كلية: الصيدلة	مقرر: صيدلة صناعية
الرمز: PHPT 734	مدرس المقرر: د. بشير القاسمي

Pharmaceutical Plant Design

Industrial pharmacy

Lecture: 1

Dr. Basheer Al-kasmi

Site selection

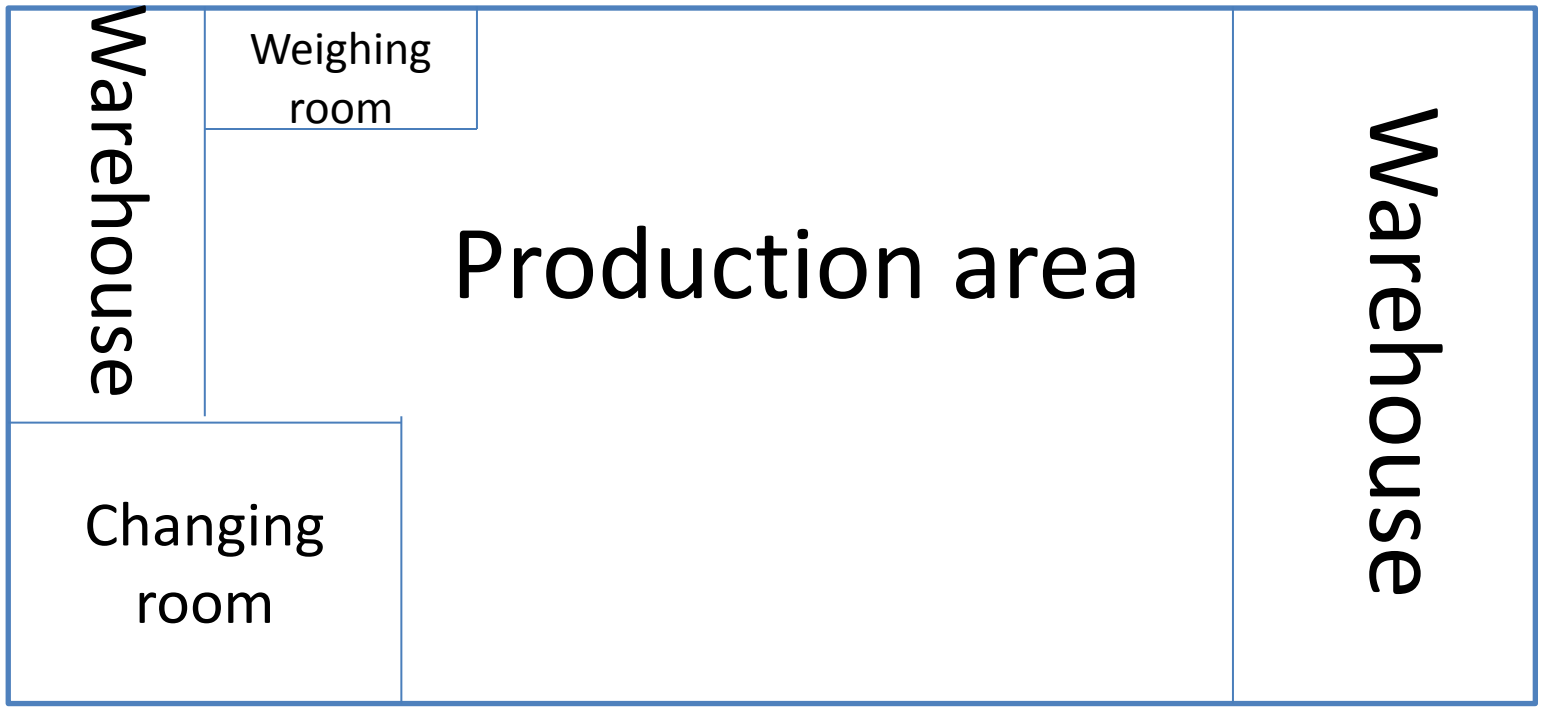
1. Enough area for developing
2. Near to market
3. Water
4. Low humidity and moderate temperature
5. workers

Pharmaceutical plant:

1. Facility
2. Utilities
3. Procedure
4. Product

Pharmaceutical plant:

1. Facility:



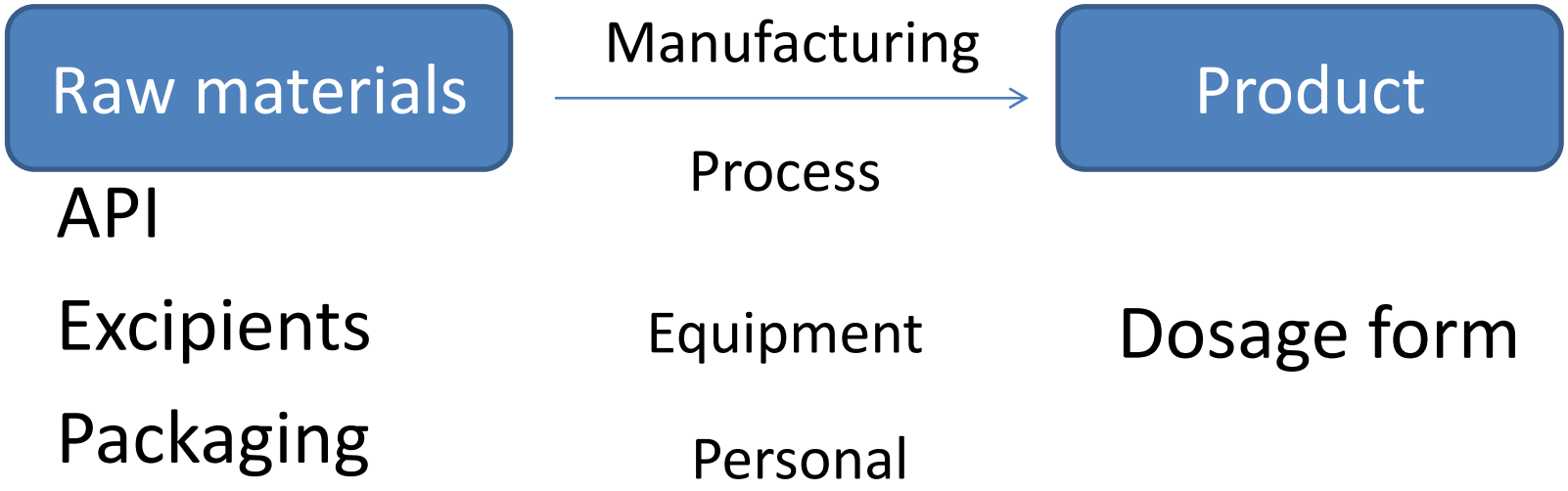
Pharmaceutical plant:

2. Utilities:

- Water treatment station
- Steam
- Compressed air
- Vacuum
- Gases (nitrogen, oxygen)

Pharmaceutical plant:

3. Product:



Pharmaceutical plant:

4. Procedure:

SOP for each activity in plant

SOP: Standard Operating Procedure

Utilities: Water treatment station

Water is widely used as a

- Raw material
- Solvent
- Cleaning applications

Utilities: Water treatment station

Feed (drink) water contains

- Water
- Organic compound
- Salts and ions
- Micro-organisms
- Solid contaminants

Utilities: Water treatment station

	Drink water Feed water Raw water	Purified water Demineralised water Deionised water	Water for injection Distilled water Ultrapure water
pH	5.6 – 9.5	5 - 7	5 - 7
Conductivity µS/cm	300	4.3 (20 C)	1.1 (20 C)
TOC (mg/l)	-	500	0.5
Microbial contamination CFU/ml	Escherichia coli 0/100 ml Other 100 CFU/ml	*Ps. aeruginosa* and *E. coli* 0/100 ml Other 100 CFU/ml	10 CFU/100 ml
endotoxin	-	-	0.25 IU/ml
Nitrates	-	0.2 ppm	0.2 ppm

Utilities: Water treatment station

Drink water Feed water	Purified water (PW) Demineralised water (DM) Deionised water (DI)	Water for injection (WFI) Distilled water Ultrapure water
Pre-rinsing of equipment	Cleaning of containers (non-sterile) Pre-rinsing of equipment (sterile)	Cleaning of containers (non-sterile)
Generation of PW	Generation of WFI	-
-	manufacture of products (non-sterile)	manufacture of products (sterile)

Water producing

Feed water

Water impurities	Used system to remove	Note
Micro-organism	Chlorine HOCl	Active Carbon or SMBS station to remove chlorine
Solid contaminants	Sand or cartridge filtration system	-
Salts and ions	Ion exchange and RO	-

PW → Distillation → WFI

Water treatment

Industrial pharmacy

Lecture: 2

Dr. Basheer Al-kasmi

Purified water

To produce it, use of one of the following technologies:

- Distillation
- Ion exchange
- Reverse osmosis

Pre-treatment:

Chlorine dosing pump (HOCl):
Oxidation organic compound and micro-organism
Chlorine oxidize RO systems and ion exchangers.

Remove chlorine by:
activated charcoal filters
Or
Sodium Metabisulfite SMBS

Pre-treatment: Remove chlorine

Using activated charcoal filters

adsorption agent removing non-polar organic substances and chlorine from the water.

Disadvantages:

very good growth conditions for microorganisms.

always has a large abrasion.

Pre-treatment: Remove chlorine

Using SMBS

Sodium metabisulfite (SMBS) initially reacts with water to form sodium bisulfite (SBS):

$$Na_2S_2O_5 + H_2O \rightarrow 2\ NaHSO_3$$

SBS reacts with hypochlorous acid to form byproducts free from free chlorines:

$$2\ NaHSO_3 + 2\ HOCl \rightarrow H_2SO_4 + 2\ HCl + Na_2SO_4$$

These by products are all readily removed by the RO system.

Pre-treatment: Remove chlorine

Using SMBS

Chlorine levels should be monitored continuously to prevent chlorine passing into the RO system.

An oxidation-reduction potential (ORP) electrode is used to monitor the presence of chlorine or other oxidants

Pre-treatment: Remove Solid contaminants

Filtration (pore size of 100 µm**)**

OR

Sand filter

Pre-treatment: **ion exchange**

strongly or weakly alkaline anion exchangers
strongly or weakly acidic cation exchangers

Ion exchangers can be used for:
conditioning (softening) and for purification (total desalination)

The conductivity often increases slightly (by 5 to 10 %) as a result of softening which can be explained by the increased movement of the sodium ions when compared to the hardening ions.

Pre-treatment: **ion exchange**

Softening:

Strongly acidic cation exchanger, (Na+): replaces all of the hardeners in the water (the calcium and magnesium ions) with sodium ions

Regeneration with: Sodium chloride

Decarbonisation:

Cation exchanger, slightly acidic (H+)

Regeneration with: Hydrochloric acid

Deacidification:

Anion exchanger, strongly alkaline (OH-)

Regeneration with: Caustic soda (NaOH)

Pre-treatment: **ion exchange**

Total desalination refers to the removal of **all salts** from the water being treated. The organic substances in the water **(TOC)** are not removed

Ion exchange technology is more cost-effective,

Disadvantages:

Environmental protection:

Large amounts of acid and base are required for regeneration. must be neutralised before waste .

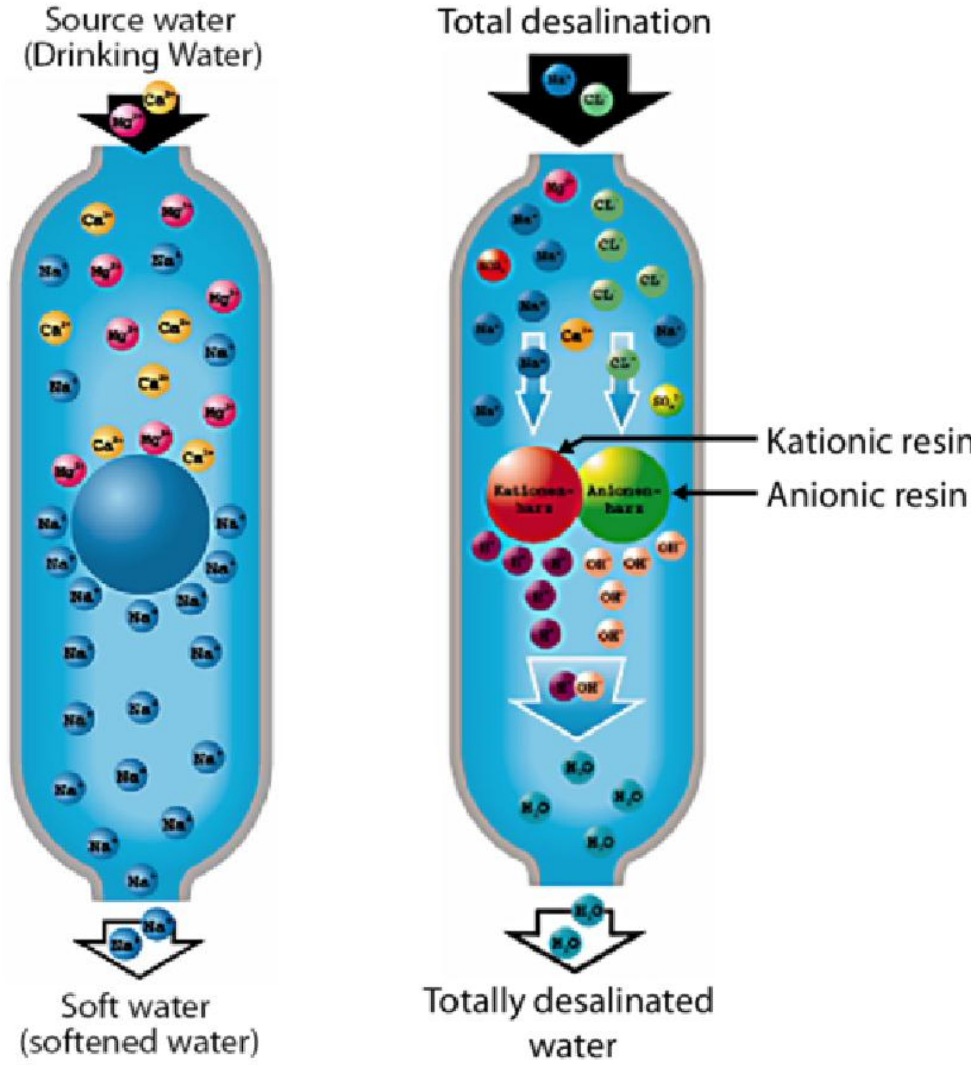
Occupational health and safety:

safety equipment when acids and bases are used.

Water quality:

The conductivity of the water increases continuously until regeneration; as a consequence, the water quality is not constant. There is also the risk of microbial contamination.

Softening using ion exchange

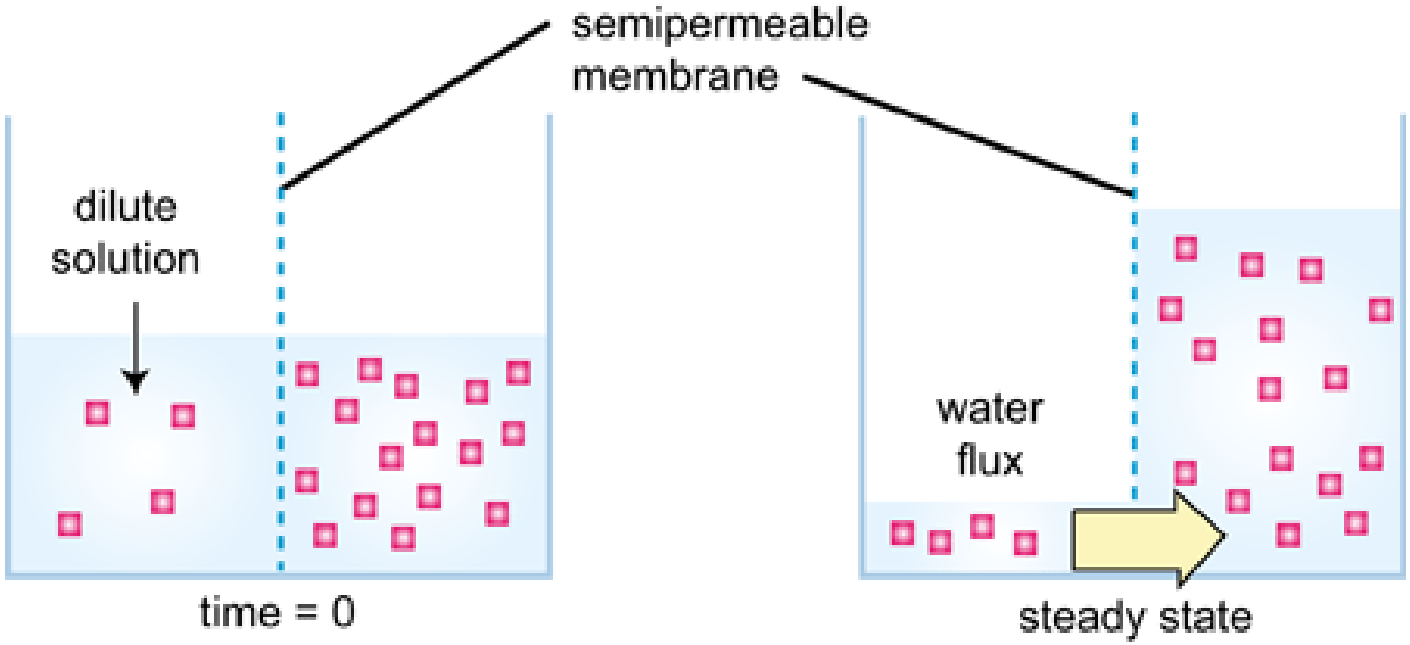


Treatment:Reverse osmosis (RO)

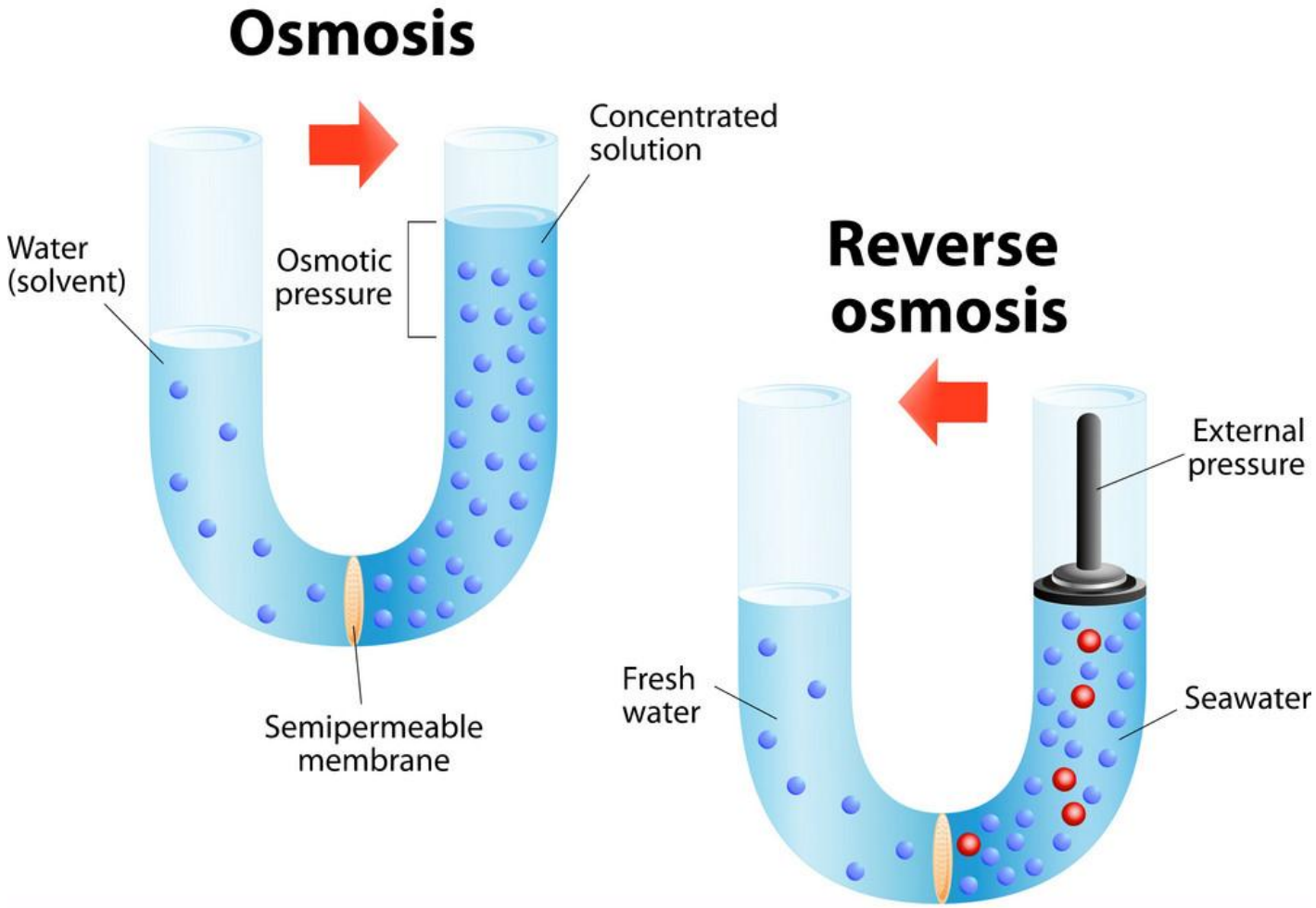
Remove:

- Chemicals
- Salt
- Microorganisms

Osmosis:

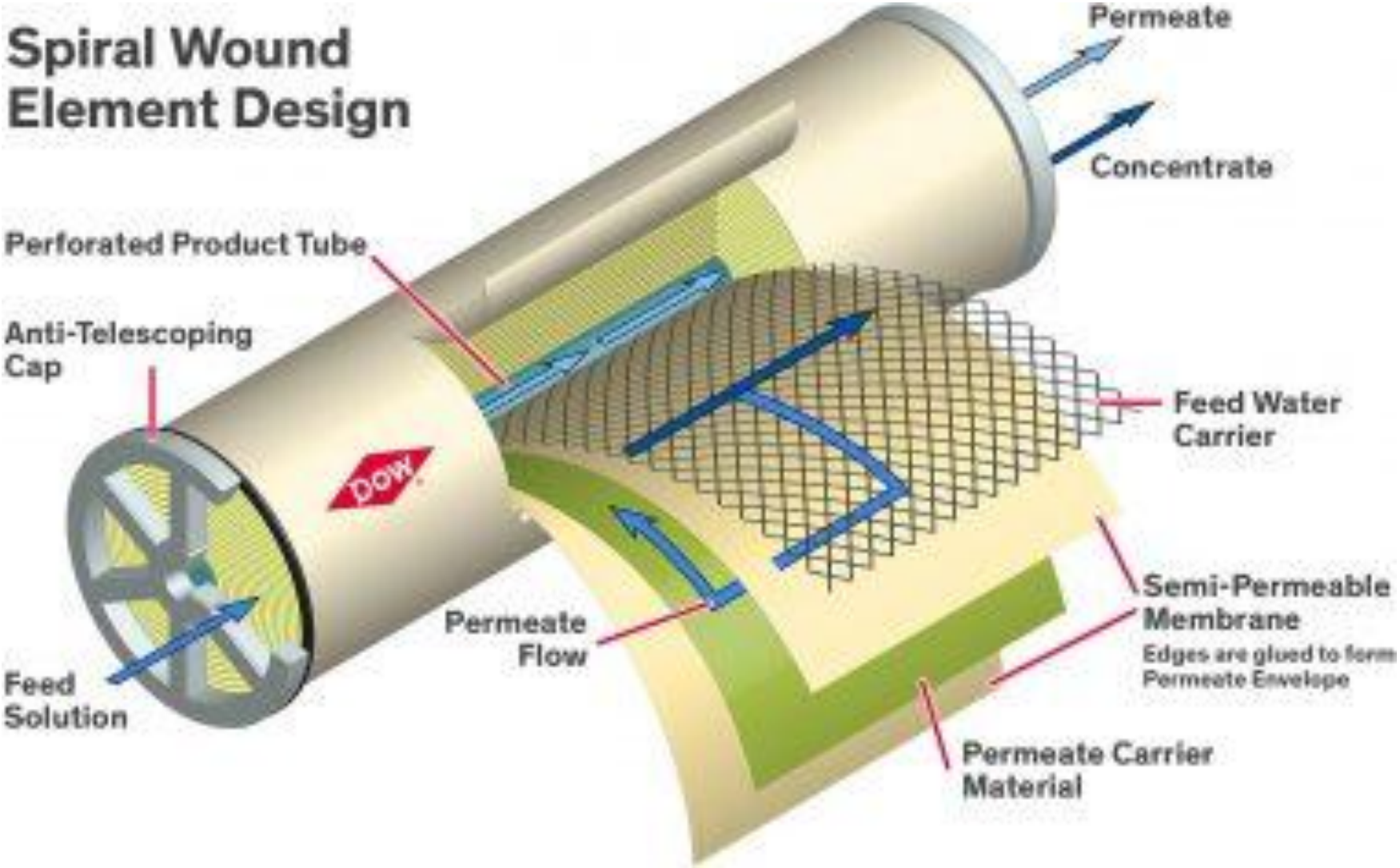

semipermeable
membrane
dilute
solution
time = 0
water
flux
steady state

Osmosis vs Reverse osmosis:



Reverse Osmosis:

Desired product (permeate)



Reverse osmosis (RO)

From time to time, backwashing of the membrane is necessary to prevent blocking

Electro-deionisation (EDI)

Electro-deionisation (EDI) is a desalination process based on electrodialysis and mixed-bed ion exchange

The technology always requires water that has already been strongly pre-desalinated, e.g. a permeate from an RO system

The anions migrate in the direction of the anode and pass an anion exchange membrane which is only permeable for anions, but not for cations or particles which are not electrically charged.

In the same way, the cations migrate in the direction of the cathode and pass a cation exchange membrane.

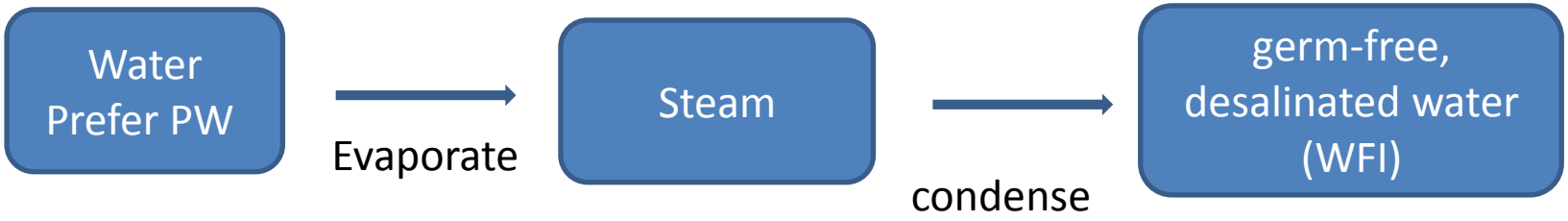
Ultrafiltration (UF)

Ultrafiltration (6,000 to 10,000 daltons) is used to remove **endotoxins (**20,000 daltons**)**

Ultrafiltration (UF) is used to separate particles that are between 0.01 and 0.1 µm

By using ultrafiltration in combination with a desalination process, it is possible to produce water of WFI quality

Distillation



Water producing

Water kind	Start from	Process to produce	Recycling temperature
PW	Drink water	Ion exchange	25 C
		RO	
		Distillation	
WFI	Drink water Soft water PW	RO + UF	80 C
		Ion exchange + UF	
		Distillation	

Sanitization

RO system:

Chemical: sodium hypochlorite or chlorine dioxide.

Or

Hot-water: 60 – 80 C for determined time

Distiller:

Vapour for determined time

UV irradiation:

Microbial count reduction
wavelength of 254, damages the DNA of microorganisms

Dechlorination
wavelength of 254 nm, chlorine compounds in the water are effectively degraded and downstream processes (e.g. reverse osmosis) are protected against oxidation

TOC removal
This not only reduces the number of microorganisms, but their components are also destroyed.

Ozone destruction

HVAC System
(Heating, Ventilation and Air-Conditioning)

Industrial pharmacy

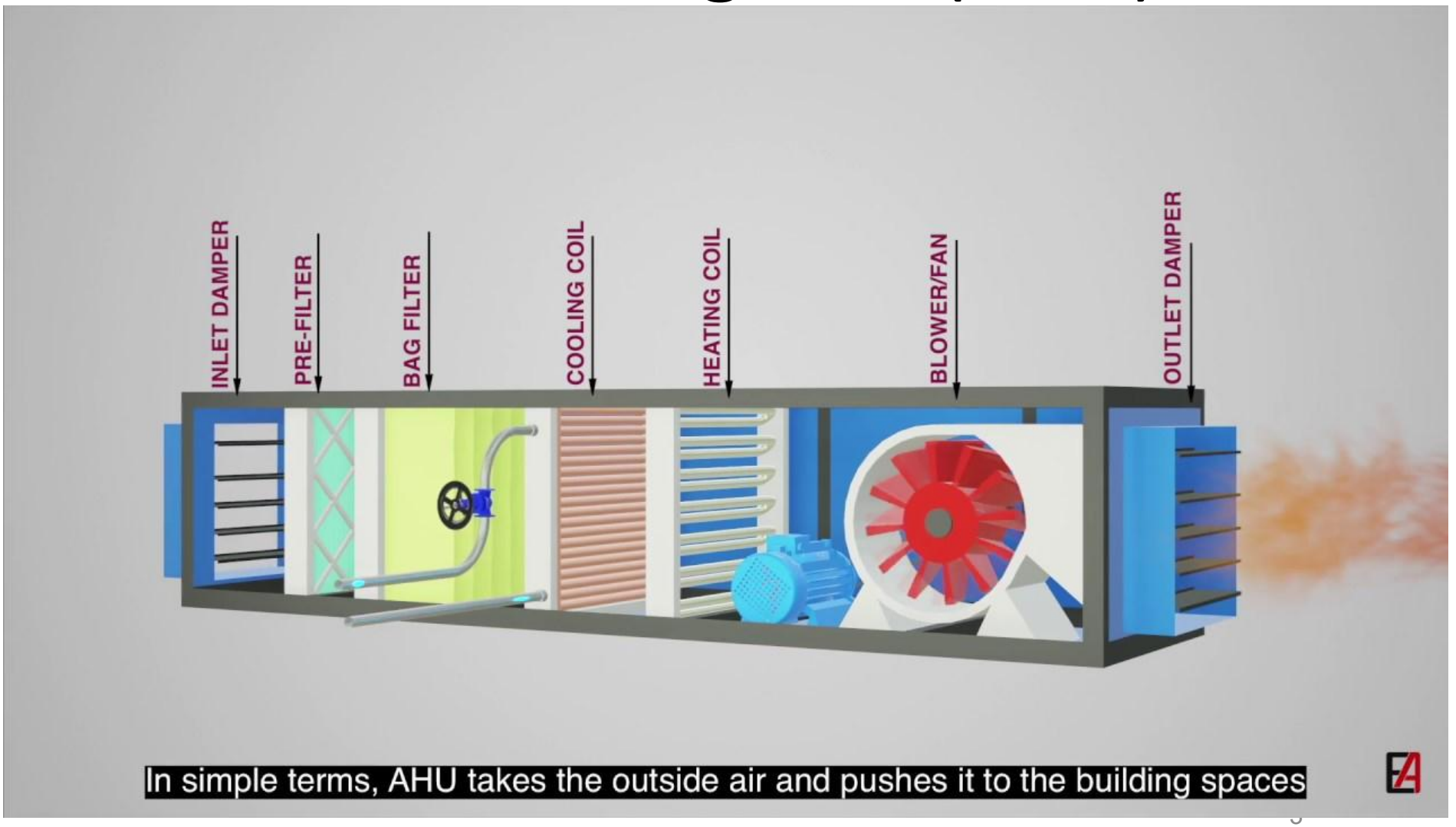
Lecture: 3

Dr. Basheer Al-kasmi

HVAC system use to control:

1. Temperature and humidity
2. Pressure (Positive or negative)
3. Purity (microbial monitoring)
4. levels of chemical substances (Particles)

Air Handling Unit (AHU)



Particles

Divide into three different categories:

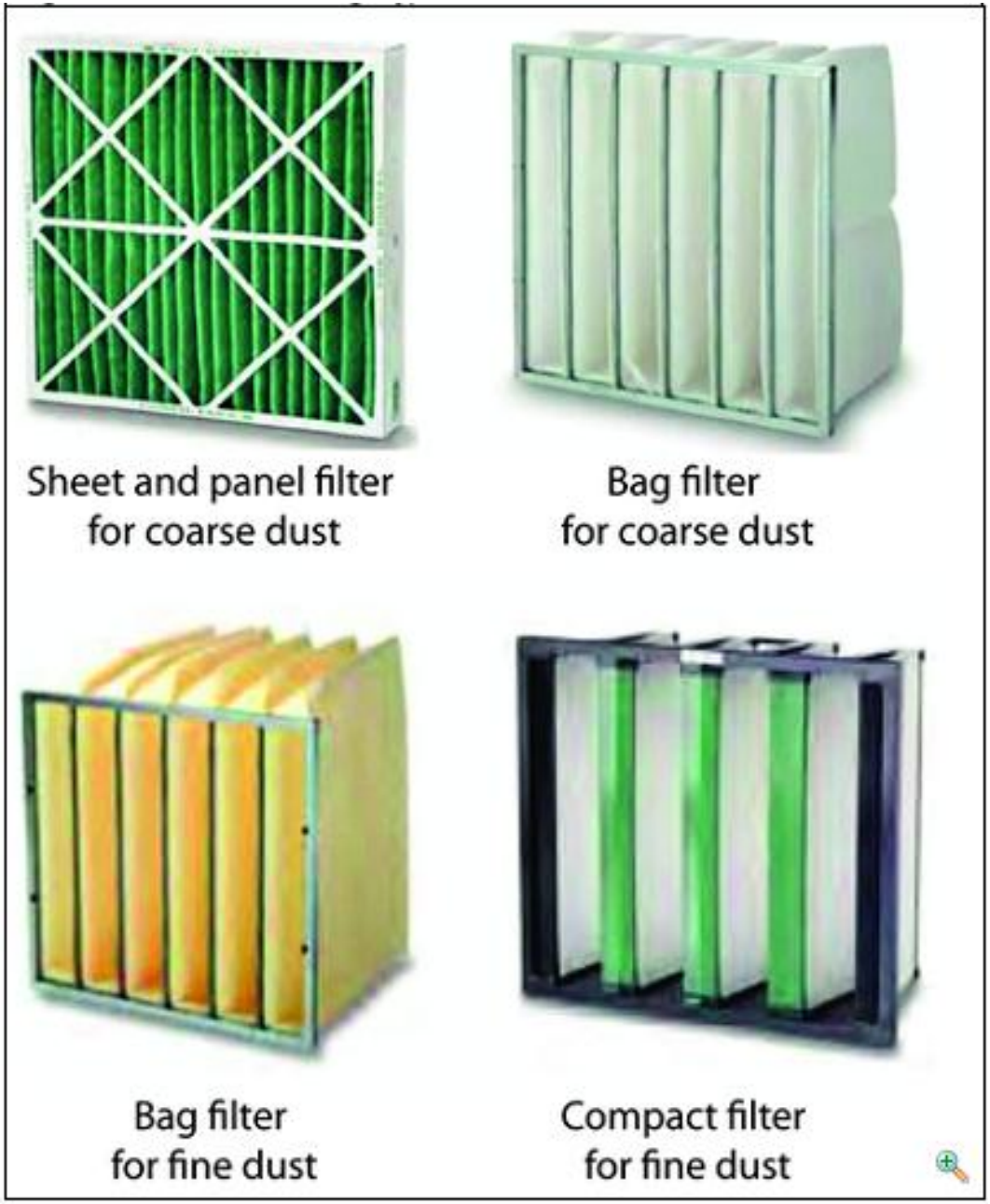
Coarse dust:
Particles >10 µm, easily visible with the naked eye
Fine dust:
Particles between 1 µm and 10 µm, nearly invisible to the naked eye
Suspended dust:
Particles <1 µm, invisible to the naked eye

Coarse and Fine Dust Filters

coarse filters :

- Separation efficiencies are too low.
- Pre-filters before the fine filters in AHUs
- For pollen, leaf, insect ….

Fine dust compact filter inserts are also available as combi-filters, i.e. they are also equipped with activated carbon and can thus adsorb odors from the air


Sheet and panel filter
for coarse dust
Bag filter
for coarse dust
Bag filter
for fine dust
Compact filter
for fine dust

Suspended particle filters

For cleanrooms

Suspended particle filters are also capable of removing dust, suspended materials and aerosols of about 0.2 µm size

Suspended particle filters

in the FDA Guide, a suspended particle filter with a separation efficiency of 99.97 % for 0.3 µm particles is defined as a HEPA (High Efficiency Particulate Air-Filter) filter, which according to EN 1822 would approximately fall between Filter class E12 and H13

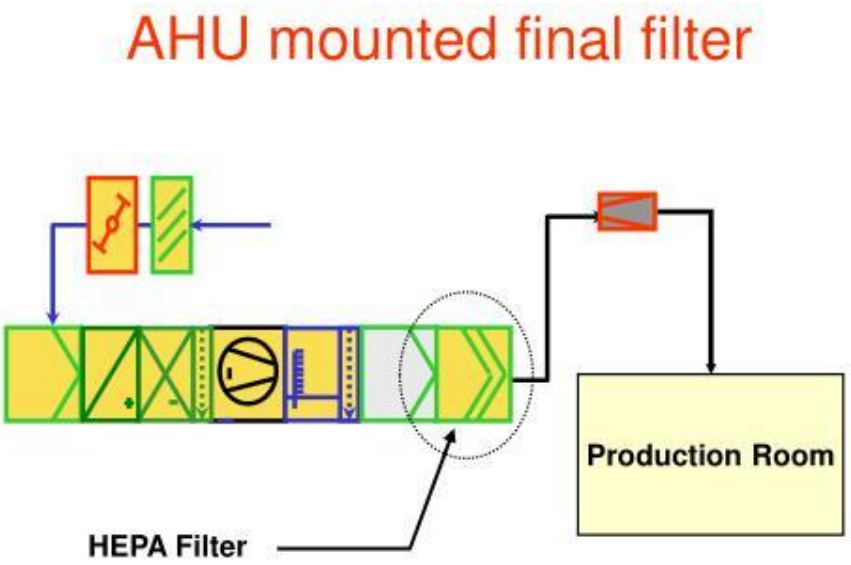
Suspended particle filters

Filter type	Particle size	Separation efficiency
U17	0.1 – 0.2	≥ 99.999995
U16	0.1 – 0.2	≥ 99.99995
U15	0.1 – 0.2	≥ 99.9995
H14	0.1 – 0.2	≥ 99.995
H13	0.1 – 0.2	≥ 99.95
E12	0.3	≥ 99.5
E11	0.3	≥ 95
E10	0.3	≥ 85

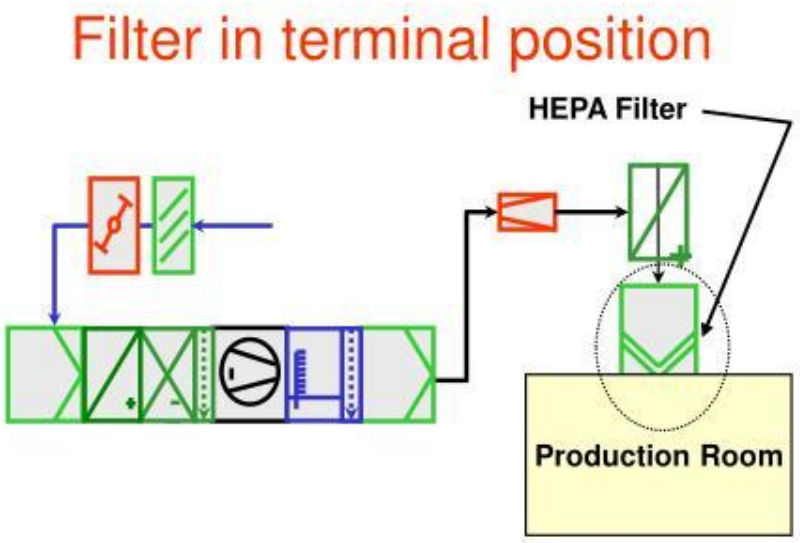
Particle monitoring of cleanrooms

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		In operation	
Grade	0.5 µm	5.0 µm	0.5 µm	5.0 µm
A	3520	20	3520	20
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3520000	29000	Not defined*	Not defined*

Particle monitoring of cleanrooms

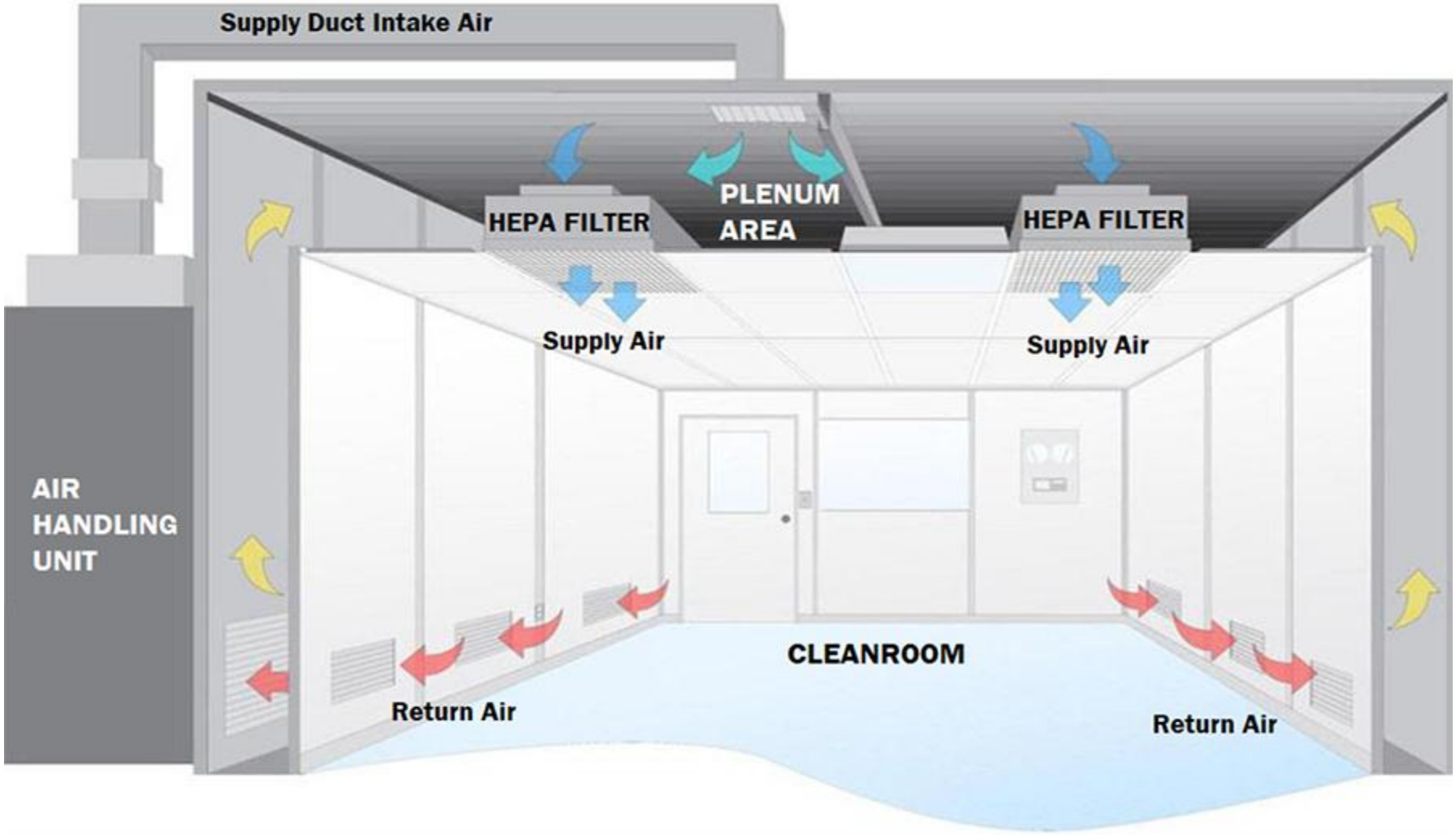


Zone D



Zone B & C

Heating Ventilation and Air Conditioning System HVAC



Cleanroom Protection Concepts

Physical Barrier Concept: Airlocks

Air Displacement Concept
A slowly flowing displacement air stream with speed of 0.2 m/s.

Differential Pressure Concept
The differential pressure between adjacent cleanrooms or clean areas with different cleanliness classes should normally be established in a range from 5 to 20 Pa (WHO)

Air Flow Rate

Cleanroom class in operation	Air exchange rate in operation (n/h)
E	5 – 12
D	10 – 5
C	12 – 20
B	20 - 40

Recovery Time:

The particle count limits for the “at rest” condition should be reached for a room free of personnel after a short clean-up phase of 15–20 minutes (guideline) once activities are completed (“in operation” status)

Room Pressure

Positive Room Pressure

is used if the process needs to be protected from potential contaminations from the environment.

Negative Room Pressure

is used if the environment is to be protected from potential contamination from the process or product

Controlled area temperature

Temperature	USP
Freezing	-25° to -10°C
Refrigerator	+2° to +8°C
Cold	< +8°C
Cool	+8° to +15°C
Controlled room temperature	+20° to +25°C

Humidity

Absolute humidity: how many grams of water are contained in one cubic meter of air

Relative humidity: division of absolute humidity by the maximum water content.

Dew point temperature (or dew point): temperature at which the actual water vapor content in the air is at its maximum (100% relative humidity)

Recommended Humidity Levels:

- for the personnel: 40 – 60%
- Humidity level <30 % the risk of static electrical charging increases
- Humidity level >70 % promotes the growth of microorganisms

Microbiological monitoring of cleanrooms

Sampling:

- **Active air sampling**
- **Settle plate (4 hrs exposure)**
- **Contact plate or swab**
- **Glove**

Microbiological monitoring of Cleanrooms

Grade	air sample cfu*/m ^{3}	settle plates (diameter 90 mm) cfu*/4 hours**	contact plates (diameter 55 mm) cfu*/plate	glove print 5 fingers cfu*/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

* cfu = colony forming units

The End

Clean Room

Industrial pharmacy

Lecture: 4

Dr. Basheer Al-kasmi

Clean room

An environment in which several parameters are controlled monitored and maintained

GMP regulations for:

- Premises
- The surface quality of the components
- Wall cladding, coating
- Clean room

GMP regulations for premises

- Appropriate for the intended use
- Adequate space for production including materials, equipment and personnel
- Design according to the current state-of-the-art
- Properly sealed components (walls, floors, suspended ceiling)
- No uncontrolled dead spaces or links to the surrounding environment.

GMP regulations for the surface quality of the components

- Smooth, sealed, leak-free surfaces without cracks or non-accessible seals.
- No emission or collection of particles possible
- No breeding ground for microorganisms
- Ease of cleaning and avoidance of hard-to-reach surfaces
- Proven compatibility for intended cleaning agents and disinfectant as well as the frequency of use
- Access for maintenance from outside the cleanroom if possible


Access for
cleaning

Wall cladding, coating

- High-quality moisture proof coating resistant to detergents and disinfectants
- Easy to apply and durable attachment to foundation
- Standard finish around window and door frames is established
- Design and integration of installations such as lighting, cable trays, pipe ducts, etc.
- Special finishing work at baseboards, at transition to ceilings as well as scratch and ram guards if integrated in the wall
- For refrigerated or cold storage rooms, check the resistance to temperature variations (from approx. +25 °C to about –20 °C) relative to expansion and brittleness

GMP Requirements for Cleanrooms

- Exposed surfaces should be smooth, impervious and unbroken and should permit the repeated application of cleaning agents and disinfectants, where used
- There should be no difficult to clean recesses and a minimum of projecting ledges, shelves, cupboards, etc.
- False ceilings should be sealed
- Pipes and ducts and other utilities should not create recesses, unsealed openings, and surfaces which are difficult to clean

GMP Requirements for Cleanrooms

- **Sinks** and **drains** should be prohibited in Grade A/B areas
- Floor drains in lower grade cleanrooms should be fitted with traps or water seals to prevent back-flow
- **Windows** are usually integrated as double-faced wall elements and exhibit no protrusions where deposits may accumulate

GMP Requirements for Cleanrooms

Changing rooms

should be designed as air-locks and meet the following criteria:

- the different stages of changing should be physically separated,
- the changing rooms should be equipped with an interlocking system or a visual and/or audible warning system to prevent the opening of more than one door at a time,
- the rooms should be flushed effectively with filtered air,
- hand washing facilities should only be provided in the first stage of the changing rooms,
- the air cleanliness in the final stage of the changing room should, in the *at rest* occupancy state, be the same grade as the area into which it leads.

GMP Requirements for Cleanrooms

Adjacent rooms of different grades should have a pressure differential of 10–15 Pa (guidance value)

- Pressure differences should be recorded regularly or otherwise documented
- Airflow patterns should be demonstrated not to present a contamination risk
- A warning system should be provided to indicate failure of the air supply

The End

Tablet manufacturing process

Industrial pharmacy

Lecture: 5

Dr. Basheer Al-kasmi

Review

Tablets:

Solid dosage form of medicament or medicaments with suitable excipients preparing by compression

Preparing method: wet granulation, dry granulation or direct compression

Tableting process

Wet granulation	Dry granulation	Direct compression
Sieving	Sieving	Sieving
Mixing (IP)	Mixing (IP)	Mixing
Granulation	Compacting	Tableting or capsule filling
Drying	Milling	
Milling	Mixing (EP)	
Mixing (EP)	Tableting or capsule filling	
Tableting or capsule filling		

Filler	Lactose Sucrose Glucose Mannitol Sorbitol Calcium phosphate Calcium carbonate Cellulose
Disintegrant	Starch Cellulose Crosslinked polyvinyl pyrrolidone Sodium starch glycolate Sodium carboxymethyl cellulose
Solution binder	Gelatin Polyvinyl pyrrolidone Cellulose derivatives (e.g. hydroxypropylmethyl cellulose) Polyethylene glycol Sucrose Starch
Dry binder	Cellulose Methyl cellulose Polyvinyl pyrrolidone Polyethylene glycol
Glidant	Silica Magnesium stearate Talc
Lubricant	Magnesium stearate Stearic acid Polyethylene glycol Sodium lauryl sulfate Sodium stearyl fumarate Liquid paraffin
Antiadherent	Magnesium stearate Talc Starch Cellulose

Excipient types:

- Filler (or diluent)
- Disintegrant
- Binder
- Glidant
- Lubricant
- Other: solubility enhancer, colorants, flavour

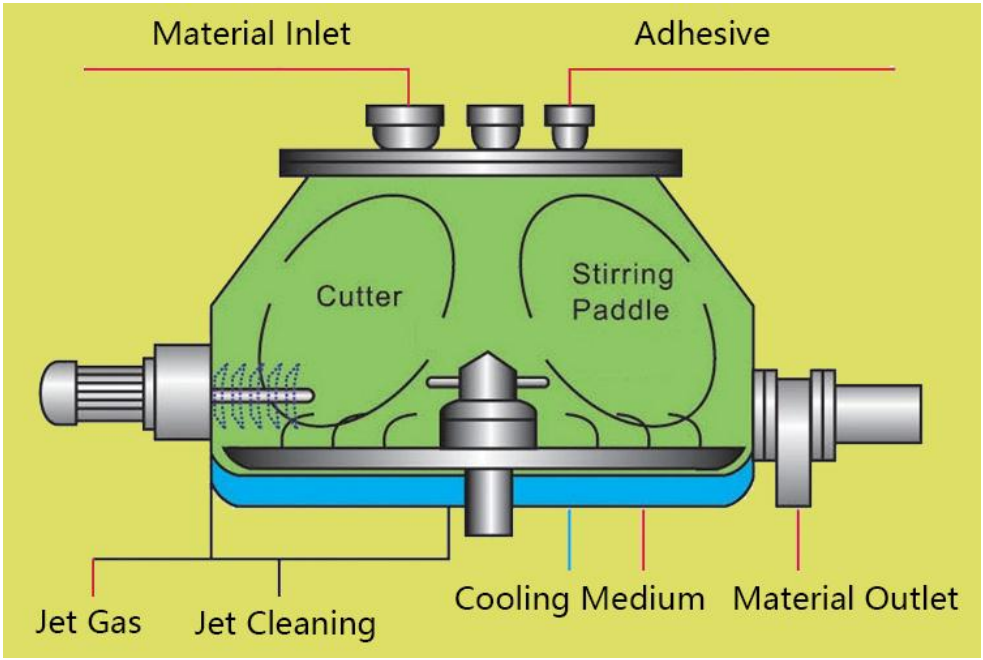
Pharmaceutical equipment:

- Contact surface with product: stainless 316 L
- Other outer surface: stainless 304
- Clean in place (CIP)
- Sterile in place (SIP)

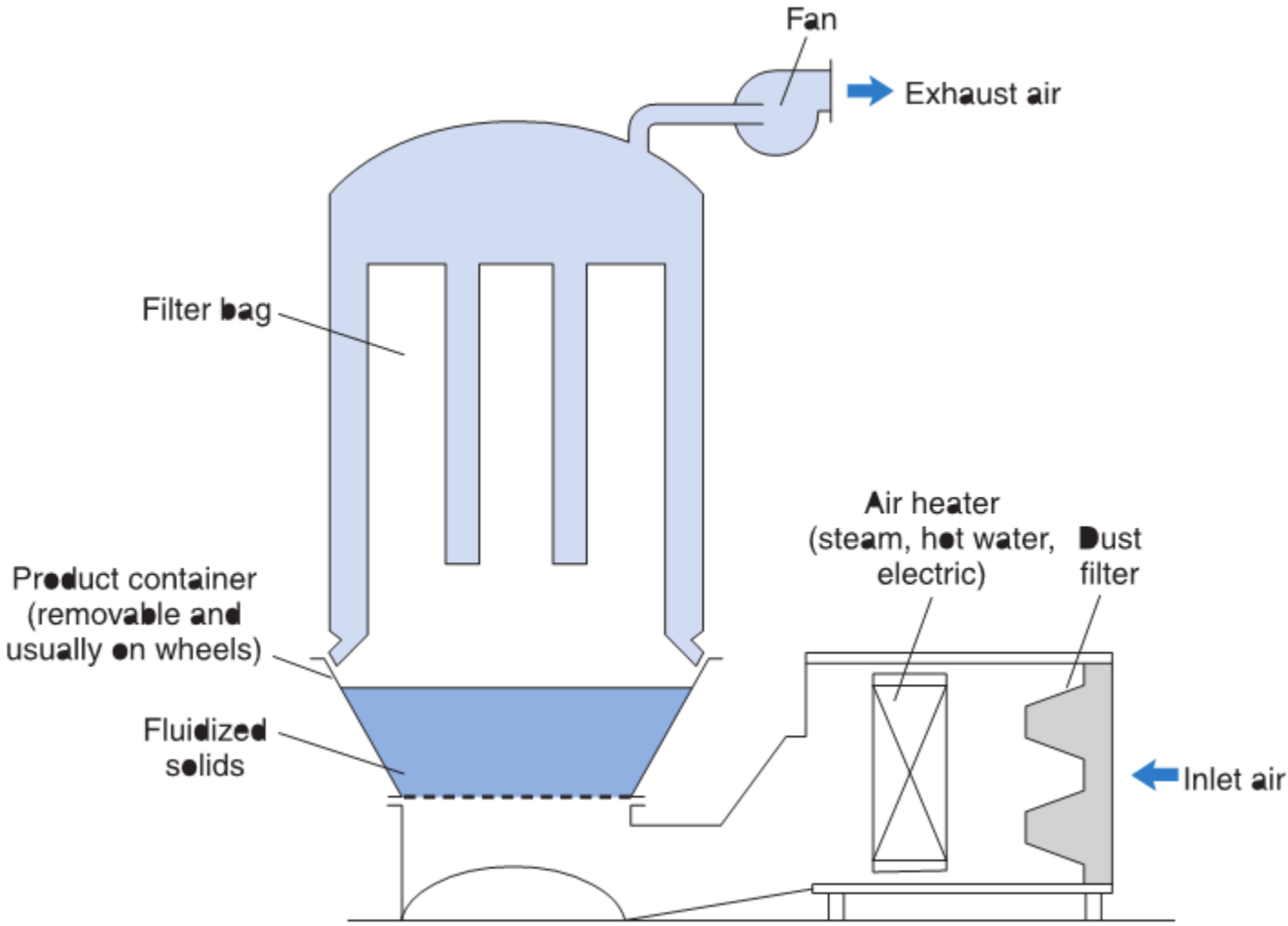
Utilities

- Zone: D
- Compressed air
- Drink and Purified water
- Industrial steam

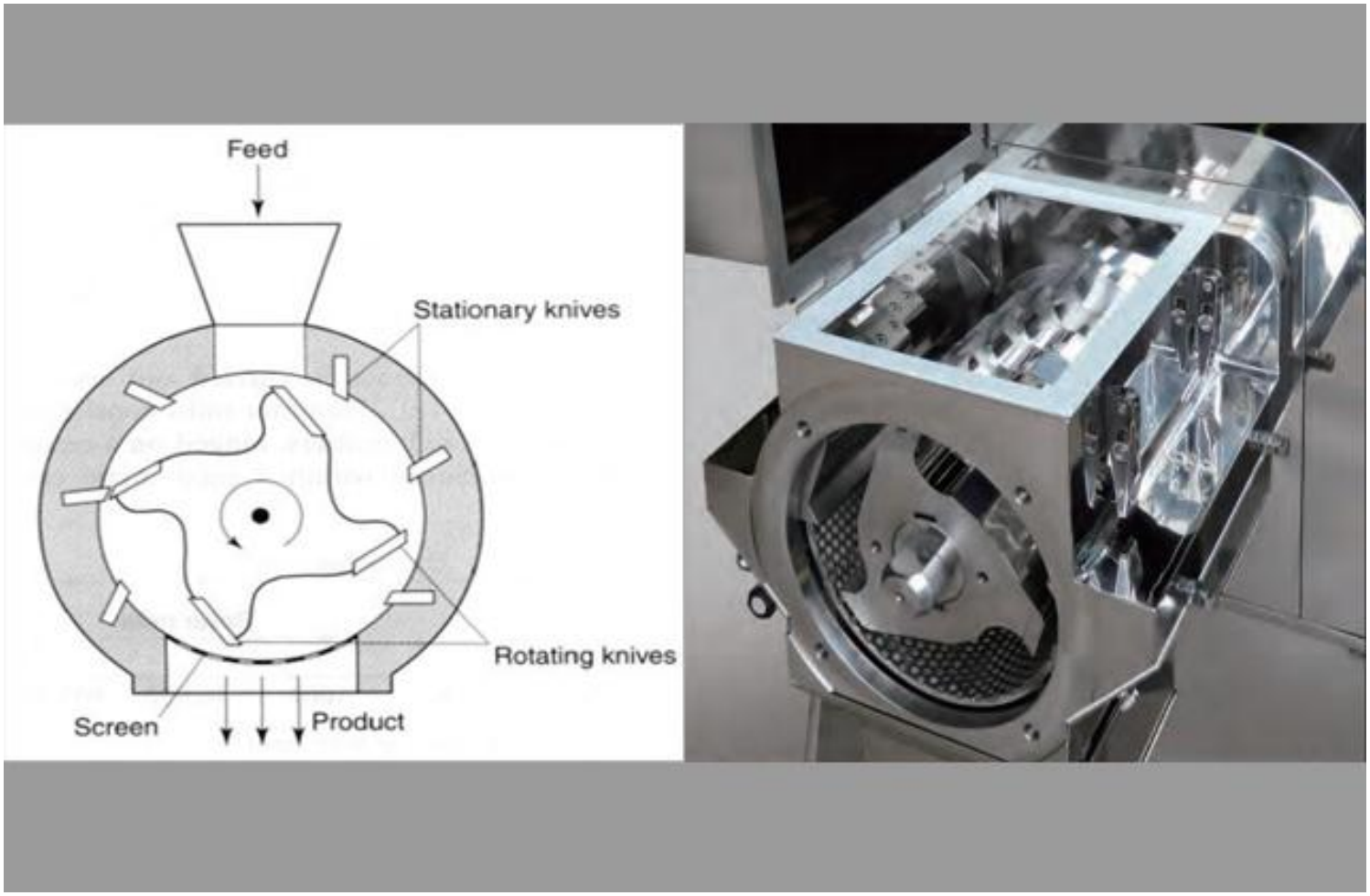
Granulation
Rapid mixer granulator (RMG)



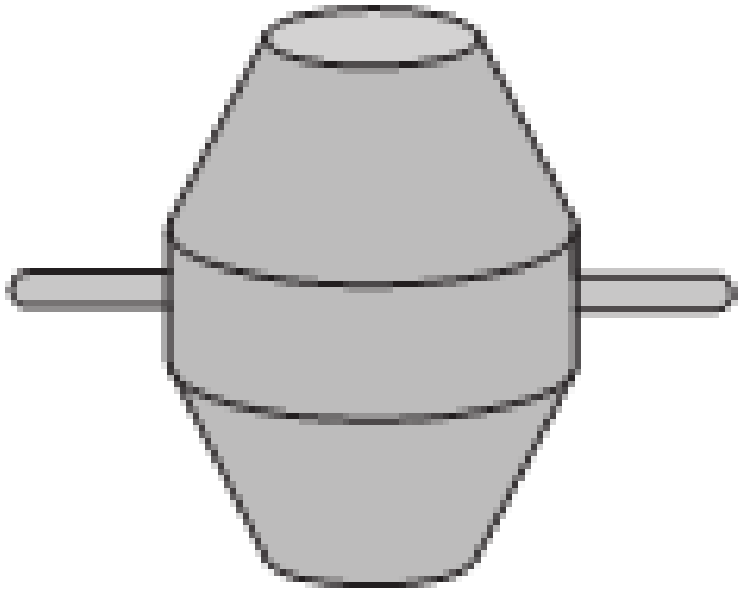
Granulation: Fluid bed dryer (FBD)

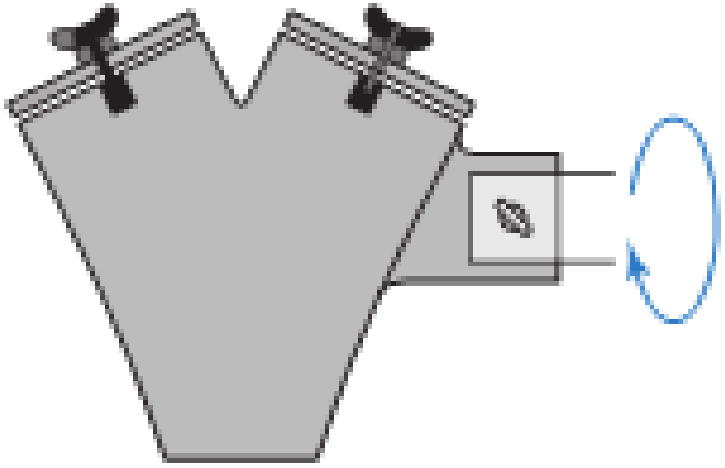


Granulation: Miller



Granulation: Mixing with external phase



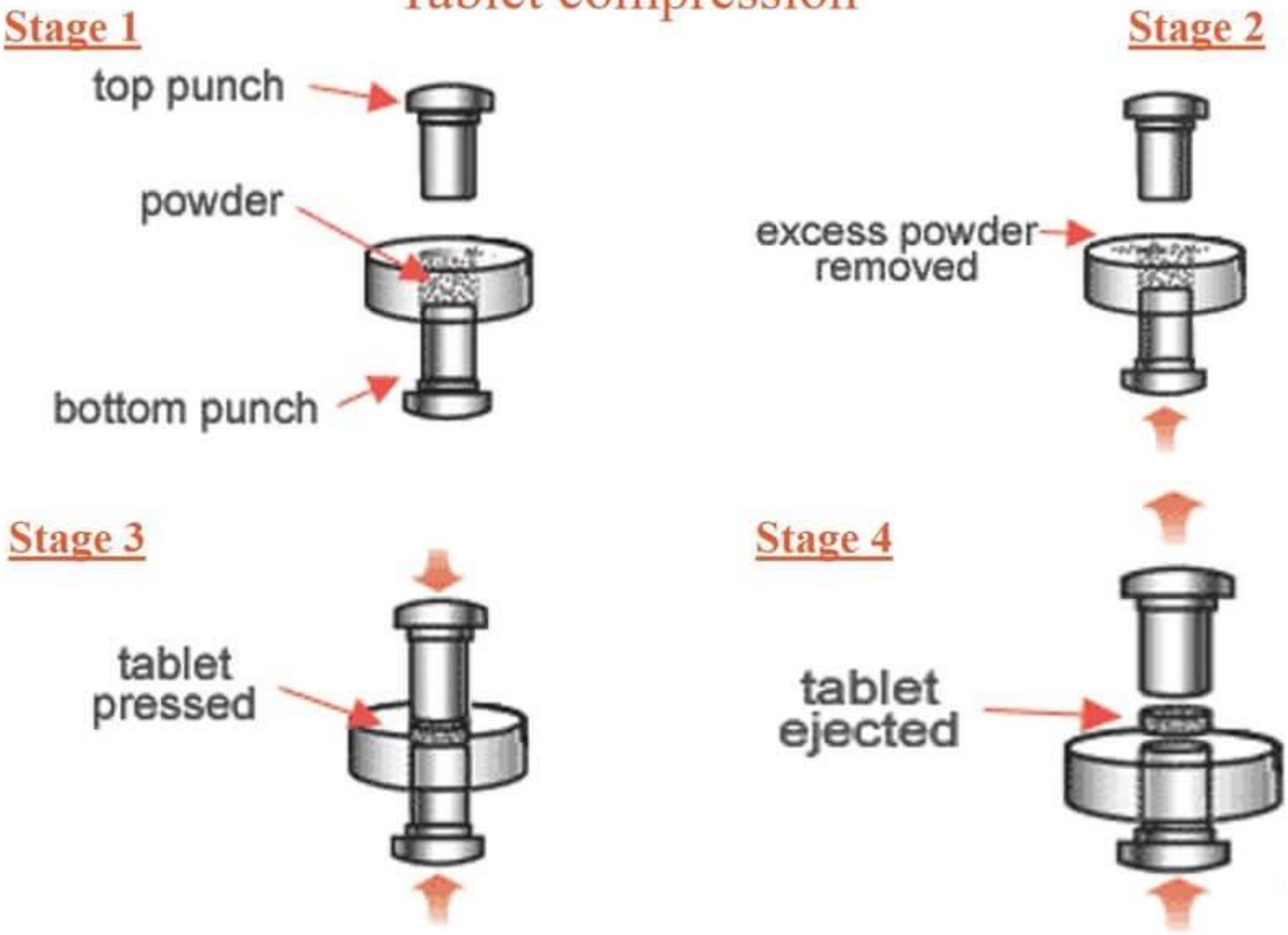


Y-cone mixer

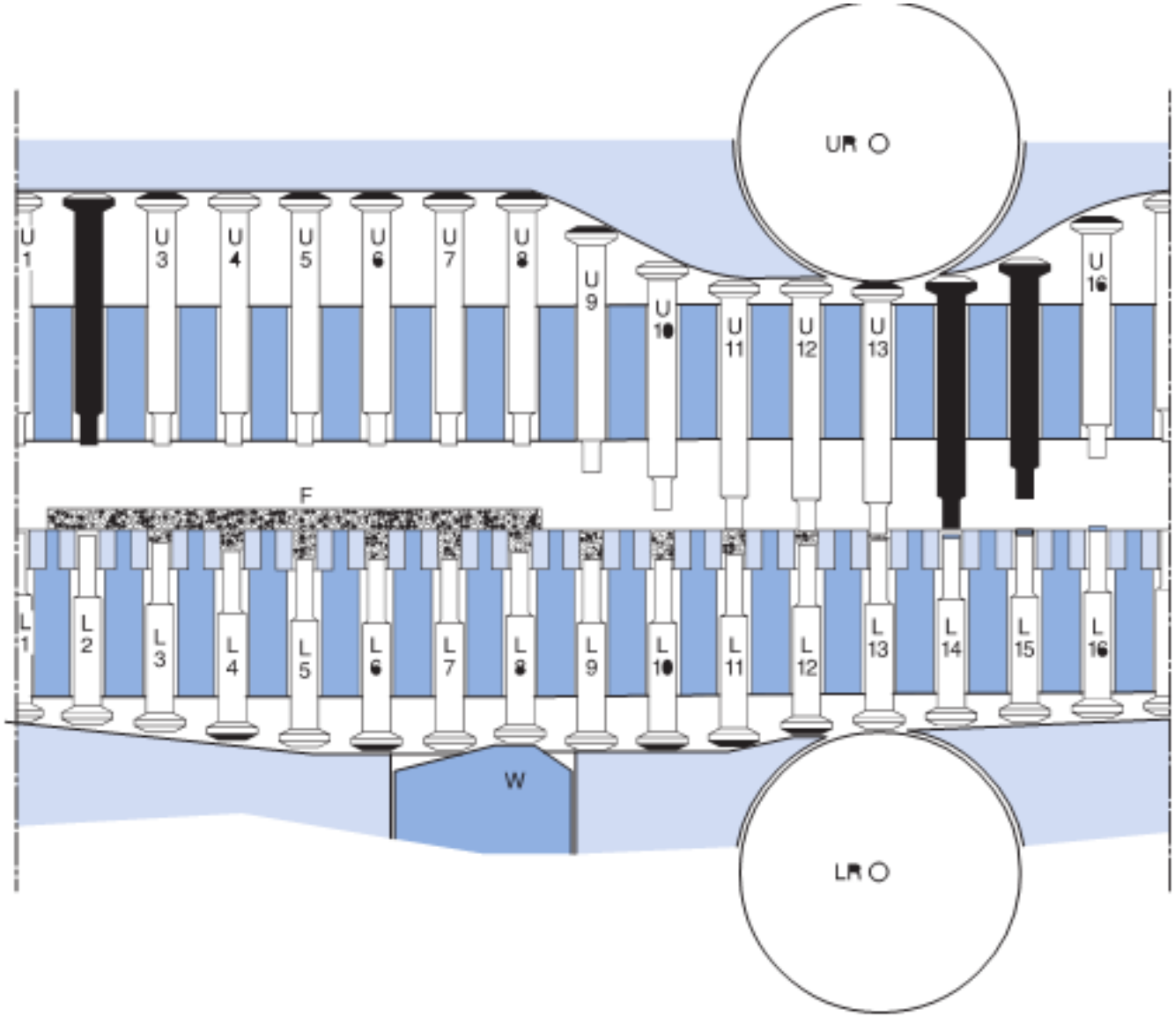
In process control (IPC)

- Particle size distribution
- Bulk and tapped density
- Loss on drying (LOD)
- Drug homogeneity

Tablet compression



Tableting


UR
U 1
U 3
U 4
U 5
U 6
U 7
U 8
U 9
U 10
U 11
U 12
U 13
U 16
F
L 1
L 2
L 3
L 4
L 5
L 6
L 7
L 8
L 9
L 10
L 11
L 12
L 13
L 14
L 15
L 16
W
LR

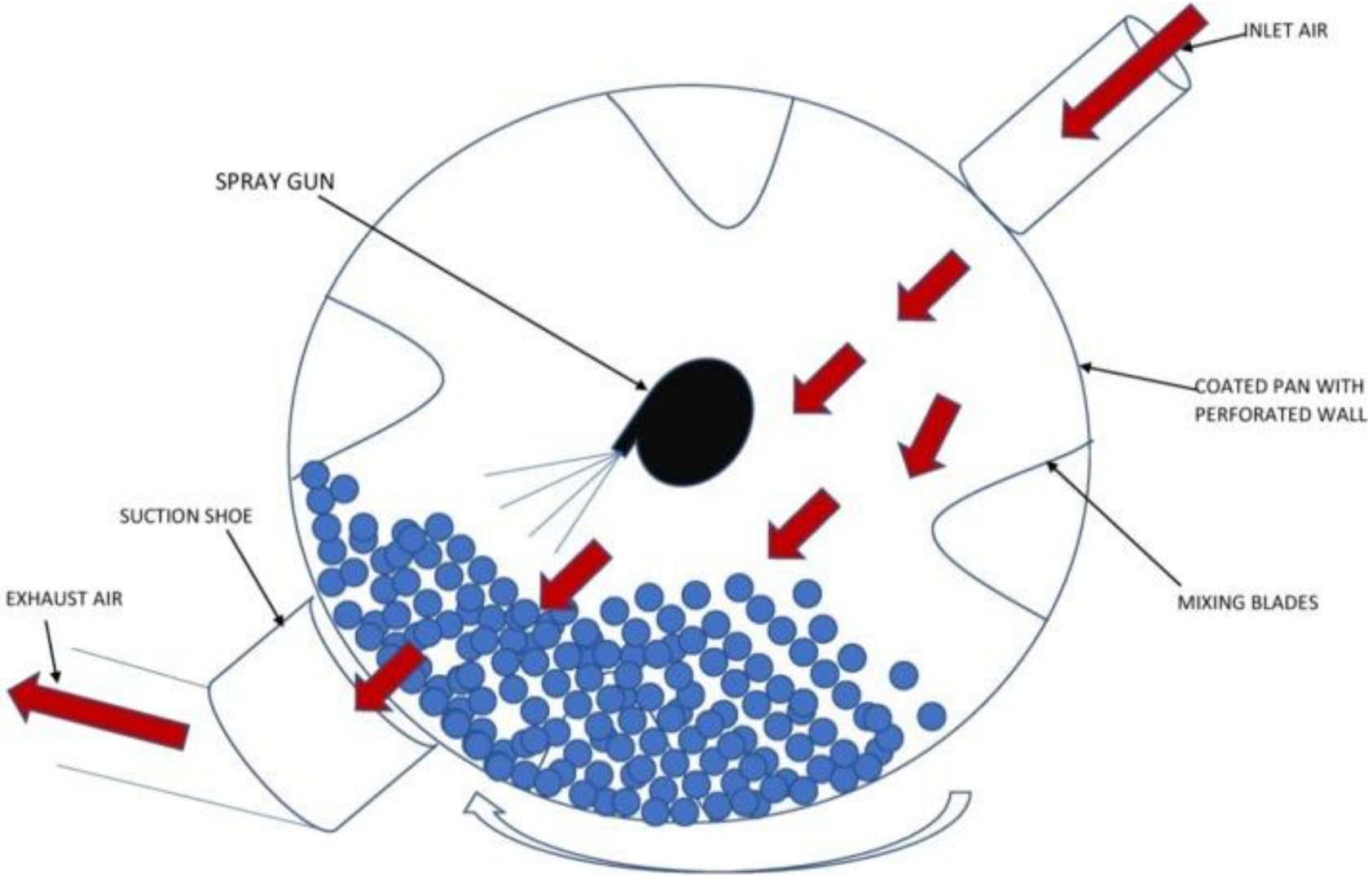
In process control (IPC)

- Appearance
- Weight variation (NMT 5%)
- Friability (NMT 1%)
- Hardness
- Disintegration (NMT 15 min)

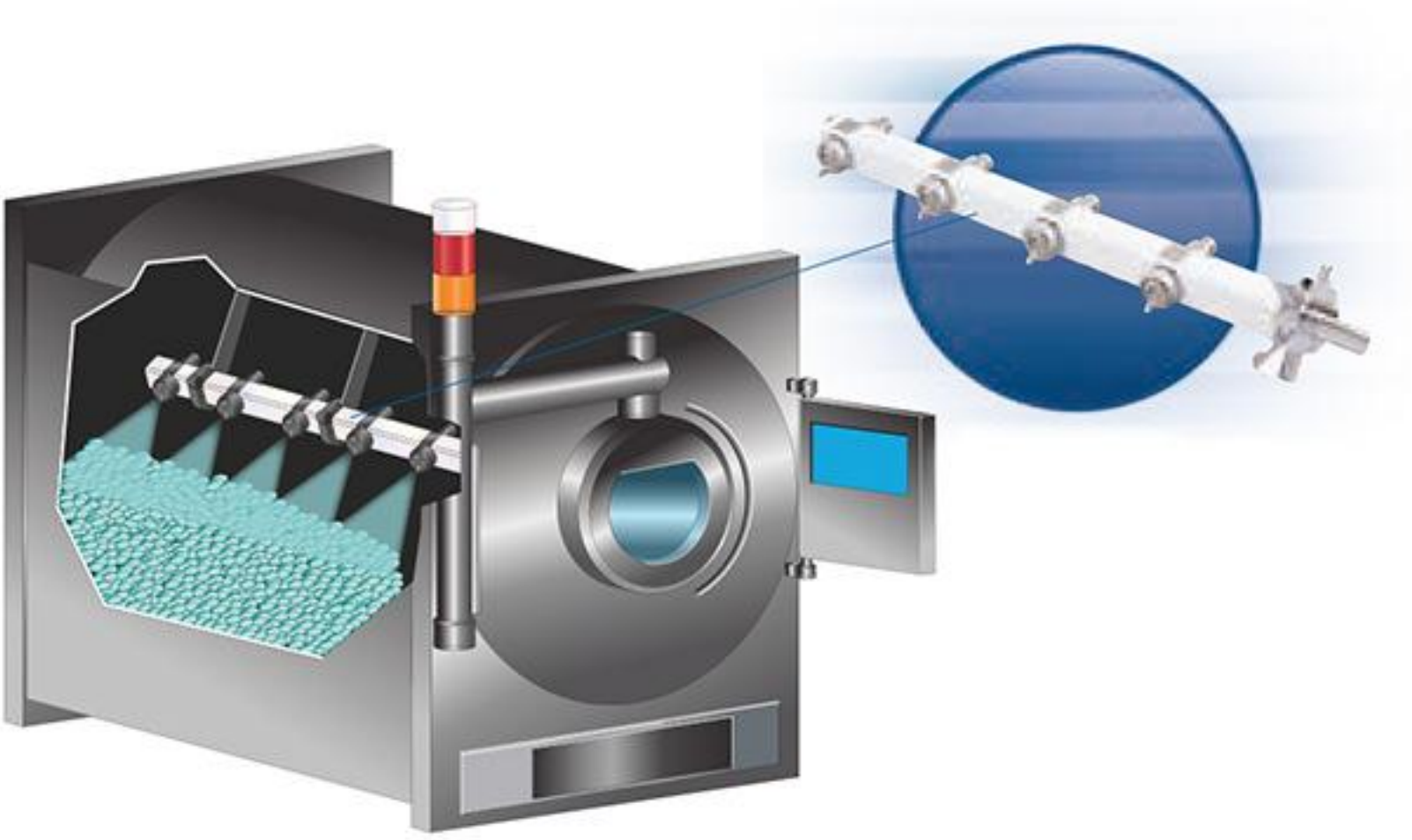
Technical problems during tableting

- High tablet variation
- Low mechanical strength of the tablets
- Capping and lamination of the tablets
- Adhesion or sticking of powder material to punch tips
- High friction during tablet ejection.

Coating


INLET AIR
SPRAY GUN
COATED PAN WITH
PERFORATED WALL
SUCTION SHOE
EXHAUST AIR
MIXING BLADES

Coating



Reasons for coating

1. Protecting the drug from the environment (light
2. and moisture)
3. Masking the taste o drug substances
4. Improving the ease of swallowing large dosage forms
5. Masking any batch differences in the appearance of raw materials within time
6. Improving product appearance and aiding in identification.
7. Enabling the coated product to be more easily handled on high-speed automatic filling and packaging equipment and reduces the risk of cross contamination by minimizing ‘dusting’ problems.
8. Modified release characteristics

Types of coating processes

- Film coating
- Sugar coating
- Compression coating.

Film-coating defects

- Processing issues: an imbalance between the rate of delivery of the coating liquid and the rate of evaporation during the drying process. Over wetting (tablet twin) or over drying (erosion and chipping)

- Formulation issues : core (tablet breakage and erosion) or the coating liquid (cracking and chipping, or inadequate film adhesion, resulting in film peeling and logo bridging).

Manufacturing quality:

Critical Process Parameters (CPPs)

is a term used in pharmaceutical production for process variables which have an impact on a critical quality attribute (CQA) and, therefore, should be monitored or controlled to ensure the drug product obtains the desired quality.

S. No	Operations during tableting	Critical Process Parameters	Potential Quality Attributes
1	Wet granulation	Mixing time Impeller speed Binder fluid addition rate & time Method of binder addition Temperature	Blend uniformity Granule size & distribution Moisture content
2	Drying	Drying time Inlet air flow Exhaust air temperature & flow	Bulk/tapped density Moisture content Granules strength & uniformity
3	Milling	Milling speed Screen size Feeding rate	Flow properties Particle size distribution Bulk/tapped density
4	Mixing	Mixer type Mixing time Order of addition	Blend Uniformity
5	Compression	Pre compression force Main compression force Dwell time Hopper design Punch penetration depth Roller type Auger screw rate Ejection force	Weight variation Hardness Friability Content uniformity Assay Dissolution Disintegration
6	Coating	Inlet air flow Time Temperature Spray pattern & rate	Thickness Hardness % of weight gain Appearance

Manufacturing quality:

Kind of quality in manufacturing process:

- Quality by design (QBD)

Or

- Quality by result (QBR)

The End

Semi-solid manufacturing process

Industrial pharmacy

Lecture: 6

Dr. Basheer Al-kasmi

Semi-solid preparation:

1. Suppositories
2. Cream
3. Ointment
4. Gel

Suppositories Process:

1. Base melting
2. Materials dispersing within melt base
3. Blister forming
4. Fill the melt base and materials in the blister
5. Cooling.

Suppositories excipient:

1. Vehicle (suppository base):

- Glyceride-type fatty bases: semi- or fully synthetic theobroma oil (cocoa butter)
- Water-soluble bases: glycerol, gelatin and polyethylene glycol

Suppositories utilities

- Zone: D for rectal
  C for vaginal
- Compressed air
- Drink and Purified water
- Industrial steam (option)

Suppositories IPC

- Homogeneity
- Shape
- Hardness
- Disintegration
- Melting point
- Weight variation

Suppositories CPP and CQA

Step	CPP	CQA
Base melting	Temperature	viscosity
Drug dispersing	Temperature Mixing time and speed	Viscosity homogeneity
Blister forming	Temperature of heating and cooling Vacuum	Blister hole volume Weight variation
Filling	Temperature Mixing	Content uniformity
cooling	temperature	shape

Ointment Process:

1. Base melting
2. Materials dispersing within melt base
3. Cooling
4. Filling in tube

Ointment excipient:

Vehicle (Ointment base):

- Hydrocarbon base: soft, hard and liquid paraffins
- Absorption bases: hydrocarbon (paraffin) + miscible substance (sorbitan monooleate)
- Emulsifying base: oil-in-water system: mixture of paraffins with cetostearyl alcohol and a surface active agent such as sodium lauryl sulphate (SLS) or cetrimide.

Ointment and cream utilities

- Zone: C
- Compressed air
- Drink and Purified water
- Industrial steam (option)
- Vacuum
- Nitrogen

Ointment and cream IPC

- Homogeneity
- Viscosity
- Weight variation
- pH
- Tube shape

Ointment CPP and CQA

Step	CPP	CQA
Base melting	Temperature	viscosity
Drug dispersing	Temperature Mixing time and speed	Viscosity homogeneity
Cooling with mixing	temperature	Viscosity Content uniformity
Filling	Dosing pump	Weight variation

Cream Process:

water-in-oil (W/O) or oil-in-water (O/W)emulsion

1. Aqueous phase: preparation and raising temperature (70 - 80º C).
2. Oily phase: preparation and raising temperature (70 - 80º C).
3. Add one phase to another (70 - 80º C) with homogenization.
4. Cooling with homogenization and vacuum
5. Filling in tube

Cream excipient:

1. Oil phase
2. Aqueous
3. Emulsifier
   - Anionic: Sodium lauryl sulphate
   - Cationic: Cetrimide
   - Non-ionic: Sorbitan monooleate (span 80), Polyoxyethylene sorbitan monooleate (Tween 80)

Cream CPP and CQA

Step	CPP	CQA
Phase preparation	Temperature mixing	Cream stability
Add one phase to another	Temperature homogenization time and speed	Cream stability homogeneity
Cooling with homogenization	Temperature Vacuum homogenization time and speed	Cream stability homogeneity
Filling	Dosing pump	Weight variation

The End

Sterile manufacturing process

Industrial pharmacy

Lecture: 7

Dr. Basheer Al-kasmi

The **sterility** of a drug:

The complete absence of viable microorganisms

Sterile products: solution, emulsion, suspension, gel or ointment. Classified as small volume parenterals (SVPs) nominal volume of 1–100 ml, and LVPs into 100–1 000 ml bottles or bags

Two possibilities of manufacture sterile medicinal product:

- Terminal sterilisation
- Aseptic processing

Quality requirements:

- Assay
- Sterile
- As far as possible particle-free
- As far as possible free of bacterial endotoxins (lipopolysaccharides which are contained in the cell membrane of gram-negative bacteria and are released when the bacteria die and decompose)

Manufacturing of terminally sterilized products:

Sterilization process:

- Steam sterilization (heating in an autoclave): 121° C for 15 min by using saturated steam under at least 15 psi of pressure
- Sterilization by means of dry heat: 160° C for 120 min
- Sterilization by means of radiation (gamma ray)

Cleanliness grades for the manufacture of terminally sterilized products:

Manufacturing operations	Room class
Preparation of solutions	Grade D zone
Filling of products for terminal sterilization	Grade C zone

Manufacturing of terminally sterilized products:

Main equipment:

- Preparation system
- Washing machine for glass containers
- Hot air sterilisation tunnel
- Filling and closing machine
- Crimping machine
- Autoclave
- Visual inspection station
- Packaging line

Preparation

critical process parameters:

- Temperature
- stirring time and speed
- homogenisation time and pressure

in-process controls:

- Density
- pH
- Assay
- Particles
- bioburden

Washing process for primary containers:

Wash water is sprayed into and onto the outside of the containers through spray nozzles/needles under pressure then are **blow-dried** using heated compressed air through nozzles/needles.

Siliconising the glass surface prevents interaction between the medicinal product and ions released from the glass. Here liquid silicone is distributed in a thin and even layer over the entire interior surface of the containers using spray nozzles/needles. When this step is used, further **drying** by injecting compressed air may be necessary.

Washing process for primary containers:

CPP:

- Cycle number/times
- Water temperatures
- Water pressure/quantity
- Compressed air pressure
- Air temperatures during drying
- Quantity of washing agents added
- Quantity of silicone added

IPC:

Inorganic salts: Conductivity

Organic contamination, e.g. from washing agents containing surfactants: Total Organic Carbon (TOC) and pH

Filling:

The filling systems are normally equipped with a germ reducing filter (0.22 µm) through which the product is passed before being filled.

IPC:

- Fill volumes/fill weights
- Particle
- Appearance
- Leak test

Aseptic processing:

The aim of aseptic processing is to maintain sterility of a preparation made of sterilized components (raw materials and primary packaging materials).

Aseptic processing:

Sterility assurance in aseptic processing depends on:

- Rooms (monitoring the air flow and overpressures in the rooms)
- Microbiological monitoring (air and surfaces)
- Personnel
- Sterilization methods
- Validation of aseptic filling methods

Cleanliness grades for the manufacture of Aseptic processing :

Manufacturing operations	Room class
Preparation of solutions to be filtered	Grade C zone
Handling and filling of aseptically prepared products	Grade A zone

Aseptic processing:

Sterilisation procedures:

- Sterile filtration for solutions
- Sterilization by dry heat for glass containers
- Sterilization by saturated steam for closures.

Sterile filtration:

Sterile filtration (0.2 µm or less) is the process of removing the microorganisms and particles which are present in liquids and gases with the help of suitable filter materials

Smaller particles and microorganisms are retained in the pores due to adsorption forces, depending on the:

- Pressure differential
- Flow rate
- Number of particles
- Surface tension and degree of ionisation

Validating aseptic processing (media fill):

1. Aaerobic culture media: casein soya peptone (caso).
2. Anaerobic culture media: Fluid thioglycolate medium

The End

Sterilisation processes

Industrial pharmacy

Lecture: 8

Dr. Basheer Al-kasmi

Definition:

Sterility: free of viable microorganisms

sterilization process: a set of measures or working steps for meeting specific requirements for sterility.

It is not possible to achieve absolute sterility through sterilisation. Sterility can only be guaranteed with a defined probability.

Sterility Assurance Level (SAL): The probability of non-sterile units occurring in a specified amount of preparations. According to the European Pharmacopeia the SAL value for sterile products is defined as 0.000001 or less

Sterilisation method:

- Sterilisation with moist heat (steam sterilisation)
- Sterilisation with dry heat (dry heat sterilisation)
- Sterilisation by radiation
- Sterilisation with microbicidal gases

Microbicidal gases, where ethylene oxide is used as sterilising agent, is not authorised for use with medicinal products but it may be used for the sterilisation of medical devices where there is no alternative

Steam sterilisation:

Sterilizing by means of pure saturated steam

It should be preferably used for aqueous products

Requirements for the effectiveness of steam sterilization:

- The steam must achieve a certain thermodynamic state (205 kPa at 121 °C).
- The steam must be saturated. Unsaturated or superheated steam has a low microbial killing effect (hydrolytic protein denaturation is restricted).
- The steam must act upon the product to be sterilized for a specified time period (e.g. 15 min).
- The steam must reach all surfaces of the product to be sterilized and a sufficient heat transfer must be ensured.

Saturated steam sterilization conditions:

Saturated steam temperature of 121 °C and an exposure time of 15 minutes. As an alternative these standards include the possibility to sterilize at a saturated steam temperature of 126 °C for 10 minutes or at a saturated steam temperature of 134 °C for at least 3 minutes

Performing a steam sterilisation process

- Deaeration phase
- Heating phase
- Balancing period
- Sterilisation time/Holding period
- Cooling phase/Suction phase
- Drying phase
- Ventilation phase

Sterilization process

Direct steam sterilization process is only applicable for solid items to be sterilized, such stainless steel tools. Here, it is absolutely essential to use suitable procedures for removing air from the items to be sterilized.

Indirect process steam is used as heat transferring medium. Tightly closed containers, such as vials, are sterilized by this process. Since it is impossible to expel air from these containers, longer exposure times will generally be required if higher amounts of air are in the headspace of the containers.

Key figures for steam sterilization:

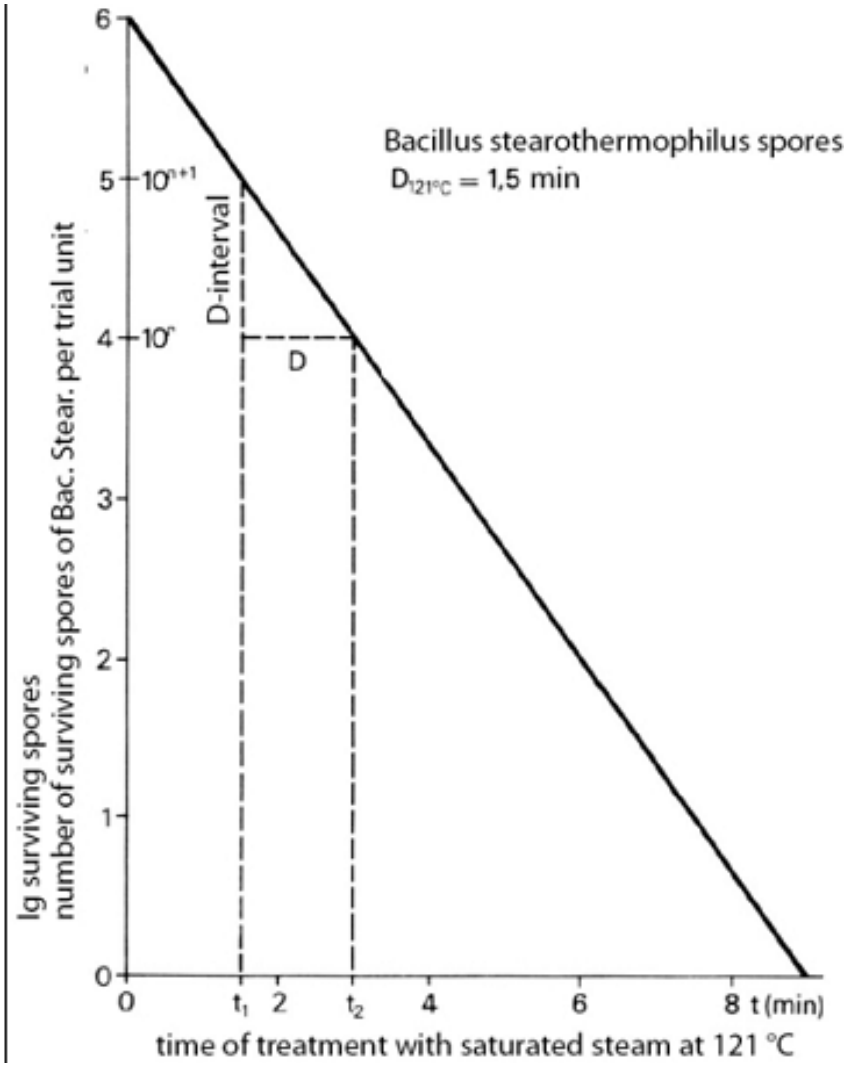
D value (min): The time in minutes that is required to kill 90% of the spores or vegetative cells of a specified microorganism at a given temperature

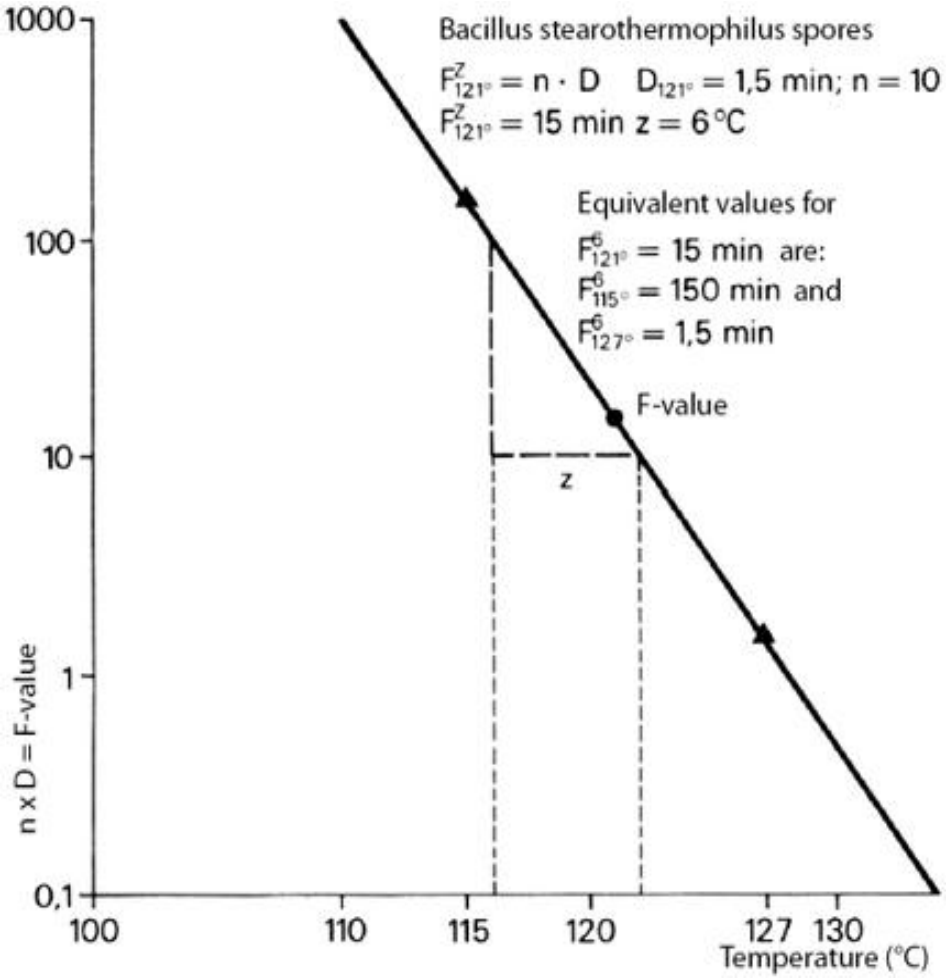
Z value (C): The change in temperature in degrees Celsius that causes the D value to change by a power of ten.

F value (min): the effectiveness (total lethality) of a sterilization process

$$F = n.D$$

n = 10


Bacillus stearothermophilus spores
$D_{121°C}$ = 1,5 min
D-interval
D
lg surviving spores
number of surviving spores of Bac. Stear. per trial unit
time of treatment with saturated steam at 121 °C
t (min)


Bacillus stearothermophilus spores
$F^z_{121°} = n \cdot D$ $D_{121°} = 1,5$ min; n = 10
$F^z_{121°} = 15$ min z = 6 °C
Equivalent values for
$F^6_{121°} = 15$ min are:
$F^6_{115°} = 150$ min and
$F^6_{127°} = 1,5$ min
F-value
z
n x D = F-value
Temperature (°C)

Key figures for steam sterilization:

L value (min): The lethality factor or lethality level (L) compares the lethality of a particular process in minutes of contact time at a temperature (T) under the conditions of a reference process.

$$L = 10^{\frac{Ti - Tb}{Z}}$$

L : lethality level
Ti : test temperature in degrees Celsius
Tb: reference temperature in degrees Celsius
Z : Z value

Equivalent process:

Equivalent processes are processes with different combinations of temperature and time with the same total lethality in relation to the standard process.

An equivalent process is calculated as follows:

$$F_T = \frac{F_{121}}{10^{\frac{T-121}{Z}}}$$

$$F_{115} = \frac{15\ \text{min}}{10^{\frac{115-121}{6}}} = 150\ \text{min}$$

Dry heat sterilisation:

The dry heat process is suitable for sterilizing heat stable items such as glassware, metal instruments and device parts.

Air is, however, a very much poorer heat conductor than saturated steam, and consequently dry heat is significantly less effective than moist heat. For this reason higher temperatures and longer sterilization times are required.

Dry heat sterilisation conditions:

- 160–170 °C ,120 min
- 170–180 °C, 60 min
- 180–190 °C, 30 min
- **Depyrogenation:** 250 - 350 °C, 30 min

Key figures for dry heat sterilization:

D and Z values

The main difference to the key figures for steam sterilization is the Z value. This is specified as 20 °C

Performing a dry heat sterilization process

- Heating phase
- Balancing period
- Sterilization time/Plateau time
- Cooling phase

Radiation sterilisation:

These are classified as alpha, beta or gamma rays according to their increasing capability to penetrate material. Gamma rays are used preferably due to their better penetrating power.

Gamma rays are electromagnetic waves like X-rays or microwaves, but much more energy-rich. The only source used for gamma rays in Europe is the radioactive isotope Cobalt-60 (60Co).

The energy absorbed during irradiation is specified in:

- kilo-Gray (1 kGy = 1 × 103 J/kg).
- Mrad (megarad), (1 Mrad = 10 kGy).

Effect of gamma rays on microorganisms:

They affect not only bacteria, but also moulds and viruses. Gamma rays kill microorganisms by attacking their DNA molecules.

Sterilization dose: 25 -40 kGy

The effectiveness of microorganism destruction depends on

- initial bacterial count
- oxygen concentration: oxygen increases the effect from 2-3 times for formation of H2O2
- water content: increases the effect for formation of H2O2

Effect of gamma rays on materials:

Change the properties of plastics:

- Material brittleness
- Loss of transparency
- Material discolouration

The End

Packaging

Industrial pharmacy

Lecture: 9

Dr. Basheer Al-kasmi

Packaging

Refer to the packaging of industrially manufactured finished pharmaceutical products. These packaging materials must satisfy specific requirements when used both singly and in combination with one another

The most important function of such packaging is to protect the tested and approved product until it reaches the end user and to ensure that it conforms, within the defined limits, to the product specification until the expiry date.

Packaging materials divide to:

1. Primary packaging materials:

Packaging materials that have direct contact with the product

2. **Secondary packaging materials**:

All other materials used in the packaging of finished pharmaceutical products such as package inserts, labels….

Primary packaging materials:

Primary packaging materials protect the packaged product against external influences and safeguard the product in accordance with its specification until it reaches the end user.

There must be no interaction between the product and the material used for packaging. The main possible types of **interaction:**

adsorption, absorption, diffusion and migration.

Primary packaging materials:

Active ingredients, preservatives, auxiliaries and solvents may be affected by **adsorption** and **absorption**. As far as the medicinal product is concerned, this may result in a loss of active ingredient, impaired antimicrobial properties, decomposition due to the loss of stabilising components and a loss of flavour.

Possible consequences for the packaging material include swelling, changes in the mechanical properties, stress corrosion, discolouration and changes in permeability.

Primary packaging materials:

Diffusion the usual scenario is that solvents diffuse out of the medicinal product, while hydrogen, oxygen and carbon dioxide diffuse into the medicinal product from outside. This can lead to oxidative degradation of the active ingredients, a change in the pH value, hydrolytic degradation, the absorption of external odours and a change in the smell or taste. The appearance of the product may also change.

Primary packaging materials:

Migration: additives (such as stabilisers, lubricants, plasticisers, colorants, fillers, catalysts, antistatic agents, UV absorbers) migrate out of the packaging materials into the medicinal product. Migration may lead to discoloration of the medicinal product, cloudiness and precipitation, degradation of the active ingredient and changes to the smell and taste.

As regards the packaging material, migration may cause discoloration as a result of pigment loss, brittleness due to the loss of plasticiser, ageing as a result of loss of stability and changes in the permeability.

Criteria for selecting primary packaging materials:

Aspect	Criterion
Product stability	• Photosensitivity • Sensitivity to moisture • Incompatibilities • Interactions
Packaging process	• Processability
Marketing requirements	• Colours • Blister shape and material • Removability • Price
Regulatory requirements	• Labelling • Printing • Child safety

Overview of the different types of packaging			
Dosage form	**Example**	**Packaging**	**Labelling**
Solid	Tablets, dragees, capsules	Blisters	Using folding cartons and preprinted foil (brand name)
		PE bottles (US market)	Using adhesive labels or printed bottles
	Powder	Pouches/sachets	Printed sachets
		Screw top jar, PE bottles	Using adhesive labels or printed bottles
Liquid (non-sterile)	Solutions (syrup, drops)	Glass bottles, drop bottles	Using adhesive labels or printed bottles
Semi-solid	Emulsions	Glass bottles, plastic bottles	Using adhesive labels or printed bottles
	Creams, ointments	Tubes (plastic or aluminium)	Printed tubes
		Tubs, tins or jars with screw tops	Using adhesive labels or printed containers

Plastic containers:

PVC (polyvinyl chloride) was cheap and widely available. To improve the water vapour barrier, the PVC sheeting was coated with different amounts of PVDC (Polyvinylidene chloride). Aluminium foils can be used for products that are extremely sensitive to moisture.

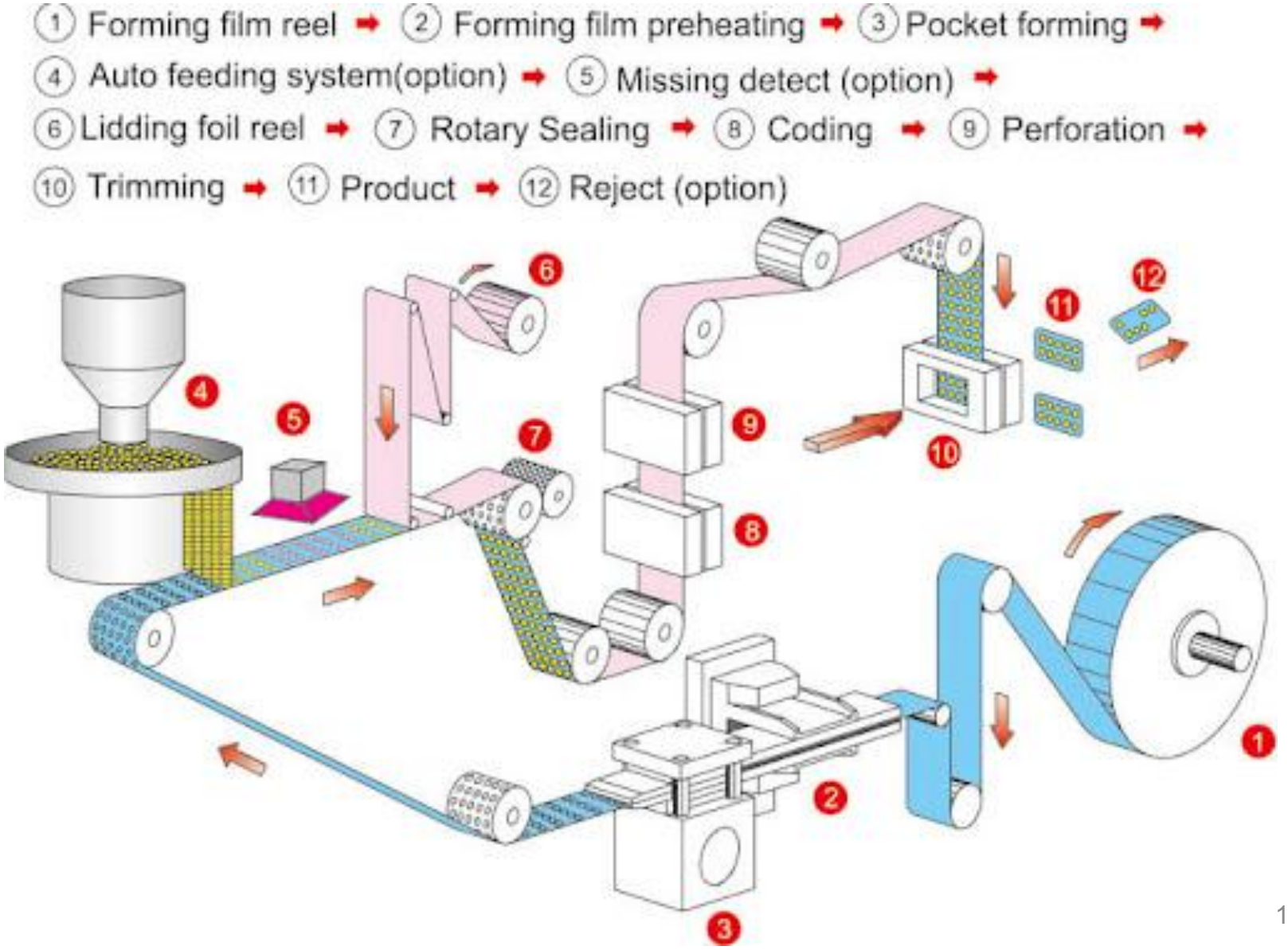
Polypropylene (PP) can be used to replace both PVC, PVC/PVDC films and aluminium sealing foil.

The quality of the seal must also be determined by vacuum leak testing procedure (methylene blue dye bath test).

Blister forming:

- Heating a preformed plastic sheet, moulding it to form cavities or pockets and then allowing it to cool.
- The tablets or capsules are placed in the cavities and sealed with thin aluminium foil.
- The resultant strip is then die-cut to give individual blister packs of the appropriate size and shape.

Blister forming:



Blister forming:

Step	CPP	CQA
Plastic film forming	Temperature Vacuum or compressed air	Hole size Hole shape
Dosage unit feeding	Vibration device	Dosage unit shape Fill all hole
Sealing	Temperature	Blister leakage Blister shape
Embossing	Pressure Good numbers and letters	Blister leakage Numbers & letters clarity

Blister IPC:

1. Shape (dosage unit and blister)
2. Leakage (vacuum with blue methylene)
3. Embossing (mfg. date, exp. Date, Batch No.)

Secondary packaging materials:

Secondary packaging refers to all the constituents of a package that do not come into direct contact with the product. Essentially this means labels, patient information leaflets (package inserts) and folding cartons.

Their main purpose is to protect the primary packaging, identify the medicinal product and ensure the cost-effective production of a pharmaceutical package and its effective handling along the distribution chain to the final consumer.

Labelling is controlled by the regulatory authorities and is normally part of the approval documents.

Packaging medicinal products:

Packaging processes are generally carried out in packaging areas that are physically separate from production, with the exception of on-line packaging

The End

Weighing

Industrial pharmacy

Lecture: 10

Dr. Basheer Al-kasmi

Importance of weighing:

weighing process is a quality-defining process step in the manufacture of pharmaceutical products. The starting materials are prepared for further processing in accordance with qualitative and quantitative requirements. A subsequent correction of errors is not possible, or is possible to a limited degree only. It is therefore important to ensure that weighing is carried out properly.

General requirements for the weighing:

- should be carried out in separate weighing rooms
- Balances of an appropriate range and precision should be used
- Operations on different materials should not be carried out simultaneously to prevent cross-contamination or mix-ups
- Protection from microbial and other contamination
- The generation and dissemination of dust should be prevented
- checked by a second person

Principles and procedures:

Weighing can be carried out using two different principles:

1. order-specific weighing of different raw materials for one product or
2. raw materials-specific weighing for different orders.

Product-specific weighing:

Two different approaches are possible:

1. **additive weighing**: the starting materials are weighed successively and placed on top of each other.
2. **individual weighing**: the starting materials are weighed individually in individual containers.

Product-specific weighing:

Two different approaches are possible:

1. **additive weighing**: the starting materials are weighed successively and placed on top of each other.
2. **individual weighing**: the starting materials are weighed individually in individual containers.

Product-specific weighing:

Aspect	Additive weighing	Individual weighing
Space (during process & storage)	+	-
Number of empty containers required	+	-
Risk of weighing errors	-	+
Losses when removing the materials during production	+	-
Distribution over different process steps	-	+
Start of shelf life	weighing date = manufacturing date	Starting production = manufacturing date
Storage capability	Potential interaction between the starting materials	no influence

Raw material-specific weighing:

Advantages:

- The weighing booth is not contaminated by different types of raw materials.
- Cleaning is only required when a different raw material is used.
- The risk of mix-ups is reduced

Centralised/decentralised weighing:

Two different concepts for the physical location of the weighing room: centralised or decentralised weighing systems can be used.
It is depended on the following factors:

- spatial conditions
- material flow
- throughput rate
- variability of the starting materials
- timing requirements with regard to the availability of the weighed materials

Requirements for premises:

Positioning:

- weighing rooms should be separated from the rest of the manufacturing area
- weighing rooms should be designed and located for the purpose of weighing

Requirements for premises:

General criteria for the positioning of the weighing area:

- Connection to storage areas or material flow
- Sufficient space for preparatory activities
- Cleaning of the material containers before weighing
- Supply of target containers
- Removal of filled target containers
- Disposal of consumables, residual materials and waste
- Returns to the staging area
- Personnel access (hygiene zones)

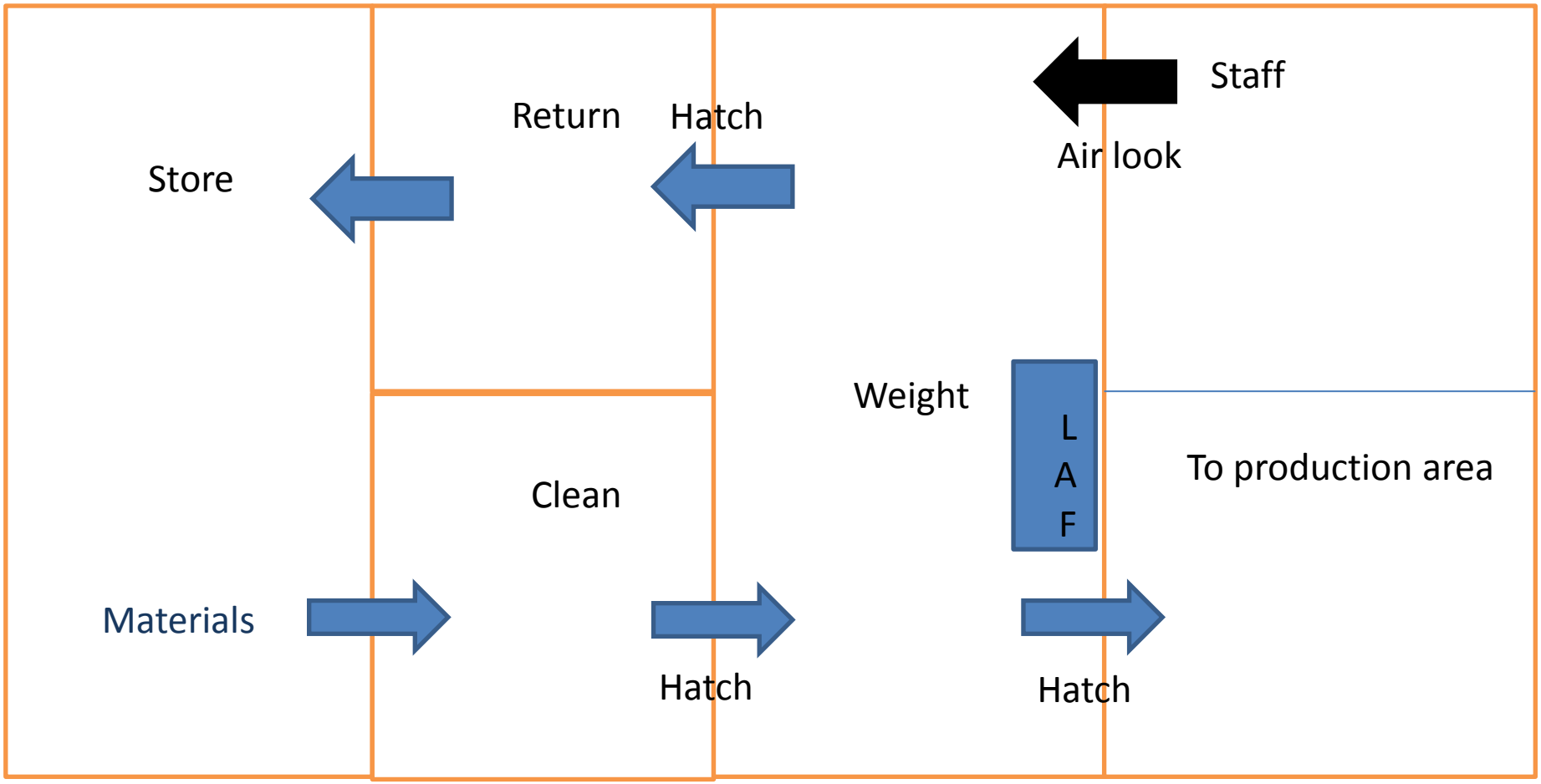
Requirements for premises:

Air lock design and hygiene requirements:

The materials are supplied directly from the storage area or from an upstream hygiene phase. Before transfer into the primary room (weighing area), the containers must be cleaned sufficiently to prevent dust emission and contamination by aspiration systems

cleaning can be done in a room upstream of the weighing room.

Layout


Staff
Air look
Return
Hatch
Store
Weight
L
A
F
To production area
Clean
Materials
Hatch
Hatch

Requirements for the design of weighing rooms:

- Prevention of contamination
- Prevention of cross-contamination
- Surfaces that are easy to clean
- Compliance with the requirements for hygiene and ambient air
- Compliance with the health and safety requirements
- Maintenance of the air-pressure difference (overpressure or underpressure)
- Locking mechanisms for doors (air looks)
- Air-conditioning

The End

Process validation

Industrial pharmacy

Lecture: 11

Dr. Basheer Al-kasmi

Validation:

Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected result.

Divide to Cleaning validation, analyticl method validation, Process validation, Equipment qualification, Utilities validation, Computer Validation

Process validation:

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

The purpose of process validation:

Quality controls cannot guarantee the required safety of medicinal products and protection of patients effectively. Product quality must be controllable. To ensure this, the manufacturer has to understand the interactions between the CPP and CQA of the products and specify suitable process controls. The results of these controls are then used to evaluate the process capability.

Process capability is the ability of a process to reliably produce quality-compliant products.

Process validation example:

Step	Process parameter	Control test	No. of sample
Mixing	Mixer type Material quantity Mixing time Mixer speed	Homogeneity	Not less than (NLT) 10
Drying in FBD	Temperature Air pressure Material quantity Drying time	LOD	NLT 10

Each validation strategy must ensure the following :

- the process design is reproducible, reliable and robust
- the process is sufficiently specified, monitored and controlled
- the control strategy in place is suitable for guaranteeing a continual process capability

Validation is divided to:

- prospective validation
- ongoing or continued verification

Life cycle of processes:

1. Development of process design:

Define process, determined CPP and control strategy.

2. Validation of process:

3. Ongoing process verification:

Collection and assessment of information, statistical analysis, change control, revalidation after critical changes

Controlled process:

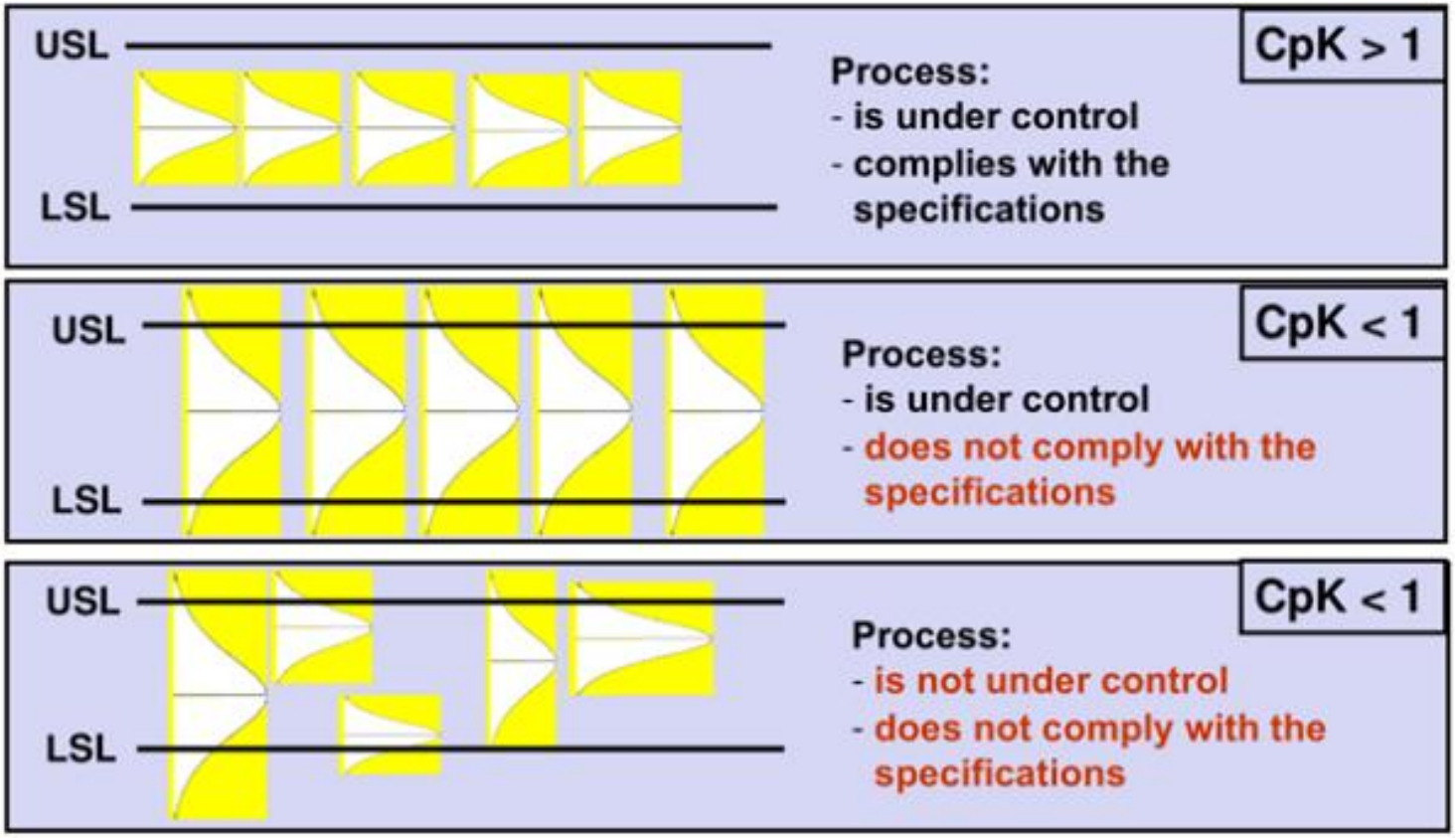
A process in which the distribution parameters for the characteristic values of the process do not change or change only in a familiar way or within known limits.

process capability index (CpK): is a measurement of the expected share of nonconforming units in the process. The larger the index, the smaller the share of nonconforming units. The Cpk is defined using

$$CpK = \min[(\mu - LSL)/3\,\sigma\ ;\ (USL-\mu)/\ 3\,\sigma]$$

the mean value μ, standard deviation σ

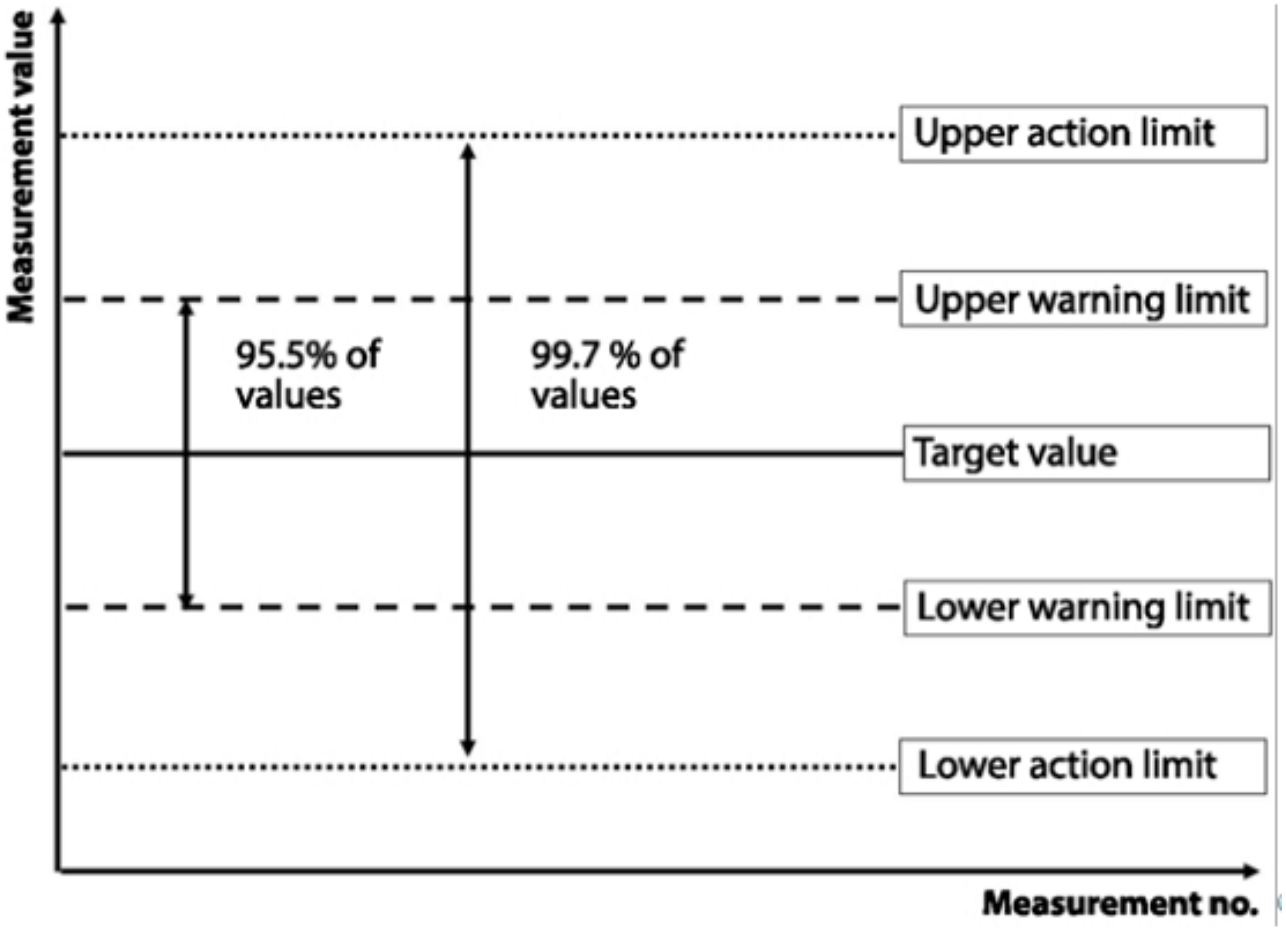
the upper or lower specification limit range (USL, LSL)



Cpk <1.0	No process capability
1.0 < Cpk <1.33	Conditional process capability
Cpk >1.33	Process capability present

Quality control chart:

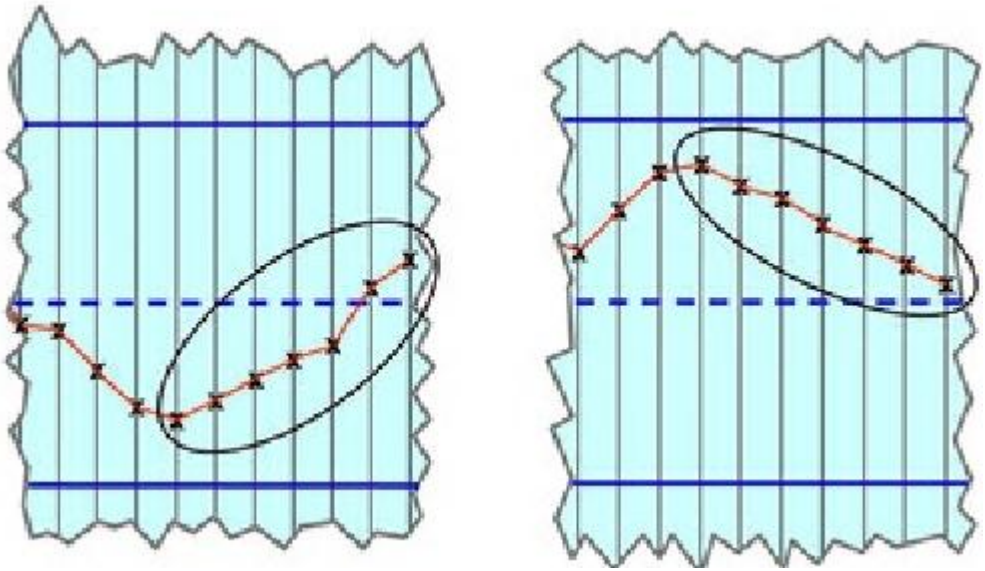
is a graph used to study how a process changes over time.



Error detection:

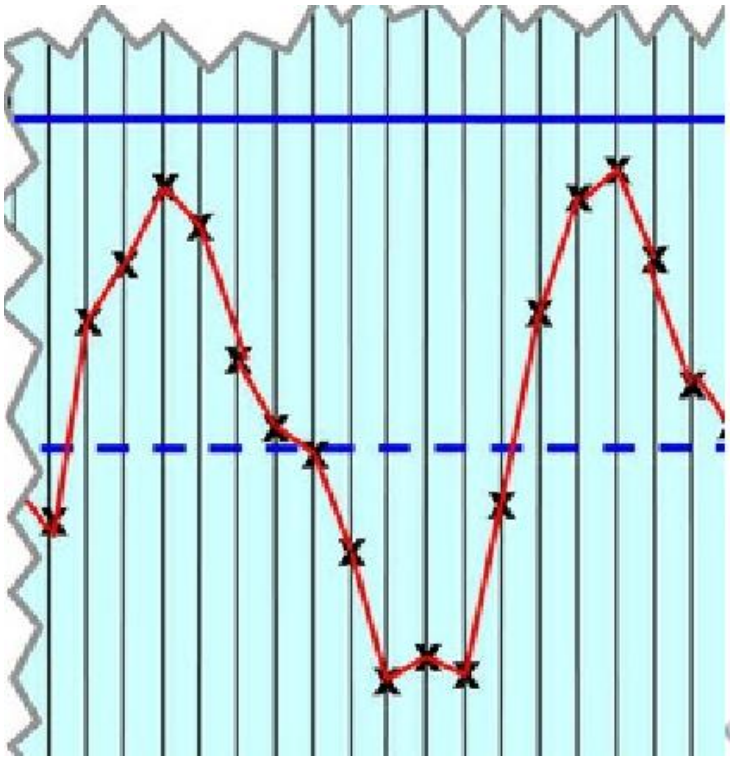
Trend: has occurred when seven successive measurement points indicate an almost linear progression towards a limit.

This may indicate a strong increase in tool wear that will eventually lead to the warning or action limit being exceeded



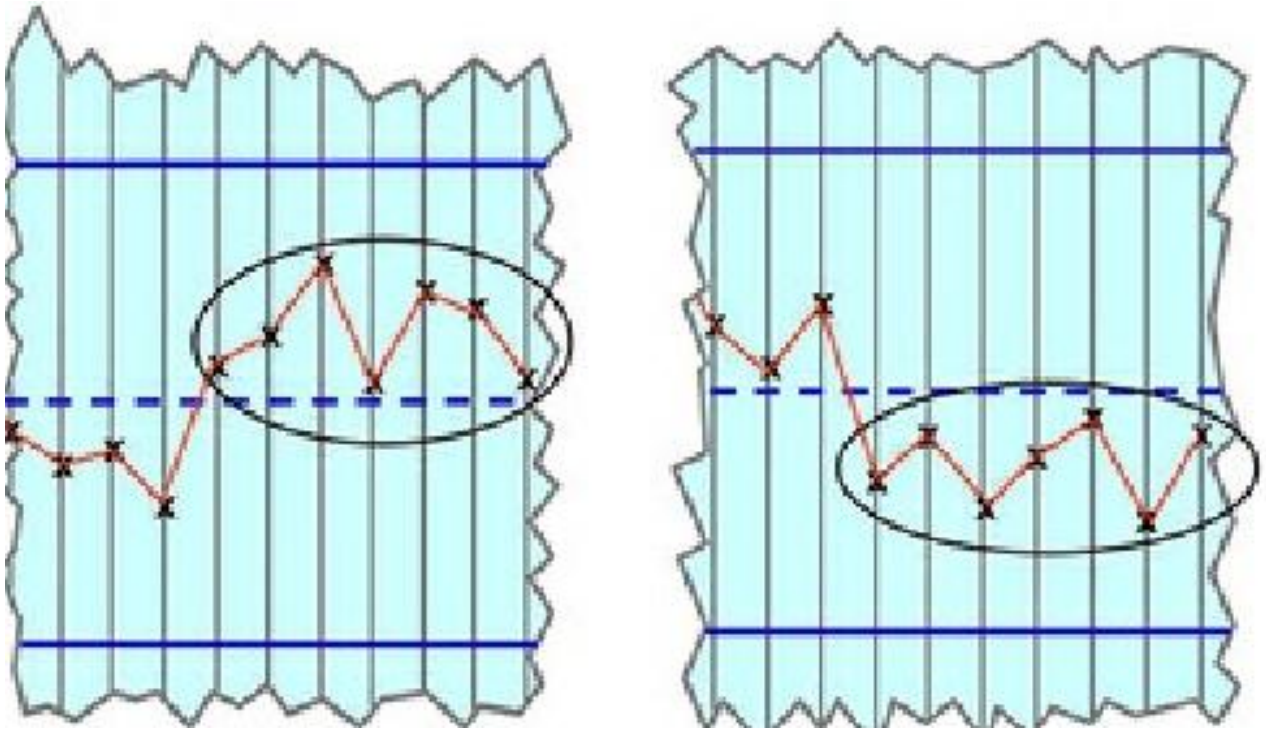
Error detection:

Pattern: the periodic oscillation around the specified mean value.



Error detection:

Run: If 7 measurement points are above or below the set mean value, a new real mean value has been created.



The End