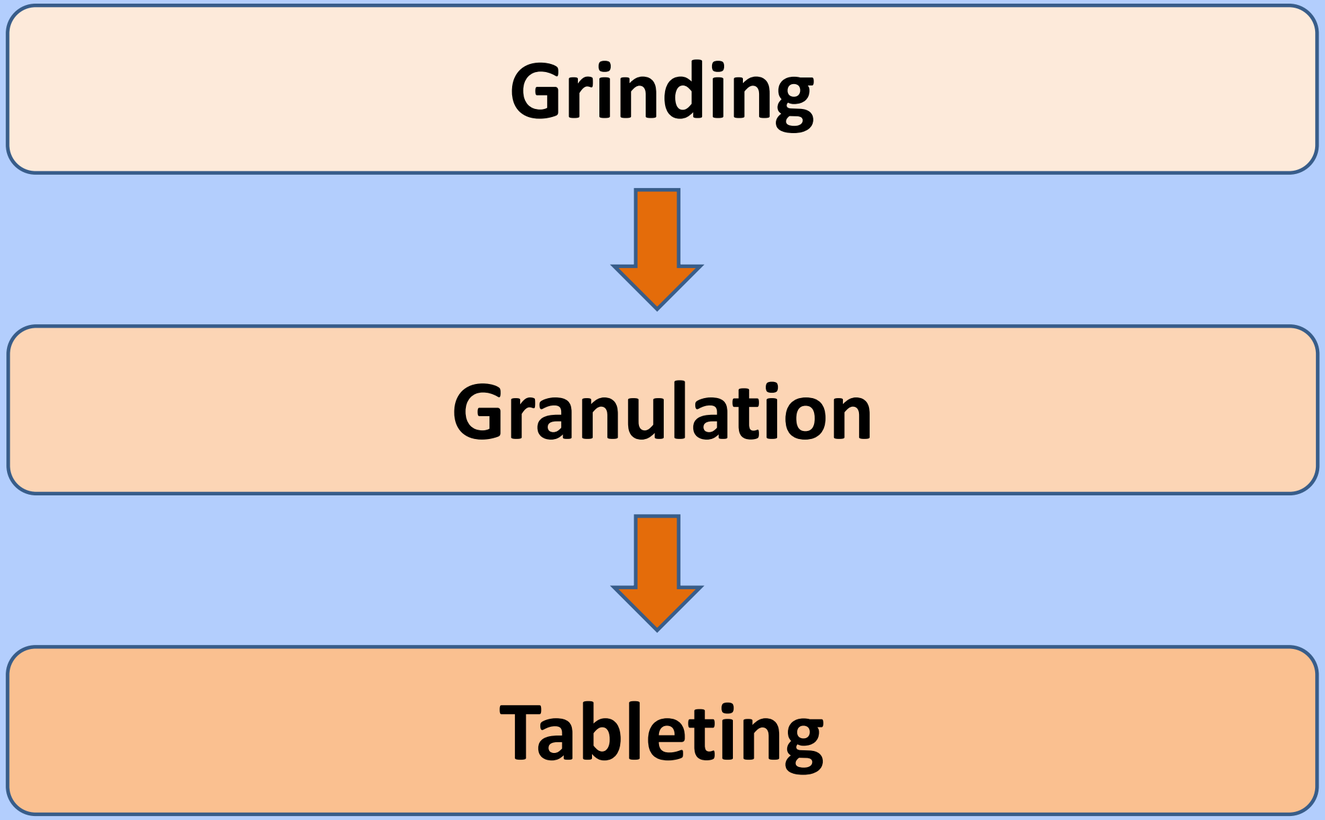
- Technological stages have their own parameters and modes, which are specified in the technological regulations.

- Failure to comply with these parameters can lead to a change in medicinal substances

Bioavailability is affected by:

- particle size
- physical and chemical properties of drugs and excipients
- quantity and type of disintegrants, method of their introduction into the tableting mass
- the presence of surfactants
- granulation method
- granulate size
- wettability of tablet mass components
- Humidity
- pressing pressure
- coating material
- hardness, type and size of tablets

Tablet technology



Grinding

- used to achieve mixing uniformity, eliminate large aggregates in clumping and sticking materials, increase technological and biological effects.

a decrease in the particle diameter of acetylsalicylic acid by 30 times (micronization) increases the bioavailability of the drug in tablets by 2-2.5 times. Using additional grinding of the substance, it is possible to produce tablets containing half as much acids with the same therapeutic effect, but with fewer side effects.

Due to micronization, it is possible to reduce the effective therapeutic dosage of steroid hormones, sulfonamides, barbiturates.

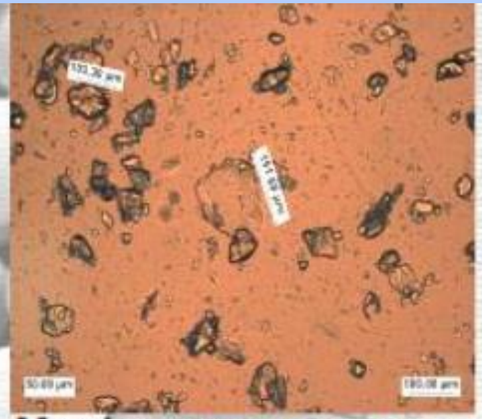
Grinding

- The choice of the degree of grinding of the API must be scientifically justified.
- Often, a sharp decrease in the particle size of the substance causes either its rapid inactivation (for example, the antimicrobial activity of erythromycin, penicillin decreases), or rapid excretion from the body, or enhances its undesirable effect on the body (for example, the toxic effect of furantoin on the mucous membranes of the gastrointestinal tract).

for certain medicinal products (especially those with a narrow therapeutic interval and a pronounced dependence of bioavailability on dispersion), pharmacopoeial articles determine the optimal particle size, compliance with which is part of the requirements for the finished dosage form.

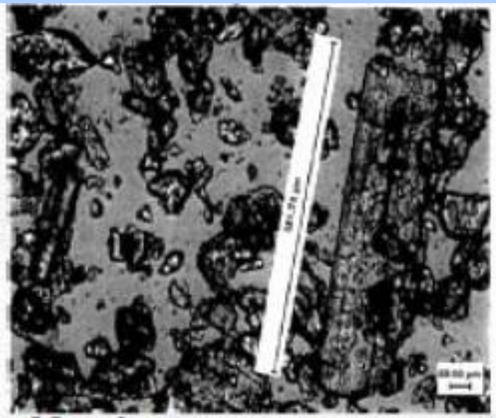
Grinding

- Particle size can also affect the reproducibility of drug technology.
- When replacing the substance of metformin hydrochloride with a particle size of up to 150 microns in the production of Gliformin 850 mg and 1000 mg tablets with a substance with a particle size of up to 700 microns, it was not possible to obtain tablets of adequate quality.



Размер частиц
до 150 мкм

Метформина гидрохлорид
«Aarti Drugs Ltd», Индия



Размер частиц –
до 700 мкм

Метформина гидрохлорид
«Shouguang Fukang
Pharmaceutical Co.», Китай

Granulation

Directional enlargement of particles, i.e. the process of converting a powdered material into grains of a certain size.

- to improve the flowability of the tablet mass, which occurs due to a significant decrease in the total surface of the particles when they stick together into granules
- prevention of delamination of a multicomponent powder mixture (separation of the component with the highest specific gravity from the mixture and dosage violation)
- the strength of the granules (less subject to abrasion and have better flowability)

Granulation

Dry granulation or grinding granulation

Wet granulation or punch granulation

Structural granulation

Wet granulation

- Provides the necessary dynamic characteristics of the resulting mass and a homogeneous content of medicinal substances in solid dosage forms, improves the quality of manufactured dosage forms.

- The most widely used method for making mixtures for capsules and tablets.

Wet granulation methods

1. Granulation of the medicinal substance (+ excipient) using a binder solution. Granulation of the medicinal substance with a mixture (+ filler) - a binder using a pure solvent.
2. Granulation of a mixture of medicinal substance (+ filler) and part of the binder using a solution of the remaining part of the binder.
3. Granulation of the medicinal substance (+filler) using a part of the binder solution, followed by adding the remaining part of the dry binder to the finished granular material.

Wet granulation methods

For many formulations, **Method 1** produces tablets with longer disintegration times and faster drug release than **Method 2**.

Method 1 results in harder tablets than method 2.

Method 3 is used when Method 1 cannot be used (for example, when the mixture cannot absorb the required amount of liquid.

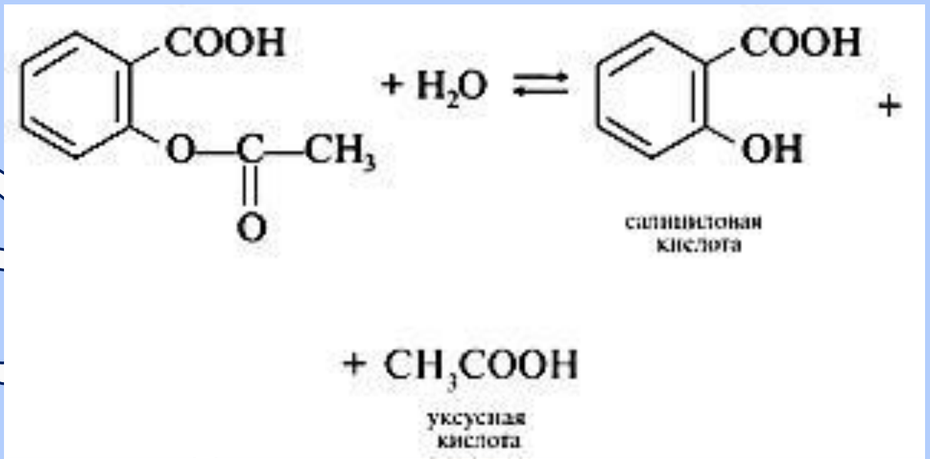
If disintegration time is a problem, **Method 4** is recommended.

Methods 2 and 3 proved to be the best for drugs with good solubility.

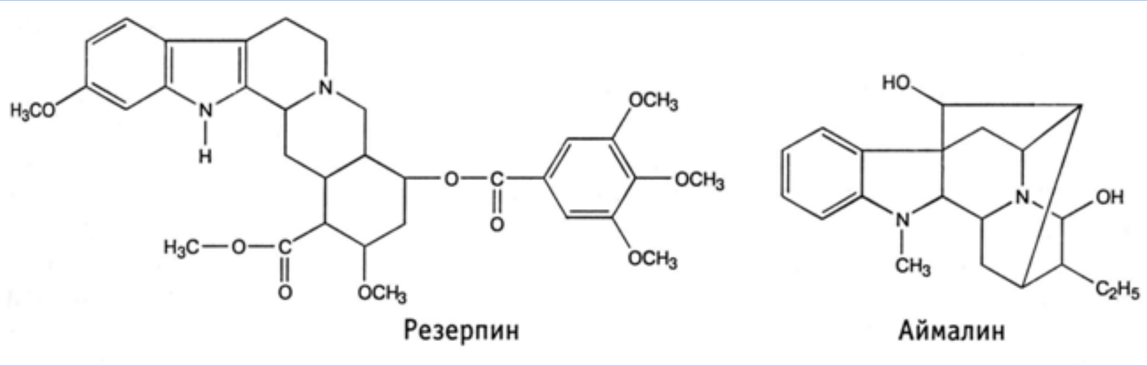
Wet granulation

- There are changes in the surface and disintegrating properties of tablets: dispersion, strength, dissolution.
- Often there are destructive processes - hydrolysis, oxidation, isomerism.

With wet granulation of acetylsalicylic acid, it decomposes with the release of salicylic acid.



Wet granulation leads to the destruction of rauwolfia alkaloids and many antibiotics.



With wet granulation, cementation of tablets can occur (analgin, amidopyrine)

Dry granulation

- chosen when wet granulation affects stability and when the physical characteristics of the drug substance do not allow direct compression.

The powder is compressed into large diameter tablets at a low compression speed. Tablets are crushed on granulators with the size of the mesh openings required to obtain granules for tableting.

The powder mixture of components is compacted using rollers with different surface configurations.

Granulation by melting

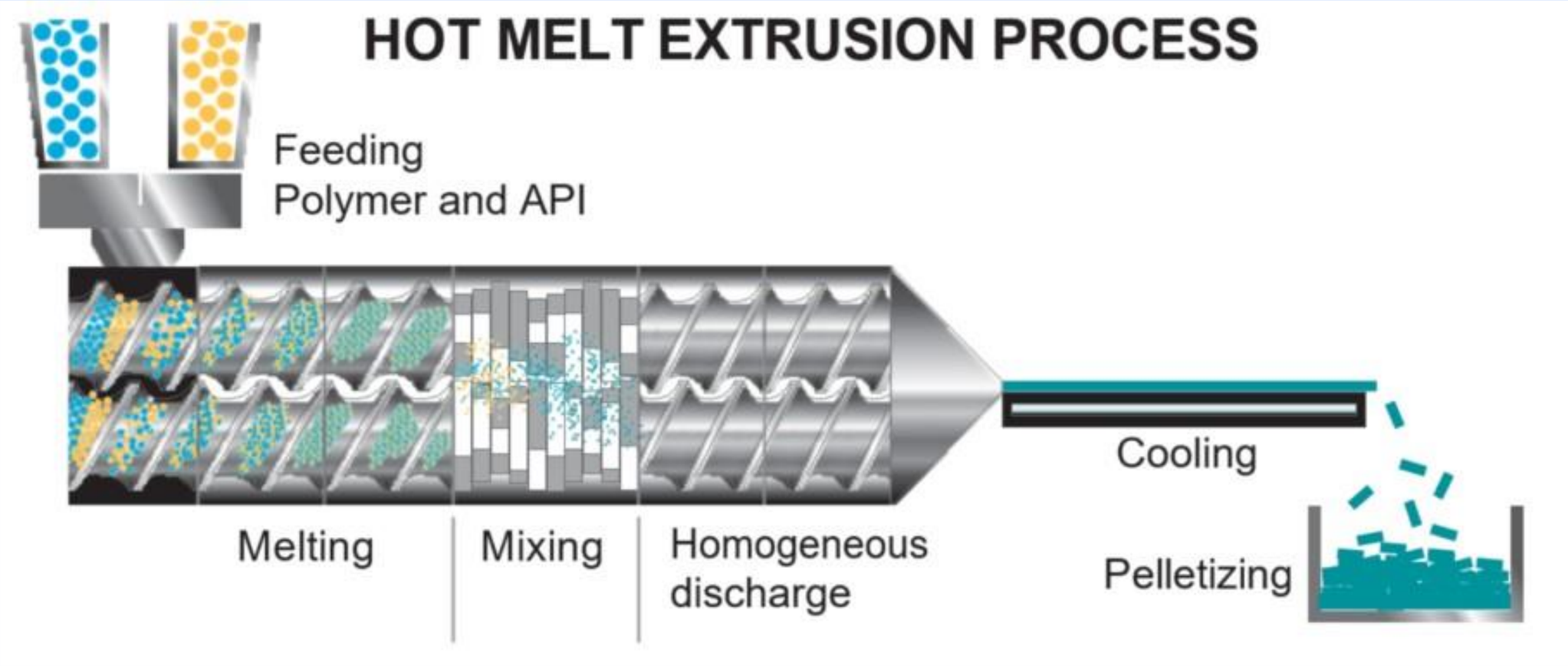
- **Melt granulation** is a process in which powder agglomeration is achieved by the addition of a binder that melts or softens at sufficiently low temperatures.
- The addition of fusible excipients (PEGs, fats, waxes) leads to the formation of granules (or pellets) without the addition of binding solutions.
- The walls of high shear mixers heat up or the impeller itself generates frictional heat, which leads to the melting of the binders and the subsequent formation of agglomerates.
- Granules are obtained by cooling

Advantages: single-stage operation, there are no moistening and drying stages.

Granulation by extrusion

- **Extrusion granulation** is a technology for producing granules by forcing a material melt through a forming hole.
- **Extrusion** is a technological process that consists in forcing a material with a high viscosity in a liquid state through a forming tool (extrusion die, die) in order to obtain an extrudate with a cross section of the desired shape.

Granulation by extrusion



An extruder is a machine for molding plastic materials by shaping them by forcing (extrusion) through a profiling tool - an extrusion head.

Structural granulation

- During structural granulation, powder particles bind to form granules with round shapes and approximately equal sizes, which helps to improve the quality and increase the accuracy of the dosage of the medicinal substance.

Spray drying granulation

Granulation in a pan

Spray drying granulation

- used in cases of undesirable prolonged contact of the granulated product with air
- If possible, should be carried out directly from the solution (production of antibiotics, enzymes, products from animal and vegetable raw materials)

Technological operations of methods for obtaining tablets

Granulation	Direct pressing
1. Mixing the substance with the filler 2. Wetting the mixture with a binder solution 3. Wet granulation 4. Drying 5. Dry granulation 6. Mixing of granules with lubricants/glidants 7. Pressing	1. Mixing agent with fillers, lubricants/glidants 2. Pressing

Pressing

- The tableting process affects the strength and disintegration of tablets, their ability to dissolve upon contact with water in a certain period of time, which guarantees their bioavailability and the desired therapeutic effect.
- It depends on the amount of pressing pressure, pressing speed, condition and wear resistance of the pressing tool.

Pressing

- the optimal pressing pressure is in the range of 800-2000 kg/cm3
- if lubricants cannot be introduced into the tablet mass (incompatibility of ingredients, tablets for obtaining transparent solutions, etc.), the press tool is made of a metal that has little adhesion to the tablet materials (phosphor bronze).

Direct compression

Direct compression is a modern tableting technology with a number of advantages:

- ❖ reduction in the number of technological operations
- ❖high labor productivity
- ❖exclusion of moisture exposure to unstable medicinal substances
- ❖less microbial contamination
- ❖saving production space
- ❖downsizing

Direct Compression Tableting Requirements

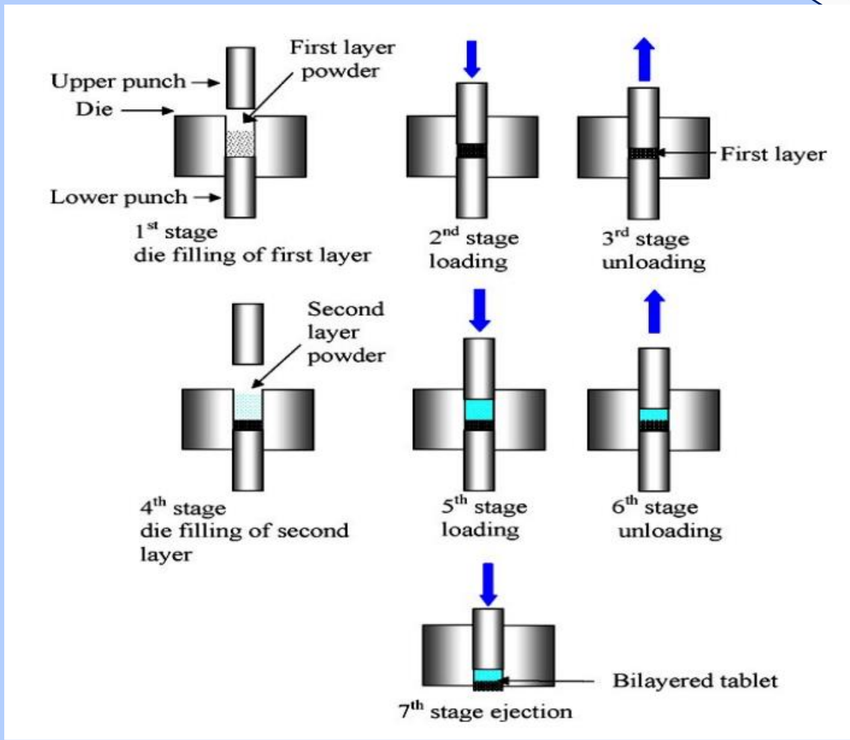
- good flowability (not less than 5-6 g/s)
- high compressibility (at least 70-100 N)
- optimal value of bulk density (not less than 0.4 - 0.5 g / ml)
- low angle of repose (less than 40˚)
- isodiametric shape of crystals
- low adhesion to tablet press tool

Types of direct pressing

Characteristics of the medicinal substance	Direct pressing type
Suitable for direct compression at the required concentration	Medicinal substances are tableted using conventional excipients
Unsuitable for direct compression at the required concentration when using common excipients	Direct Compression Auxiliary Used
	The granules of the medicinal substance suitable for direct compression are used.

Double layer tablets

1. Filling the matrix with powder of the first layer
2. Pre-compression of the first layer with reduced pressing force – preparatory step for the second layer
3. Adjusting the volume of the matrix for the second layer
4. Filling the matrix with powder for the second layer on top of the first layer
5. Compression of whole tablets
6. Pill release



- **Inclusion of different medicinal substances**
- **Separation of incompatible medicinal substances**
- **Different disintegration time for each layer**
- **Combination of different dissolution profiles**