Equipment

Allersma, Derk; Odou, Pascal; Gareb, Bahez

Published in:
Practical Pharmaceutics

DOI:
10.1007/978-3-031-20298-8_28

Equipment

28

Derk Allersma, Pascal Odou, and Bahez Gareb

Contents

Abstract

This chapter is about the design, quality and application of equipment for the preparation of medicines in a pharmacy or for preparation in small scale pharmaceutical industry. The type of pharmaceutical equipment needed depends on the type of products to be produced, on the required productive capacity and the batch size. A list of essential and critical equipment for production and quality control must be included as attachment in the URS (User Requirements Specification) of any facility. The equipment, requirements, qualification methods, main applications, maintenance and cleaning procedures are described for:

- Powder exhaust units, Laminar airflow units, Safety cabinets and Isolators
- Pharmaceutical water production

D. Allersma · B. Gareb (✉)
Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, the Netherlands
e-mail: d_allersma@hotmail.com; b.gareb01@umcg.nl

P. Odou
Groupe de Recherche sur les Formes Injectables et les Technologies Associées, University Lille, CHU Lille, ULR 7365-GRITA, Lille, France
e-mail: pascal.odou@univ-lille.fr

P. Le Brun et al. (eds.), *Practical Pharmaceutics*, https://doi.org/10.1007/978-3-031-20298-8_28

- Storage and distribution of pharmaceutical water
- Heating and Ultrasonic water baths
- Grinding, mixing and dispersing
- Filling, dosing and closing for liquids, suppositories, capsules and tubes
- Fridges and freezers
- Automatic filling and robotics
- 3D printing

What Is New

This chapter is based on the chapter Equipment in the previous edition written by Marco Prins and Willem Boeke. The text was updated; several paragraphs were extended and several new paragraphs about automation, robotics and 3D printing were added. A paragraph about water storage was merged from the chapter Premises to this chapter.

Learning Objectives

- The reader will have knowledge of most used equipment in preparation and manufacturing.
- The reader will have knowledge of the working principle of diverse equipment essential for preparation.
- General requirements will support the purchase and installation.

28.1 Orientation

What type of equipment is needed in the pharmacy or preparation facility depends on the type of products to be prepared or manufactured, the required production capacity and the batch size. The choice of apparatus discussed in this chapter is arbitrary. Larger apparatus and installations such as large stainless steel autoclavable mixing tanks are intentionally not discussed, neither are infusion fluid production lines, filling lines for injection vials, syringes and ampoule machines.

In this chapter we discuss the main applications of equipment that is commonly used in pharmacies and small scale industry as well as the maintenance and cleaning procedures or installation. Small equipment and materials such as volumetric glassware and weighing equipment are described in Chap. 29. Sterilisation and sterile filtration equipment is discussed in Chap. 30.

The publications of ISPE (see Chap. 11) are recommended for more detailed technical information on equipment, for instance Water and Steam systems, Cold chain management.

Some ISO (see Chap. 11) standards are appropriate as well, such as EN 14175 Fume cupboards. PIC/S documents (see Chap. 11) may be helpful such as on Isolators used for aseptic processing and sterility testing (PE 014-4).

28.2 General Requirements and Qualification of Equipment

Pharmaceutical equipment should be appropriately qualified and fit for use. That means that the device or equipment is:

- Safe for the user, but also for the environment (check, for example, the required CE marking)
- Easy to use in daily operational practice for its intended use
- Capable of being effectively cleaned, disinfected and sterilised if applicable
- Provided with accurate and complete technical and operational documentation
- Provided with essentials spare parts

It must be proven that a device will be suitable for the intended function in the preparation process by appropriate validation or qualification, see Chap. 32. Qualification and validation must be planned, described and documented. Qualification efforts are highly dependent on the criticality of the equipment and the direct or indirect effect (impact) of the device on the quality of the preparation process and product. When purchasing a new device it is often possible to ask the supplier (by quality agreement) to qualify the equipment. This involves, usually, the Installation Qualification (IQ) and the Operational Qualification (OQ), sometimes also parts of the Performance qualification (PQ), although usually the user of the equipment has to take the responsibility for the execution of the PQ (see Chap. 32).

Preferably the essential list of equipment is included as attachment in the so called URS (User Requirement Specification) of the facility.

28.2.1 Design

A set of a well-formulated User Requirements Specification (URS), Functional specifications and Detail specifications has key importance proceeding any purchase (see Chap. 32). A good URS is used in the performance qualification and relates the actual production capacity and variety to the required machine qualities.

With a couple of potential suppliers a limited list can be drawn up of apparatus that might qualify for selection.

Specifications have to be listed, such as:

- Ease of cleaning and of sterilisation
- Ease of mounting and demounting and of exchange of tools
- Hygienic design for product-contact surfaces, sealing rubbers and membranes
- Product loss at starting and stopping
- Ease of operating, and the extent that operating or hand-operated adjustments have impact on the product

- Safety
- Failures should not pass unnoticed
- Capacity and performance
- Dimensions

At the final selection the compliance with the original URS should be warranted and from this a large number of premises issues will ensue, such as:

- Required capacities of utilities (electricity, water, steam, gasses, and if applicable, IP-network connections, etc.)
- Floor load and possibilities of setting up; routing possibilities for transporting equipment to its final installation place or exchange in the future
- Heat release and other influences on the HVAC during operation
- Product transport in and out and accessibility: logistic aspects of personnel and product to and from the machine

Although the manufacturer will build a chosen machine with standard components, the final result will be more or less unique. The manufacturer will often only accept limited liability for the performance of the machine in a specific situation. Agreement on a so-called Factory Acceptance Test (FAT) is recommended and it should be executed at the site of the manufacturer when the apparatus has reached the ready for testing status. At this stage it is possible to solve any unforeseen problems that would be either impossible to solve, or only against huge costs after installing at the final destination.

Agreement on a so-called Site Acceptance Test (SAT) is recommended as well, as is the execution immediately after setting up. This is especially important when there is a considerable amount of time between the time of delivery and the actual operation in practice as a consequence of elaborate qualification tests. Issues as the starting date for the guarantee period, the setting off of the maintenance plan and the transfer of remaining ownership responsibilities should be well indicated in advance. The SAT offers a good opportunity to reveal issues such as transport damage, any forgotten components or spare parts, etc. and it is also a check of the fulfilment of understandings made during the FAT.

28.3 Local Air Filtration and Exhaust Units

In this section local air filtration and exhaust units are discussed. Filtration is necessary for removing micro-organisms and dust from the air. Exhaust is necessary for carrying away contaminated air. Dedicated HVAC installations for heating, venting and air conditioning of clean rooms are described in Chap. 27.

28.3.1 Functionalities

This equipment is needed for supplementary and dedicated air filtration or exhaust at the site of preparation. In pharmaceutical preparation or quality control the objectives of air filtration and exhaust may be the protection of the product or the operator and the environment or both.

28.3.1.1 Protection of the Operator and Environment

During the preparation of medicines, steam, vapour, aerosols, dust and fumes can be released, which may pose a health risk for the operator. It is not always possible to change the process of releasing these hazardous substances. As a consequence it can be necessary to protect operators in preparation or quality control areas from exposure to the product or the active substance. This can be done by active ventilation and exhaust and by filtration in order to protect the environment.The appropriate equipment may be fume cupboards, moveable exhaust ducts, powder exhaust units, class II and III safety cabinets and (III also only called isolator in some countries) Fumes, gas mixtures and volatiles might be absorbed by special filters, but in pharmacy practice only the technique of exhausting and screen filtration is usually used.

28.3.1.2 Protection of the Product

The operator might be a microbiological hazard for the pharmaceutical product, because of the operator's micro-organisms coming from the skin, hands, nose etc. Apart from shielding the body to prevent these particles being discharged into the product, working in airflow directed from the product may contribute to the protection of the product. The air in the production area must be of sufficient quality not to be a contamination source.

Annex 1 of the EU GMP defines the quality of the air in the preparation of sterile products.

28.3.1.3 Types of Equipment

The terminology for local exhaust units is sometimes unclear and non-specific. E.g. the term 'biological safety cabinet', which is historically derived from working with microorganisms, is rather confusing. Any definitions can be found in [1].

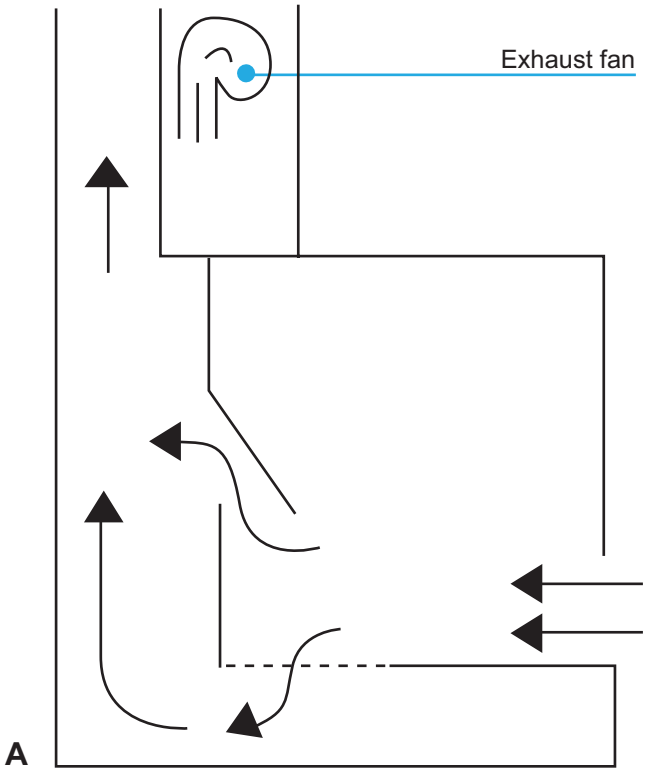
In this section a distinction is made based on EN 12469 between with sometimes used older terms between brackets:

- Fume cupboard
- Moveable exhaust duct
- Powder exhaust unit
- Class I safety cabinet (LAF unit or booth)
- Class II safety cabinet
- Class III safety cabinet (Isolator)

Figure 28.1 shows the general (schematic) construction of the different types of local exhaust and air filtering equipment.

For the protection of the operator and co-workers the most basic engineering control measure to minimise inhalation exposure is ventilation of the work area. A ventilation rate of 2 h^{-1} or 5 h^{-1} is common for offices but not sufficiently efficient for preparation areas. A better effect will be obtained by containment of the activities that release hazardous substances. In order to prevent contaminated air from entering the room, the exhaust is guided to the outside of the building and discharged in the environment or the exhausted air is filtered before re-entering the room. Filtration of exhaust air will decrease any exposure of the environment outside the building and filtration is generally expected. Recirculation of air (while mixing with a % of fresh air) is preferred (if acceptable from exposure point of view) because of energy consumption when only fresh air is used

For the protection of the product, working in a laminar airflow directed from the critical places or working in a complete gas tight box are options used in practice.



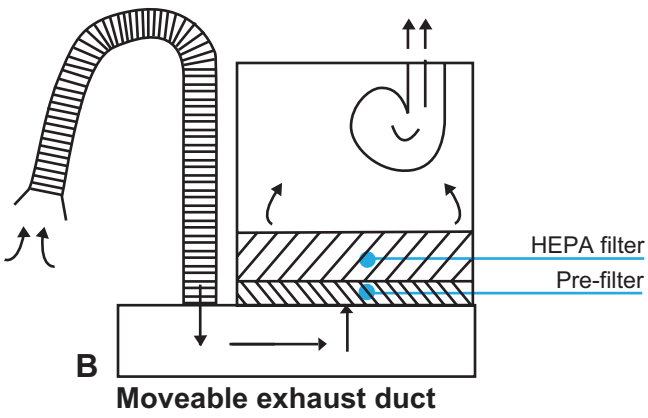
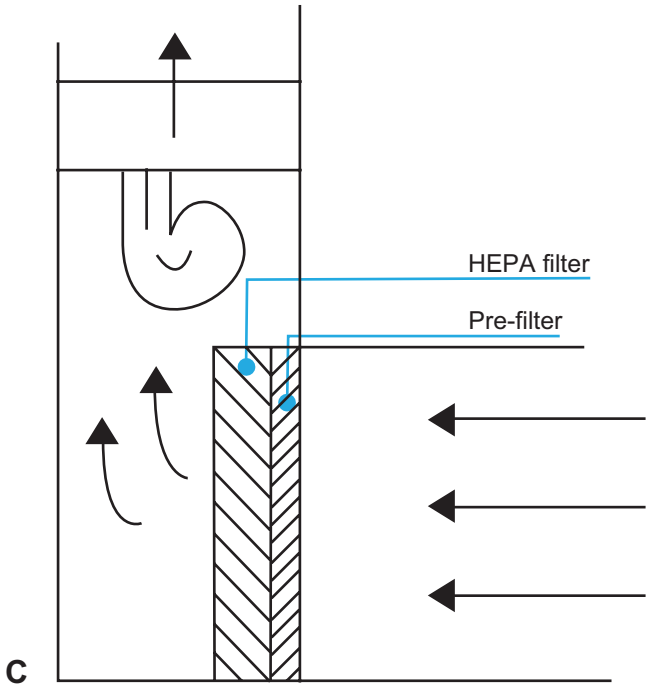


Fig. 28.1 Schematic construction of exhaust and air filtering equipment (**a**–**g**)



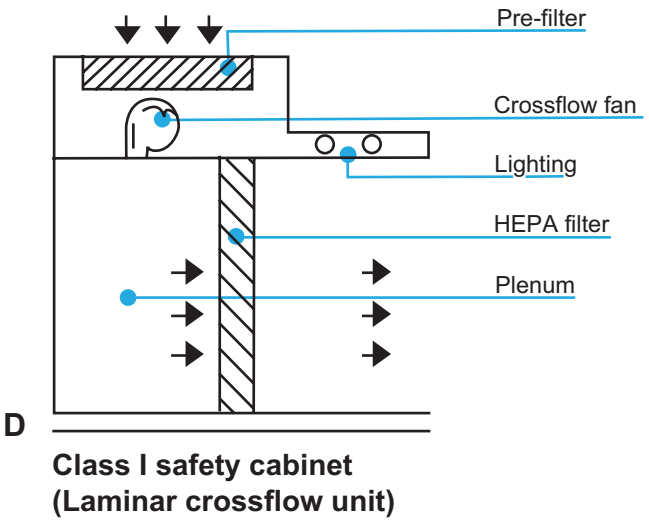
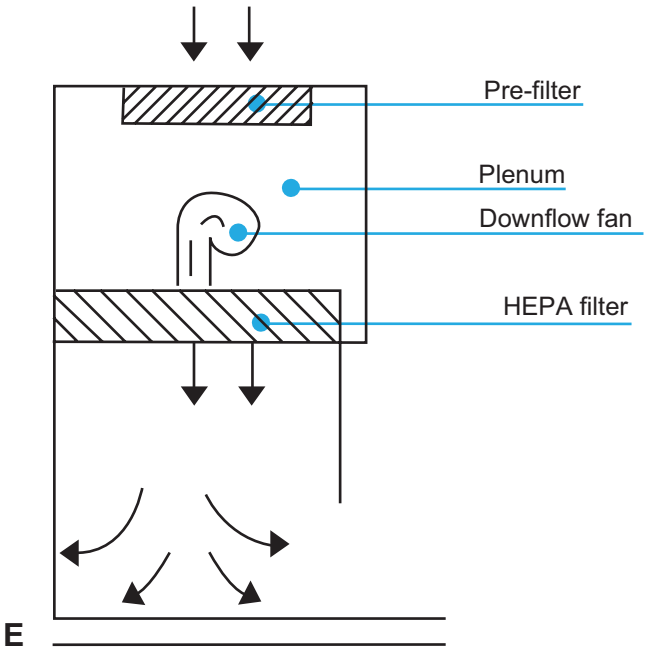


Fig. 28.1 (continued)



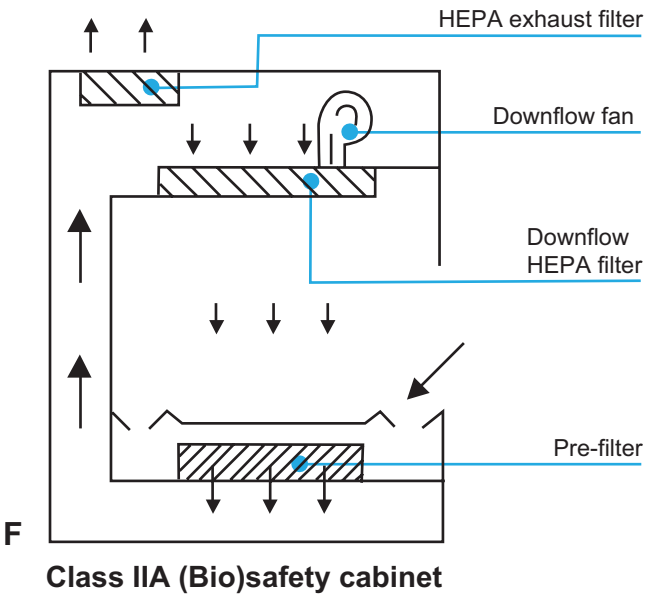


Fig. 28.1 (continued)

Complete protection of operator and product can be achieved by a Class III safety cabinet (isolator) (see Sect. 28.3.7). Apart from complete product and operator protection other advantages are: controlled disinfection procedures, lower initial investment costs of the background area and exploitation costs. Disadvantages are higher costs compared to a LAF unit and its elaborate cleaning and maintenance. Therefore, in practice the choice of type of local exhaust equipment is determined

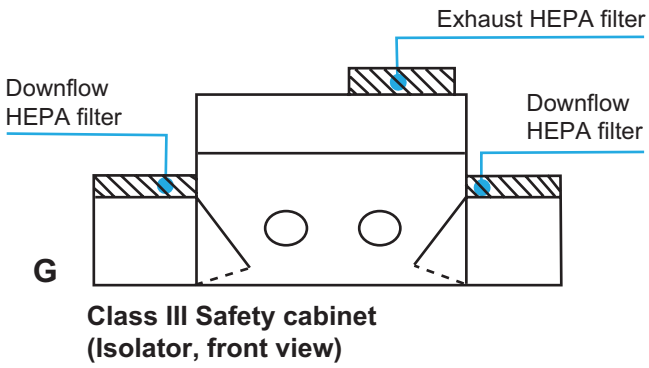


Fig. 28.1 (continued)

by a risk assessment of the process (taking into account the contamination of the product and of health damage of the operator), the available investment and the local experience.

For a systematic approach to the choice of the right local exhaust ventilation, the allowed level of exposure is compared with the actual exposure level and the assumed effectiveness of the exhaust device. Reference is made to [2]. Local exhaust ventilation is generally expected to establish a ten-fold reduction of the exposure level, whereas full and enclosed containment with 'small-scale breaches' is considered to establish a 100-fold reduction. Maximum containment is accomplished by using an isolator.

For a general approach of preparation situations in community and hospital pharmacies (working with maximal 100 g of substances of hazard classes 1–5) reference is made to Chap. 26. For higher exposure levels the Advanced REACH Tool (see Chap. 26) offers guidance. The small scale preparation in pharmacies may generally require:

- A powder exhaust unit for most dust releasing operations: weighing, capsule filling, mixing of solids, rotor-stator mixing based on a proper risk assessment
- A Class I safety cabinet (horizontal or vertical LAF unit) for the common aseptic handling with closed containers (see Chap. 31 where also the pro's and con's of horizontal and vertical flow are explained)
- A Class II safety cabinet or Class III safety cabinet (isolator) for processing class 4 and 5 substances
- A Class III safety cabinet (isolator) if capsules have to be prepared with class 5 substances
- A fume cupboard for processing volatile, inflammable or corrosive substances

It cannot be stated that a 'normal' down flow cabinet, with open front and without sleeves to the worktop (so not a safety cabinet), or a down flow unit is safe for the operator if working with half-open or open systems. It may very much depend on airflow patterns if any contamination with a substance will be actively blown in the direction of the operator. If so, the exposure would be higher, in which case no ventilation or exhaust is preferred.

Influence of Local Devices on the Performance of Room HVAC

Local safety cabinets of any type will influence the air pattern, temperature and HVAC system in the preparation area. (HVAC means heating, ventilation, air-conditioning; see Chap. 27). The influence will vary. Sometimes all doors of the room must be closed in order to ensure a correct function of a fume cupboard. Air expelled by the local safety flow systems will also influence the ventilation and the pressure in the room. Local devices produce energy in the form of heat and, unless exhausted, will change the room temperature.

28.3.2 Fume Cupboard

Fume cupboards are meant to protect the operator from fumes, steam, volatiles and corrosive fluids.

Fume cupboards are not effective enough for the safe handling of aerosols and powders.

28.3.2.1 Description

In pharmacy practice mainly the ducted type of flow hood is used, which is not recirculating the air into the room. The air in the hood, eventually mixed with the volatiles is discharged into the open air outside the building, often by flexible special ducting. The extractor (fan) of a fume cupboard does not come in contact with these volatiles. This is the reason why explosive or highly combustible material can be exhausted safely.

The direction of the flow inside a fume cupboard is upwards at the end, see Fig. 28.1a. Heavy volatiles concentrate on the bottom of the fume cupboard; lighter volatiles can be found somewhat higher in the fume cupboard. In both areas of the fume cupboard sufficient force of the airflow is obligatory: 0.5 m/s for vapours and 1 m/s for dust [3]. However, the speed of the inflow in a fume cupboard is not high enough for the exhaust of small solid particles. The material of the fume cupboard and the exhaust fan and duct must be resistant to corrosion, in order to work with corrosive or caustic agents.

In front of the fume cupboard there is a transparent safety sash, sliding gently up or down with a counterbalance mechanism to reach precisely the defined and properly validated working or loading position. The loading position is not safe, but high enough to place equipment inside. Low airflow alarm control panels are common. The working position creates a safe area under the glass window to work in with (gloved) hands and arm covers for that part of the arm entering the fume cupboard working area.

28.3.2.2 Maintenance and Inspections

Fume hood maintenance involves periodical (daily, quarterly, annual) cleaning, maintenance, calibration, qualification and inspections. In daily inspection the fume hood area is visually inspected by the operator. Hood function indicating devices (LEDs) are normally a part of the fume cupboard. Periodic inspection covers capture or face velocity measured with a velometer or anemometer.

Annual maintenance: Yearly the fume cupboard must be maintained, calibrated and tested by a certified firm and competent person and the results of the official tests reported. Exhaust fan maintenance comprises lubrication, belt tension, fan blade deterioration and speed of the fan. Air velocity at different points, window performance, brightness of the light in the cupboard are tested in the working situation, with all doors of the room closed. Control of the frequency and method of cleaning the interior is also important.

Validation of the velocity of the incoming air in the area under the sash and validation of the volume of the exhausted air is not sufficient proof of the safety of the fume cupboard. The quality of design of a good fume cupboard is as important as it guarantees a stable vortex of the airstream. A good technical design of the ventilation system is essential too, as is the dimensioning of the interior of the fume cupboard itself. Last but not least: without good operating procedures and trained operators a good technical design is useless.

The main goal of the operation within a fume cupboard is that it will not be possible for contaminated air to enter the area or room outside the fume cupboard.

Never start activities in a brand new fume cupboard with certificate of the manufacturer only, because on site initial qualification and validation of the performance and proper training of the operators is essential.

Once the fume cupboard is installed in its room, for initial validation (and periodical revalidation) mostly a combination of tests is carried out:

- Validation of the velocity of the exhausted air in the opening under the glass window and validation of the volume of the exhausted air (extract volume flow rate test).
- Containment testing – sometimes this test shows initially differences between test results in the test environment of the manufacturer (as built) and the results obtained in the pharmacy or in the laboratory of the end user (on site, as installed).
- The test protocol of European Standard EN 14175-4 [4].

28.3.2.3 Operation

It is important not to disturb the performance and airflow pattern of the fume cupboard. Staff standing or walking in front of the fume cupboard will disturb the air exhaust. The operator must have sufficient space in front of the fume cupboard to work easily and comfortably. Room doors that open frequently during operation in a fume cupboard and (strong) inflowing air from the room ventilation system (in the direction of the fume cupboard) may have a negative impact on the performance of the fume cupboard. Airflow visualisation with smoke is illustrative and often necessary.

28.3.3 Moveable Exhaust Equipment

28.3.3.1 Applications

Moveable extraction equipment can be used for the local and small scale exhaust of fumes and vapours at the point where these fumes and vapours are produced in an environment with no classic fume cupboard available. For example the handling of organic solvents in a laboratory, near the analysis equipment.

An extraction duct may not be the best choice for the extraction of powders and dust. However, by placing the hood very close to the point where the dust is produced we can create a situation with high air velocity and an effective exhaust for dust. In that case the exhaust duct is a dust remover, but eventually without a dust collector bag for the dust. A problem is that collected dust in the duct or the hood can fall back on (other) products. This is a serious risk for cross contamination and needs a proper cleaning schedule in place.

A better solution for exhausting dust and powder is combining the exhaust unit with filters, see Fig. 28.1b. Contaminated air enters the pick-up hood and is drawn through the hose and into the dust containment unit. The flexible duct with pick-up hood is easily adjusted to any position by an externally mounted, self supported, adjustable arm. Larger, heavier particles are collected in a removable collection pan for easy maintenance. The first stage of filtration is a pleated pre-filter, designed to capture mid-sized particles before reaching the main filter, therefore extending the life of the main filter. The main filter is a high efficiency 95% filter designed to capture fine particulate before being exhausted. Other main filter options are available including a 99.97% efficient HEPA Filter. Clean filtered air is returned to the environment.

Professional dust removers are used in tableting, capsule filling and closing machines and powder filling machines. They are used to clean the equipment during processing or to remove adsorbed dust and powder from the pharmaceutical product. Dust removers are not designed to extract fumes, because fumes pass the filter unit and are blown back in the room.

Mobile dust removers (vacuum cleaners) with integrated HEPA filters are used in clean rooms, most of the time to clean the floor and ceilings. Dust removers are not designed to extract fumes, because fumes pass the filter unit and are blown back in the room. The HEPA filter has to be replaced periodically.

28.3.3.2 Description

Extractors for industrial or laboratory environments are available in several duct diameters (Ø 75–200 mm), duct materials and sizes, with various constructions for ceiling, wall and bench installations. The standard model for fume extraction is used in most laboratory environments. The joints are made from polypropylene and ducts from anodised aluminium, for example. Polypropylene PP is used in environments containing high concentrations of corrosive pollutants; joints and tubes are made from polypropylene. ATEX regulations must be implemented when hazardous explosive atmospheres may occur (see Directive 2014/34/EU); joints and tubes are made from conductive polypropylene.

28.3.4 Powder Exhaust Units

28.3.4.1 Application

Powder exhaust units are often benches with horizontal backward flow and final vertical HEPA filters (see Fig. 28.1c), suitable to protect the operator largely from fine powder particles in the air or from water-based aerosols that otherwise would be released in the working area. These exhaust units might recirculate the exhausted air and pollutants can (also through basic filtration material) enter the room. In a Wibojekt® powder exhaust unit the extracted air with particles is blown towards a special slit. That air is filtered and exhausted outside the room.

The filtration efficiency depends on the type of filter but is as said above generally expected to establish a ten-fold reduction of exposure.

These types of exhaust units usually don't have a duct leading to the outside of the building and therefore are not suitable for the extraction of gasses, fumes and volatile products.

28.3.4.2 Description

Fine dust particles or small aerosol droplets generated in a powder exhaust unit must be extracted from the operator's working space horizontally in the backward direction. The airflow is sometimes downwards into a special slit (Wibojekt®).

After passing a coarse pre-filter and a final ULPA filter the exhausted air can be exhausted into the preparation room. In that case the unit is recirculating the air. It is possible to discharge the air via a duct outside the building. As a result the room pressure might be influenced and needs attention.

The efficacy of an exhaust unit depends on the air velocity in the unit. For that reason the area of the filters is not too small. Settled dust cannot be exhausted once it has fallen down onto the horizontal work area in the unit.

The place in the room where the exhaust unit is installed and qualified has to be chosen carefully. A recirculating exhaust unit needs enough space to blow the exhausted air around the unit. An exhaust unit very close to a door will be influenced by the changing air pattern every time the door swings open or is closed.

The velocity of the incoming air stream in an exhaust unit must be between 0.25 and 0.50 m/s, with no major disturbing air pattern around or in front of the exhaust unit. A higher exhaust velocity causes unwanted turbulence before and in the unit.

Weighing in an exhaust unit is possible. Depending on the results of the accuracy of the weighing tests it can be necessary to shut down the exhaust unit at the very moment that the weighing result is recorded.

28.3.4.3 Operating Instructions

- Switch on the exhaust unit just before starting the activities. Clean the unit inside before and after activities.
- Check the velocity meter. Check the status of the filtration area, no damage may be seen.
- Check the unit once a year on air velocity; a leak test for HEPA or ULPA filters is easy to perform by an expert.
- Change all pre-filters and the HEPA filter only after leakage or damage.

28.3.4.4 Replacement of the Pre-filters

The pre-filters have to be changed when after a visual check the pre-filter is dirty or saturated, or after a chosen time interval (once per 1–3 months for example).

During a change of the pre-filter the operator has to wear a protective FFP2- or FFP3 mask for dust and aerosols. The exhaust unit fan is switched on, so dust particles are trapped in the HEPA or ULPA filter cassette. Clean the filter frames and remove the old filters in a closed bag.

28.3.5 Class I Safety Cabinets (Laminar Airflow Units)

A class I safety cabinet, also called laminar flow -cabinet, -closet, -hood or -bench is a general and rather non-specific term for an enclosed workbench, with a HEPA filtered laminar airflow inside.

The laminar airflow is unidirectional, so not turbulent. This is achieved by choosing the right design, technology, air velocity and filter sets. This unidirectional airflow must not be disturbed too much by the environment or movements of the operator. So a specific working technique and behaviour for the operator(s) is necessary. The direction of the filtered and clean laminar airflow can be horizontal (from the left to the right or from the back of the cabinet towards the operator), or downwards: from the HEPA filter in the top of the cabinet to the bottom (which often is a flat stainless steel work area). See Fig. 28.1d, e. In pharmaceutical terminology: HEPA filtered horizontal or vertical laminar airflow (cross- or downflow) in a laminar flow bench creates an ISO 14644-1 (Class 5)/GMP Annex 1 (Class A) work area and prevents contaminated ambient air entering the work area. With the right working techniques, a trained operator and the right classified background this can result in good product protection.

28.3.5.1 Application

In pharmacies a laminar flow unit is used to protect the product against microbiological contamination from the operator. With a cross flow Class I cabinet the HEPA filtered air is directed over the working area to the operator. This type of Class I cabinet thus cannot be used for operations with hazardous substances (hazardous being defined as any substance with a H statement, so with a hazard class higher than one, see Chap. 26). It can be used for aseptic preparation processes with closed systems, such as aseptic handling, see Chap. 31.

For larger equipment a down flow LAF unit is common, e.g. a HEPA plenum in a preparation area for sterile products. A HEPA plenum with plastic curtains mounted in and hanging from the ceiling creates a dedicated area for aseptic processes. A plenum can be used for example to protect washed and opened glass infusion containers, moving in a filling line in the downflow of the plenum to the point of aseptic filling. As said, it depends on airflow patterns if any substance is actively blown in the direction of the operator. If so, the exposure may be higher than when no ventilation or exhaust takes place. This means that a down flow LAF unit cannot be used for open processing substances with a hazard class higher than one.

28.3.5.2 Description

In general, the air from the production area enters the front of the Class I cabinet in a controlled way, passes at first a set of pre-filters in the cabinet that separates coarse dust. Sometimes more HEPA filters placed in series after the pre-filters act as supplementary pre-filters (in certain types of safety cabinets). After pre-filtration the air is forced via a ventilator box through a set of framed HEPA filters and finally enters the

aseptic process area as sterile filtered air in a unidirectional flow. The speed of the unidirectional flow is kept between limits. Finally the exhaust air re-enters the room (crossflow Class I units), or can be exhausted to the outside with or without extra HEPA filtration (safety cabinets).

With these principles in mind horizontal crossflow Class I cabinets, downflow Class I safety cabinets or downflow LAF units with a large area (HEPA filter plenums) are constructed.

The exact positioning of pre-filters in a LAF cabinet depends on the brand and type of the LAF cabinet and is an important part of the functional and detail specifications of it.

Testing of HEPA Filter Units

Filter efficiency, particle holding capacity and differential pressure changes are tested frequently.

HEPA filters can be tested with different methods. A wide range of test equipment for on-site measurements include particle counters, pressure gauges, airflow meters, energy data loggers, corrosion monitors and gas analysis equipment. One of the tests is the measurement of penetration of dispersed oil particles (DOP) through the HEPA filters. DOP used to be the abbreviation of DiOctylPhtalate, which however has been replaced by safer products.

By dispersing the oil aerosol towards the HEPA filters in the air channel the testing operator can measure how many particles penetrate the HEPA filter and can be counted at the clean part of the HEPA filter. According to ISO 14644-3 the filter area is scanned in small well-defined sequential parts. This percentage of penetrated particles can be dependent on the exact position on the filter where the particle counter measures. Inferior and good parts of the filter area are detected and the position is documented. The condition of the filter is expressed as percentage penetration giving filter efficiency. The penetration is the percentage of the particles that passed; the filter efficiency is the part that was blocked by the filter material. The efficiency for the most penetrating particle in a H14 HEPA filter can be 99.995% and for the particles with a size larger than 0.3 μm the efficiency can be 99.999% or more.

Other important functional details of Class I safety cabinets are:

- The light intensity in the cabinet, measured on the work spot must be sufficient to reach a minimum level of 1000 lux. The lighting unit must be built inside the cabinet and the frame of it must be easily cleaned and disinfected.
- The speed of the ventilator must be adjustable, and automatically controlled in order to reach the required quality of laminar flow and speed.
- Detection of full speed, half speed, on and off or night function.
- The speed of the unidirectional flow must be monitored and shown on a display to detect disturbances in the flow by a clogged filter or a defective ventilator.

To keep the flow as unidirectional as possible a minimal number of extra utilities inside the working area of a Class I cabinet are allowed. Extra utilities might be:

- Nitrogen and compressed air valves, for membrane filtration devices.
- Vacuum valve, used only in dedicated LAF units for microbiological quality control: the filtration of fluids for sterility testing or bioburden control.
- Electricity sockets.
- Electronic balances. They can be used inside the cabinet but disturb the laminar airflow and in return the cabinet might disturb the weighing result. Use only following a risk analysis.
- Clamps outside on the front of the cabinet, to attach temporary documentation.
- A stainless steel rail with hooks in the LAF area to attach infusion bottles and bags for the aseptic processing.
- Computer monitor for instructions.
- (Continuous) monitoring equipment.

It is advised to require silent, modern ventilators. The expected daily noise of a Class I safety cabinet unit in operation must be reasonably low and specified in dB. The best solution is to choose a cabinet ventilator with enough spare capacity. In that case the ventilator will not work at the maximum capacity and the noise level will be reasonable or low. In practise the sum of all noises has to be considered in a working area and should be below national accepted levels.

A laminar flow cabinet will continuously produce heat from the ventilators. If the exhaust airflow from the unit is returned into the room (recirculation), the temperature in the room will rise and more room ventilation and cooling is necessary. Air exhaust outside the room will give less heating to the room.

28.3.5.3 Operating Instructions

Commonly two operators are at work in a Class I cabinet. One is the operator, working with the arms and hands inside the cabinet. The second person is standing aside, supporting and controlling the operator, or supporting two operators working simultaneously in two different cabinets.

These people must move gently in the room. Opening a door will have some effect on the balance of the airflow in the cabinet. So try to avoid opening clean room doors during aseptic processing.

Spillage of material must be removed as soon as possible for example with a cloth wetted with disinfectant.

The interior of the cabinet (horizontal bench, two sides left and right and the back inside of the bench) is disinfected with alcohol 70–80% at the end of each working session (shift of about 2 h) and at the end of the working day. For Class I cabinets that keep running 24 h a daily disinfection of the horizontal working bench only between sessions and before start of the activities the next morning might be allowed. This decision is based on a risk analysis, and might be allowed because the rest of the interior was disinfected at the end of the past working day. In addition to disinfection the interior must be cleaned frequently with lukewarm water and a detergent, followed by a disinfection.

Class I safety cabinets that do not run 24 h a day must be switched on first; after 15 min operating at full speed the cabinet must be disinfected and can be used.

Disinfection efficacy must be proved with contact plates (see Chap. 31); specifications of the results can be found in Annex 1 of the European GMP.

Validation of the aseptic process can also be found in Chap. 31.

28.3.5.4 Qualification of a Class I Safety Cabinet (LAF Unit)

Once or twice a year (depending on the criticality of the processes) the safety cabinet is inspected, calibrated and qualified. Commonly a contract is signed with a specialised external firm for this.

The following aspects are important in qualification:

- Inspection and installation of new pre-filters. Sometimes the filters are grey or coloured, as proof of the need for change.
- Efficacy of the HEPA filters. It is not necessary to change the HEPA filters too often. Change of a HEPA filter is expensive and must be a result of documented defects that cannot be repaired.
- Air velocity.
- Intensity of the light.

28.3.6 Class II Safety Cabinets

28.3.6.1 Application

A Class II safety cabinet is a laminar down flow cabinet, which is constructed specifically for protection of both the sterile product and the operator. It is frequently used in (hospital) pharmacies for aseptic preparation (when products are not fully closed) and for aseptic handling of class 4 or 5 substances (see Chap. 26). Laminar down flow has the advantage compared to cross flow that the operator does not feel the continuous flow in his direction. Other names for a safety cabinet are: biosafety cabinet, biosafety bench, biohazard bench, biohazard cabinet, biological safety cabinet etc.

In safety cabinets with a "slope" glass window the operator works with both arms under the window into the half-open sterile working area.

28.3.6.2 Description

The air within a Class II safety cabinet comes from the HEPA filter in the top of the cabinet (see Fig. 28.1f). The flow is led into exit grills at the back and the front of the work bench. A second airflow is drawn from the working room into the front grill where the elbows of the operator are. This flow prevents air or aerosols from the working area escaping the cabinet and protects the operator from inhaling aerosols. After being collected through the slits the air is pre filtered through coarse disposable filter material situated under the workbench in a tray.

In Class II safety cabinets of the type partial or total exhaust, the air eventually is collected in a box on top of the bench, connected via a HEPA-filter with the air in the room (see Fig. 28.1f). The box has underpressure due to the exhaust air velocity. In case the safety cabinet has a breakdown, the box construction prevents the ventilator of the exhaust channel to continue while the down flow ventilator in the cabinet stops. Otherwise contaminated air from the room would be sucked under the sash, contaminating the clean side of the HEPA filter in the work area of the safety cabinet.

28.3.6.3 Specifications and Classification

The specifications of the airflow pattern in a safety cabinet might be confusing. Following EN 12469 (Biotechnology – Performance criteria for microbiological safety cabinets) [5] the velocity of the incoming room air under the glass panel must be between 0.4 and 0.7 m/s; the mean downflow velocity must be between 0.25 and 0.50 m/s, with no individual measurement outside +/−20% of the mean. However, in pharmacy the GMP [6] takes precedence. In Annex 1 the down flow air velocity differs somewhat from the EN 12469. The mean velocity for the down flow in Annex 1 (Class A) must be 0.45 m/s +/−20%. It is important to stress EU GMP compliance during installation and initial qualification of a new safety cabinet in a pharmaceutical environment. National guidelines may differ.

The air in a Class II safety cabinet is filtered through prefilters and HEPA filters so the resulting workspace inside the bench complies to EU GMP Class A. All safety cabinets of type II are built with a HEPA filter at the point where the used air is finally expelled through the exhaust channel. This is an extra HEPA barrier, preventing aerosols contaminating the HVAC system.

Classification of Class II SAFETY CABINets

Safety cabinets must comply with Class II of the European Standard EN-12469. Some types comply moreover to the German DIN 12980. Document your specifications well before purchase and be aware that in pharmacy practice a down flow velocity of the air in a safety cabinet must comply with current EU GMP unless national guidelines say different. Communication about GMP is very important, because these safety cabinets are used in non-GMP laboratories too.

The Classification IIA and IIB is not found in the EN-12469 but in US-CDC guidelines (see further down). In a Class IIA cabinet the (potentially contaminated) air from the workbench is led without filtration to the last exhaust HEPA filter; in this way the ventilator compartment can be contaminated after sustained use of this type of safety cabinet. In Class IIB cabinets an extra HEPA filtration cassette is placed below the work bench; as a result HEPA filtrated (potentially contaminated) air from the workbench enters the ventilator part before it passes the last HEPA exhaust filter. The ventilator compartment remains cleaner by this extra HEPA filtration step. The environment is better protected, as well as service personnel working inside the safety cabinet.

Safety cabinets placed in a room with underpressure (for the preparation of radiopharmaceuticals for example) must have an extra exhaust ventilator, discharging the exhaust air outside the building. This exhaust ventilator must be tested also in daily practice and at periodical electricity break tests. Safety cabinets have visual and acoustic alarms that warn for deviations in airflow (down flow and in flow alarms).

The classification by the U.S. Centers for Disease Control and Prevention (CDC) is to be found in Appendix C: Types of Biological Safety Cabinets (BSC) of the draft USP monograph Hazardous drugs – handling in healthcare settings [7]. Terminology (biological safety) may be confusing but is historically determined: the first safety cabinets were developed for working with dangerous microbiological materials. The classification of the cabinets is based on their technical construction which is described in this Appendix. The fields of application are suggested for each class.

Class I: A BSC that protects personnel and the environment but does not protect the product/preparation. Personnel protection is provided when a minimum velocity of 75 linear feet/min of unfiltered room air is drawn through the front opening and across the work surface. The air is then passed through a HEPA/ULPA filter either into the room or to the outside in the exhaust plenum, providing environmental protection.

Class II: Class II (Types A1, A2, B1, and B2) BSCs are partial barrier systems that rely on the movement of air to provide personnel, environmental, and product/preparation protection. Personnel and product/preparation protection is provided by the combination of inward and downward airflow captured by the front grid of the cabinet. Side-to-side cross-contamination of products/preparations is minimised by the internal downward flow of HEPA/ULPA filtered air moving toward the work surface and then drawn into the front and rear exhaust grids. Environmental protection is provided when the cabinet exhaust air is passed through a HEPA/ULPA filter.

Type A1 (formerly, Type A): These Class II BSCs maintain a minimum inflow velocity of 75 ft/min, have HEPA-filtered, down-flow air that is a portion of the mixed down-flow and inflow air from a common plenum, may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy, and may have positive-pressure contaminated ducts and plenums that are not surrounded by negative-pressure plenums. They are not suitable for use with volatile toxic chemicals and volatile radionucleotides.

Type A2 (formerly, Type B3): These Class II BSCs maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered, down-flow air that is a portion of the mixed down-flow and inflow air from a common exhaust plenum, may exhaust HEPA filtered air back into the laboratory or to the environment through an exhaust canopy, and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for minute quantities of volatile toxic chemicals and trace amounts of radionucleotides, they must be exhausted through properly functioning exhaust canopies.

Type B1: These Class II BSCs maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered down-flow air composed largely of uncontaminated, recirculated inflow air, exhaust most of the contaminated down-flow air through a dedicated duct exhausted to the atmosphere after passing it through a HEPA filter, and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for work involving minute quantities of volatile toxic chemicals and trace amounts of radionucleotides, the work must

(continued)

be done in the directly exhausted portion of the cabinet.

Type B2 (total exhaust): These Class II BSCs maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered down-flow air drawn from the laboratory or the outside, exhaust all inflow and down-flow air to the atmosphere after filtration through a HEPA filter without recirculation inside the cabinet or return to the laboratory, and have all contaminated ducts and plenums under negative pressure or surrounded by directly exhausted negative-pressure ducts and plenums. These cabinets may be used with volatile toxic chemicals and radionucleotides.

Class III: The Class III BSC is designed for work with highly infectious microbiological agents and other hazardous operations. It provides maximum protection for the environment and the worker. It is a gas-tight enclosure with a viewing window that is secured with locks and/or requires the use of tools to open. Both supply and exhaust air are HEPA/ULPA filtered. Exhaust air must pass through two HEPA/ULPA filters in series before discharge to the outdoors.

28.3.6.4 Operating Instructions

The operational aspects of maintenance and calibration for Class II safety cabinets are almost the same as for Class I cabinets (see Sect. 28.3.5). Additionally the inflow as a protective barrier has to be measured.

Daily cleaning and disinfection of the interior of a safety cabinet is important. The tray under the workbench as well as the pre-filter contains spilled fluids. This area has to be cleaned and disinfected at least once a week wearing a FFP3 mask and protective impermeable clothing. The pre-filters must be changed every 3–6 months; the HEPA filters must be changed only after significant failure at qualification tests, repair being not possible any more.

28.3.6.5 Qualification

The protection performance of a Classs II safety cabinet is given by the so-called Aperture Protection Factor, which is determined by the Potassium Iodide test. Potassium Iodide solution is dropped on a spinning drive. An aerosol inside the work area of the cabinet is formed; some droplets are forced in the direction of the protecting air curtain. The number of aerosol particles inside the bench is counted (A). Outside the cabinet (where the operator normally is sitting) the number of aerosol particles that escaped the air curtain in front of the bench is counted again (B). A/B is the protection factor. The protection factor has to be at least 1.5×10^5.

A second test is a test with spores of bacteria. This is a factory test for obvious reasons, see EN-12469.

The potassium Iodide test is time-consuming. This test is performed in OQ/PQ qualification or when possible harm could have occurred, for instance when the cabinet is moved to another place.

28.3.7 Class III Safety Cabinets (Isolators)

An isolator, as is in its name, offers physical isolation of the operator from the product. It offers complete containment. The word “isolator” is generally used to mean a “physical barrier” system in view of minimizing human intervention. There are many definitions for isolators. The definition of PIC/S recommendation “Isolators used for aseptic processing and sterility testing” is as follows: An isolator is an arrangement of physical barriers that are integrated to the extent that the isolator can be sealed in order to carry out a routine leak test based on pressure to meet specified limits. Internally it provides a workspace, which is separated from the surrounding environment. Manipulations can be carried out within the space from the outside without compromising its integrity An isolator is an example of a class III safety cabinet and in the following we will use the word ‘isolator’

Its presence in pharmacies differs considerably between countries.

In industry an isolator technique is used for critical aseptic processes and for sterility testing. Other techniques with robots and barrier system isolator technology are in use also. Isolators for aseptic manufacturing can be placed in class C or D clean rooms, whereas Class I LAF cabinets should be placed in GMP class B according to EU-GMP.

28.3.7.1 Description

An isolator is according to the description of EN-12469 a Class III safety cabinet, as said a complete physical barrier, see Fig. 28.1g. The air inside the isolator is HEPA filtered, so inside the isolator a GMP Class A air quality is maintained. The gloves or full or half suits are the physical barrier between the sterile product inside the isolator and the operator standing outside and the integrity of this barrier requires very much attention.

The main compartment of an isolator is often made of stainless steel and has two rubber gloves in the front of a clear viewing panel. The HEPA filtered airflow can be laminar or turbulent.

The pressure inside the main compartment is higher or lower than the background area of the isolator. Containment isolators often employ negative internal air pressure and most isolators use positive pressure for aseptic processing. A sporicidal process, usually delivered by gassing, can be used to aid microbiological control. A gas generator delivers the gas (e.g. peracetic acid or hydrogen peroxide) via defined ducts [8].

If the isolator is only used for non-hazardous products the exhaust air can be discharged into the background area. However, commonly the air is discharged outside the building.

In some cases, the isolator may be filled with a gas other than air, for example to allow the preparation of oxidisable sterile drugs. Different procedures are then used to allow the elimination of air in all products introduced inside.

Some isolators have a modular construction for many different kinds of applications. Sometimes an extra HEPA filter is built in, underneath the working surface. An isolator may have no, one or two hatches, constructed as a lock. The hatches may have their own HEPA filters and have a door to the main compartment and another door to the background area. The isolator has an interlock system for the hatches to prevent loss of air pressure. As an alternative for the hatches special isolator transport and loading boxes can be used with a tight (screw) fitting to the main compartment ('mousehole'). In practice the terms 'open' and 'closed' isolators are used. In 'closed' isolators all materials are inside the isolator during the gaseous disinfection and the aseptic handling is done without opening hatches or mouseholes.

The operator wears disposable gloves and puts the hands and arms in the long rubber isolator gloves, which have inflatable gaskets for tight fitting to the isolator. Half or full suits are also a possibility.

The isolator gives an acoustic alarm when the pressure drops or with other deviations.

Maintenance or repair of an isolator has to be done with gloves, a protective mask and protective clothing. Change of HEPA filters has to be done very carefully and with qualification after replacement. Further descriptions can be found in [8].

28.3.7.2 Using an Isolator

After delivery of a new isolator a qualification protocol is followed.The interior of the isolator must comply with EU GMP Class A (particles and microbiological tests). A program to minimize the risk of loss of integrity of gloves, sleeves and suits should be present including operator practice, vigilance and the absence of sharp edges. The glove ports and, if applicable, the suits present particular risk because they are more prone to damage and if not noticed will contaminate the product. Transfer of material in and out should not compromise the critical zone. The transfer is especially critical if no gassing is used. In that case a proper disinfection procedure such as used in normal LAF has to be used.

As the absence of microorganisms is expected, the question of laminar versus turbulent flow and the strict application of aseptic procedures during operations might be irrelevant.

The isolator and gloves are tested daily for leakage. Airflow velocity if applicable is measured in-line with a calibrated instrument. The pressure inside the isolator is checked continuously. Furthermore, gas detection in case gaseous disinfection is used.

Before working the inside of the isolator has to be cleaned and disinfected. Disinfection can be done with peracetic acid or hydrogen peroxide, using special disinfection devices and procedures. For small scale or incidental use ethanol 70–80 % may be used as an alternative.

28.4 Apparatus for the Production and Storage of Pharmaceutical Water

Water is the most important pharmaceutical substance. The requirements to be met are being discussed in Chap. 7.

Pharmaceutical water (Ph. Eur.) is produced by a multi-staged process using different techniques with different apparatus in series [9, 10]. In this section those different apparatus producing water with a pharmaceutical quality are discussed, e.g.:

- Water softeners
- Demineralisation apparatus based on ion exchange
- Apparatus for reverse osmosis
- Apparatus for electro-deionisation
- Distillation apparatus

The equipment for storage and distribution (loop system, pump and storage vessel) is commonly considered as a built-in installation as part of the premises. A quality problem, namely the development of biofilms in this type of equipment is discussed in Chap. 7.

28.4.1 Water Softeners

28.4.1.1 Application

The water softening process removes most calcium and magnesium ions from tap water. By doing so a downstream placed apparatus, such as reverse osmosis, electro-deionisation or distillation apparatus, is protected against the deposit of calcium and magnesium salts ('limescale').

28.4.1.2 Description

The principle of a water softener is based on ion exchange using synthetic resins. The synthetic resin has negatively charged functional groups with sodium as a counterion. Calcium and magnesium ions from the water are exchanged for the sodium ions of the resin. Therefore, this type of water softener is called cation exchanger. See Chap. 7 for the hardness degrees. The resin pearls do not retain any other contamination such as solid particles.

28.4.1.3 Operating Procedure

Water softeners must be regenerated periodically. This regeneration involves the immersion of the resin, being saturated with calcium and magnesium ions, in a concentrated sodium chloride solution (brine). This brine is prepared and kept in a separate vessel. The calcium and magnesium ions bound to the resin will exchange with the sodium ions in the brine. After regeneration the brine containing calcium and magnesium must be flushed thoroughly. Often the softening apparatus is provided with fully automatic regeneration equipment. In that case regeneration will occur periodically or be triggered by an in-line hardness tester.

Larger installations for continuous water purification usually have two automated softening apparatus mounted in a parallel arrangement. As soon as one of them has to be regenerated an automated control system will switch that water softener off. The other one will continue delivering soft water in the meantime.

Water softeners are a good substrate for bacteria. Therefore, apart from being regenerated, the system must be disinfected periodically as well. Some (automated) softeners can generate chlorine gas from the brine solution during regeneration. This chlorine gas dissolves in the water as hypochlorite and acts as a disinfectant. All chlorine must be flushed away thoroughly after the combined regeneration and disinfection process.

The quality of the water will be controlled by means of pressure and flow meters and by a hardness tester. The hardness tester consists of an automated titration apparatus. The reservoir, with combined titre and indicator solution, should be refilled regularly.

28.4.2 Demineralisation Apparatus Based on Ion Exchange

28.4.2.1 Application

Purified water (Ph. Eur.) can be produced from tap water or from pre-softened tap water by demineralisation. As this production method easily leads to microbiological growth the product will not always meet the microbiological requirements. Passing through a bacteria retentive filter may render the demi-water compliant. However this treatment should be monitored because of microorganisms growing through the filter. Endotoxins will not be removed by filtration.

28.4.2.2 Description

Ion exchangers can be applied both as a water softener and as a demineralisation apparatus. After softening of tap water, calcium and magnesium ions have been removed; however any other mono and bivalent ions (cations such as potassium and sodium and anions such as nitrate, chloride, sulphate, bicarbonate and carbonate) have still to be removed in order to obtain Purified Water Ph. Eur. This process is called deionisation or demineralisation. It proceeds at room temperature. Demineralisation apparatus based on ion exchange consist of columns filled with several varieties of synthetic resin pearls that remove unwanted ions from the water by exchanging them for hydrogen and hydroxyl ions. The general principle is that all cations are being exchanged for hydrogen ions and all anions for hydroxyl ions. Finally the recombination of hydrogen and hydroxyl ions results in pure water.

An ion exchange resin is a synthetic resin with positively and negatively charged functional groups. The demineralisation process (which might proceed over one combined or over separate columns) exchanges cations from the water for hydrogen ions from the cation exchange resin and anions from the water for hydroxyl ions from the anion exchange resin. Exemplified (s = solid):

$$Na^{+}(aq) + RH^{+}(s) \rightarrow RNa^{+}(s) + H^{+}(aq)$$

Any bivalent anion, e.g. sulphate, exchanges for 2 hydroxyl ions in an anion exchange resin.

Two different types of anion resin are used for demineralisation: weak basic and strong basic exchange resins. Both types exchange anions such as chloride, sulphate, bicarbonate and carbonate for hydroxyl ions. However strong basic exchange resins can additionally exchange silicic acid and silicates for hydroxyl ions.

The quality of demineralised water depends on several factors, such as the quality of the feeding water, the type of exchange resin, the quantity of resin and the number of resin containing tanks.

In a mixed-bed demi-tank or column, cationic resins and anionic resins are thoroughly mixed in just one container. The alternating cationic – anionic resin pearls in one column can provide water of excellent quality. A mixed bed column can achieve a water quality with a conductivity of less than 1 microSiemens/cm.

Dual-bed demineralisation columns consist of two serially arranged containers, one with cationic resin and one with anionic resin pearls. A dual-bed weak basic demi-column delivers water with a conductivity of approximately 20 microSiemens/cm. A dual-bed strong basic demi-column delivers water of approximately 5 microSiemens/cm.

An ion exchange demineraliser has to be regenerated periodically by flushing the resin pearls with a highly concentrated regeneration fluid. The type of regeneration fluid depends on the specific type of ion exchange resin. Commonly a solution of sodium hydroxide or hydrochloric acid is used. Afterwards, the regeneration medium has to be flushed thoroughly and the ion exchanger can be reused again. Regeneration sometimes takes place at the site of the user, sometimes used columns are exchanged for regenerated ones by the supplier.

28.4.2.3 Operating Procedure

The quality of the water is controlled with conductivity meters, pressure meters and flow meters.

If the feed water contains a relatively high concentration of dissolved substances a dual-bed system is usually preferred. If the feed water contains low concentrations a mixed bed ion exchange demineralisation will be preferred. As said above for water softeners, the resins pearls in a demineralisation column do not retain any other contamination such as solid particles. They constitute a rather good substrate for the growth of bacteria; mixed bed systems are even more vulnerable. The investment costs are comparatively low in contrast to the relatively high operational costs including regeneration. If the installation must produce Purified Water Ph. Eur. the microbiological quality has to be monitored or the bacteria filter has to be changed frequently.

28.4.3 Apparatus for Reverse Osmosis

28.4.3.1 Application

An apparatus for reverse osmosis removes more than 95% of all ions and more than 99% of all particles, colloids and dissolved organic material including endotoxins. Nevertheless the permeate still contains too many small, univalent ions to comply with the requirements for purified water after one filtration step. Therefore, reverse osmosis is often used as a preliminary treatment, preceding distillation or demineralisation. The available reverse osmosis systems will only be economically feasible if a rather large amount of purified water is required. As an example reverse osmosis installations are being used, in combination with other purification methods, as a preliminary treatment in the production of Water for Injections and in the production of purified water for haemodialysis. The principle of reverse osmosis can be used to produce water for injection combining preliminary treatment and final treatment. Sometimes purified water is prepared using just a series of semi-permeable membranes. Reverse osmosis has the advantage compared to demineralisation that few chemicals are being consumed. However, as the process does not involve any heating, a substantial risk exists of microbiological contamination and biofouling. Decontamination of storage tank and distribution loop(s) is possible by heating the circulating water for a predefined time period.

28.4.3.2 Description

Reverse osmosis utilises semi-permeable membranes. The name "reverse osmosis" (abbreviated as "RO") uses the fact that the osmotic pressure building up over a semipermeable membrane has to be overcompensated. In a reverse osmosis process the water is forced by high pressure to flow through a semipermeable membrane thereby eliminating any particle or larger ion, see Fig. 28.2.

RO membranes are designed to pass water through the intersegmental space between the polymer molecules. This space is wide enough to allow individual water molecules to pass, but too small for any hydrated ions. Because the system has many additional surfaces beyond the membrane, on which undisturbed biofilms could build up, the prevention of

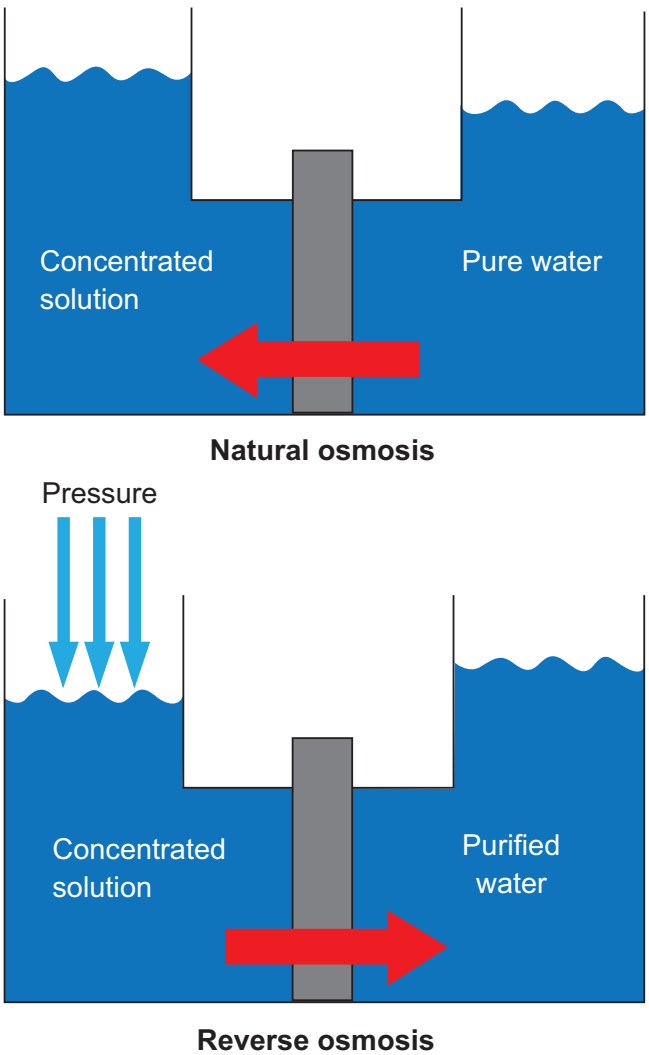


Fig. 28.2 Principle of reverse osmosis. (Source: Recepteerkunde 2009, ©KNMP)

microbiological contamination in a reverse osmosis system is a challenge. Biofouling is effectively limited by a smart choice of materials and by avoiding blind angles, however intensive control is still mandatory.

28.4.3.3 Operating Procedure

Apparatus for reverse osmosis can function for a long time without much maintenance. The semi-permeable membrane should be replaced periodically because of ageing. The average lifetime of a membrane is 2–3 years.

During the first start-up a balance has to be found between the amount of water being produced as permeate and the amount that is flushed away as concentrate. Usually an optimal result in water quality and quantity will be achieved when approximately 10% of the feed water is drained away as concentrate. By choosing a higher percentage the quality of the permeate might increase. However, this will have a negative impact on the yield of the installation. A lower concentrate percentage will decrease the quality of the permeate.

Most attention should be paid to the microbiological quality of the water. Again a well-monitored bacteria retentive filter can be significant.

28.4.4 Apparatus for Electro-Deionisation

28.4.4.1 Application

Electro-deionisation (EDI) is used in combination with other purification methods. Electro-deionisation is applied to the production of Purified Water Ph. Eur. or Highly Purified Water Ph. Eur. Highly purified water may be used in the haemodialysis department for in-line production of dialysis fluids for continuous dialysis. EDI in combination with other techniques can be used for in-line dialysis, it requires thorough in process controls. A distillation apparatus, suitable for water for injection, would not comply with the large peak demand at dialysis unless equipped with a very large storage vessel and an extremely powerful (energetically unrealistic) cooling system.

Sometimes hospital pharmacies use an EDI installation for the preparation of water for pharmaceutical non-sterile stock preparations.

28.4.4.2 Description

Electro-deionisation (EDI), also called *continuous* electro-deionisation (CEDI), is a special type of demineralisation.

The apparatus using this technique is equipped with mixed resin pearls and selectively permeable membranes. It functions by applying an electrical current fed through resin and membranes. The feeding water will be normally deionised by flushing through the resin. However, the "captured" ions subsequently do not stick to the resin, but are being removed under the influence of the applied potential difference and drained through the selectively permeable membranes. The potential difference also splits a part of the pure water into H^+ and OH^- ions that regenerate the resin at their turn, see Fig. 28.3.

The potential difference and the pH-gradient impede the growth of micro-organisms additionally, but the risk of growth of microorganisms still exists.

28.4.4.3 Operating Procedure

A (C)EDI-installation requires relatively limited maintenance efforts. To maintain the potential gradient a pure sodium chloride solution has to be fed behind the selective permeable membrane. This sodium chloride solution is drained away with a part of the feed water. The stock sodium chloride must be refilled regularly. The product water should be checked for its conductivity.

Tap water must be softened before being used as feed water. This water still contains microorganisms and particles as well as quite a lot of minerals. Therefore, the water should be filtered as well. To achieve a stable and reliable supply of the required water quality, it is common practice to apply a softening installation, a reverse osmosis installation and a (C)EDI installation in sequence.

The application of a firm potential difference in the water not just causes the migration of H^+ and OH^- ions to the ion exchange resin pearls, but leads to the generation of small amounts of free hydrogen and oxygen gas as well. Therefore, an effective degassing of the storage vessel containing the product water is necessary to prevent the accumulation of these gasses which otherwise might cause an explosive mixture.

28.4.5 Distillation

28.4.5.1 Application

With distillation chemically pure and sterile water can be produced. Provided that any carry-over of water droplets is effectively avoided, it can be relied upon that not just chemical impurities but micro-organisms and endotoxins as well will be removed. Distilled water complies to the requirements of being pyrogen-free according to the Water for Injections Ph. Eur. monograph.

To maintain the sterility and apyrogenicity of the distillate it is necessary to collect and store the water in a sterile and pyrogen-free way as well. In larger installations this is achieved by keeping the water in a storage vessel at least at 80 °C and by pumping it around in a loop in a turbulent flow.

The sterility and apyrogenicity immediately after the purification process constitute the most important distinction with other purification methods.

28.4.5.2 Description

For distillation the feed water is heated to boiling. On the evaporation of the water any chemical and microbiological

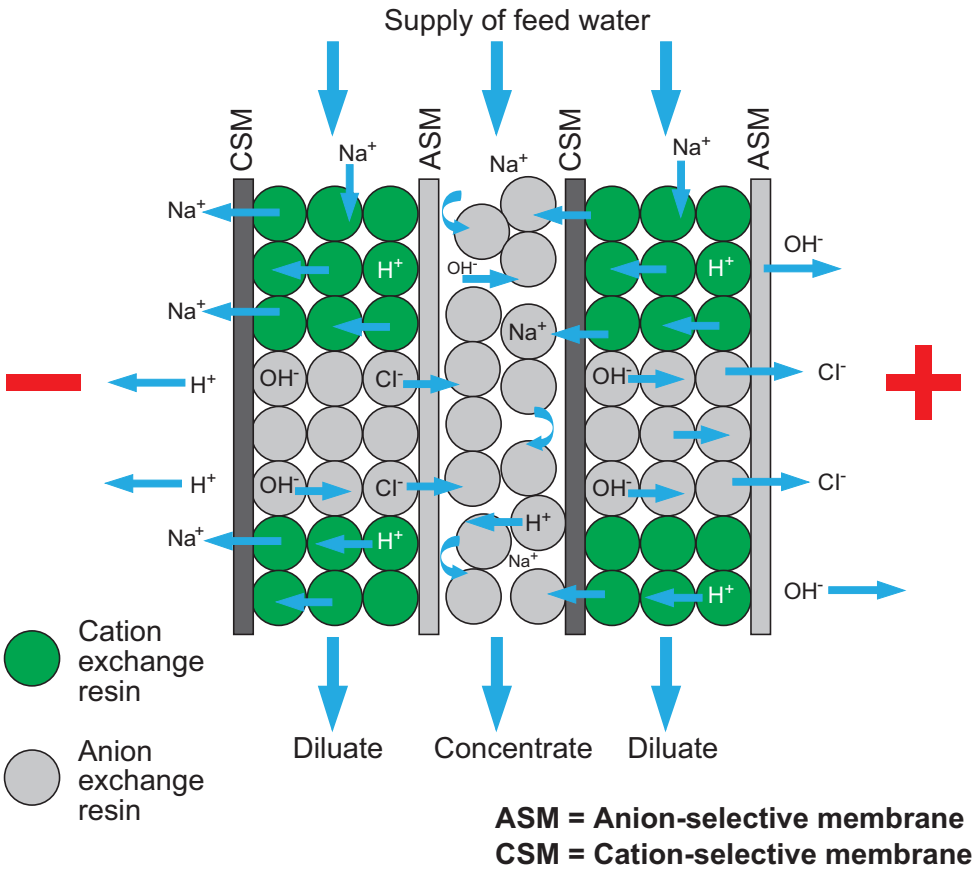


Fig. 28.3 Principles of electro-deionisation. (Source: Recepteerkunde 2009, ©KNMP)

impurities are retained in the boiling water. The pure water vapour is then condensed. However, even this method of purification cannot yield absolute purity. Even the highest quality distillation apparatus will not be able to remove 100% of all ions and endotoxins. It is commonly accepted that a maximum of a log 3–4 reduction in the concentration of impurities can be achieved. For this reason it is important to put requirements on the quality of the feed water for a distillation apparatus.

For small scale distillation a simple (single effect design) water distillation apparatus can be used. For a middle or large scale distillation stainless steel built apparatus are constructed in a different way, using multi stage distillation, steam compression or thermo compression, to yield a much higher capacity and a better efficiency, see Fig. 28.4.

In the past stainless steel was known for its release of metal ions, but that is not the case any more in presently deployed steel qualities. Nevertheless it is important to make inquiries of the supplier about this.

A simple classical water distillation apparatus consists of a boiling vessel from glass, holding a heating element made of metal or quarts and fitted to a glass condenser. To reduce water and energy consumption the feed water is first used as a coolant in the condenser or it is preheated with the aid of a heat exchanger, see Fig. 28.5. The velocity of the vapour carry-over is relatively small. Consequently the risk of carry-over of any water droplets is small as well. In larger apparatus specific measures have been taken to prevent this carry-over.

Provided a correct design and performance, distillation is a very reliable process. However the apparatus does not tolerate being fed with tap water quality because calcium, magnesium and silicates would precipitate in the evaporator. In addition volatile components from the tap water could co-distil and condensate in the product water. Examples of those volatile constituents are trihalomethanes, ammonia and carbon dioxide. Therefore the feed water has to be pre-treated. Purified Water Ph. Eur. is suitable as feed water. The chemical and microbiological properties of this water are defined unequivocally. Other non qualified water should not be accepted as feed water for a pharmaceutical distillation apparatus.

28.4.5.3 Operating Procedure

A distillation apparatus usually requires little operational attention. Obviously regular maintenance is mandatory and all measurement probes for temperature, pressure and conductivity must always be calibrated.

The permanent exposure of the stainless steel to steam and ultrapure hot water might provoke the development of so-called rouging. This phenomenon and its prevention is further discussed in Sect. 28.4.6.1.

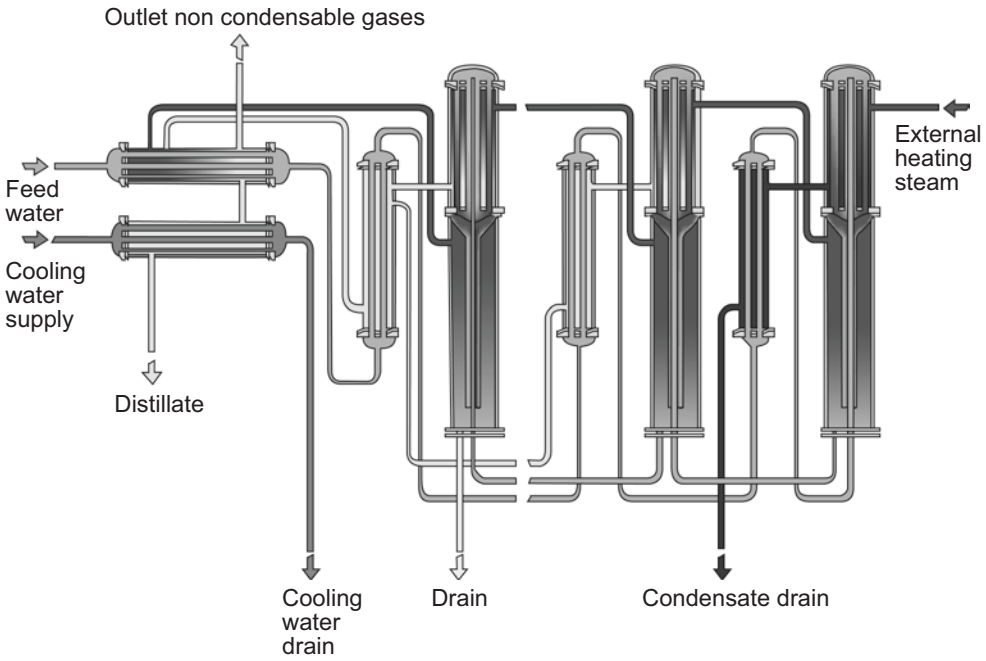


Fig. 28.4 Multi stage distillation. (Source: Recepteerkunde 2009, ©KNMP)

28.4.6 Equipment (Installations) for Storage and Distribution of Pharmaceutical Water

In this subsection installations required for storage and distribution of pharmaceutical water are discussed. In most situations this installation is built-in.

Water of pharmaceutical quality is used as a raw material, excipient, solvent, and as cleansing agent. In addition the pharmaceutical production facility needs water for (thermal) disinfection or sterilisation and for the preparation of pharmaceutical quality reagents [11].

Engineering of installations for the storage and distribution of pharmaceutical water can only be understood with knowledge of the specifications of pharmaceutical quality water. The most important characteristics and the categorisation of pharmaceutical water, according to the European Pharmacopoeia, is discussed in Chap. 7.

The leading principle in storage and distribution of pharmaceutical water in bulk is continuous circulation in a loop that includes at least the following:

- apparatus for the measurement of temperature, conductivity and TOC (Total Organic Carbon; i.e. the total carbon load of organic, carbon containing substances), etc.;
- a storage vessel;
- filter(s) in the production part of the installation and for pressure levelling out with air from the outside of the system;
- apparatus for heating;
- apparatus for cooling;
- taps;
- apparatus for disinfection (only for cold water systems). See Fig 28.6.

Distinct requirements that apply for different qualities of pharmaceutical water will be discussed:

Purified water in bulk.

The most commonly used systems for the production of purified water, deliver water with temperatures around room temperature. Therefore adequate measures have to be taken to manage and control total viable aerobic counts during preparation and storage.

The design capacity should be balanced with the predicted need per instance, e.g. for the most water consuming activity and the predicted need over time. Involved are considerations of production time per batch, investment costs and the time to refill the storage vessel. It should be taken into account that drawing off or flushing out the water will curtail the ongoing growth of microorganisms.

During transport through the loop the water passes several valves in which biofilm formation may occur. This biofilm can easily extend beyond the valve as the system for purified water usually is not heated. Therefore the most critical place in the loop is the point beyond valves, i.e. where the water runs back into the storage vessel. That is the right spot for placing critical measurement apparatus in the loop, such as for temperature and conductivity.

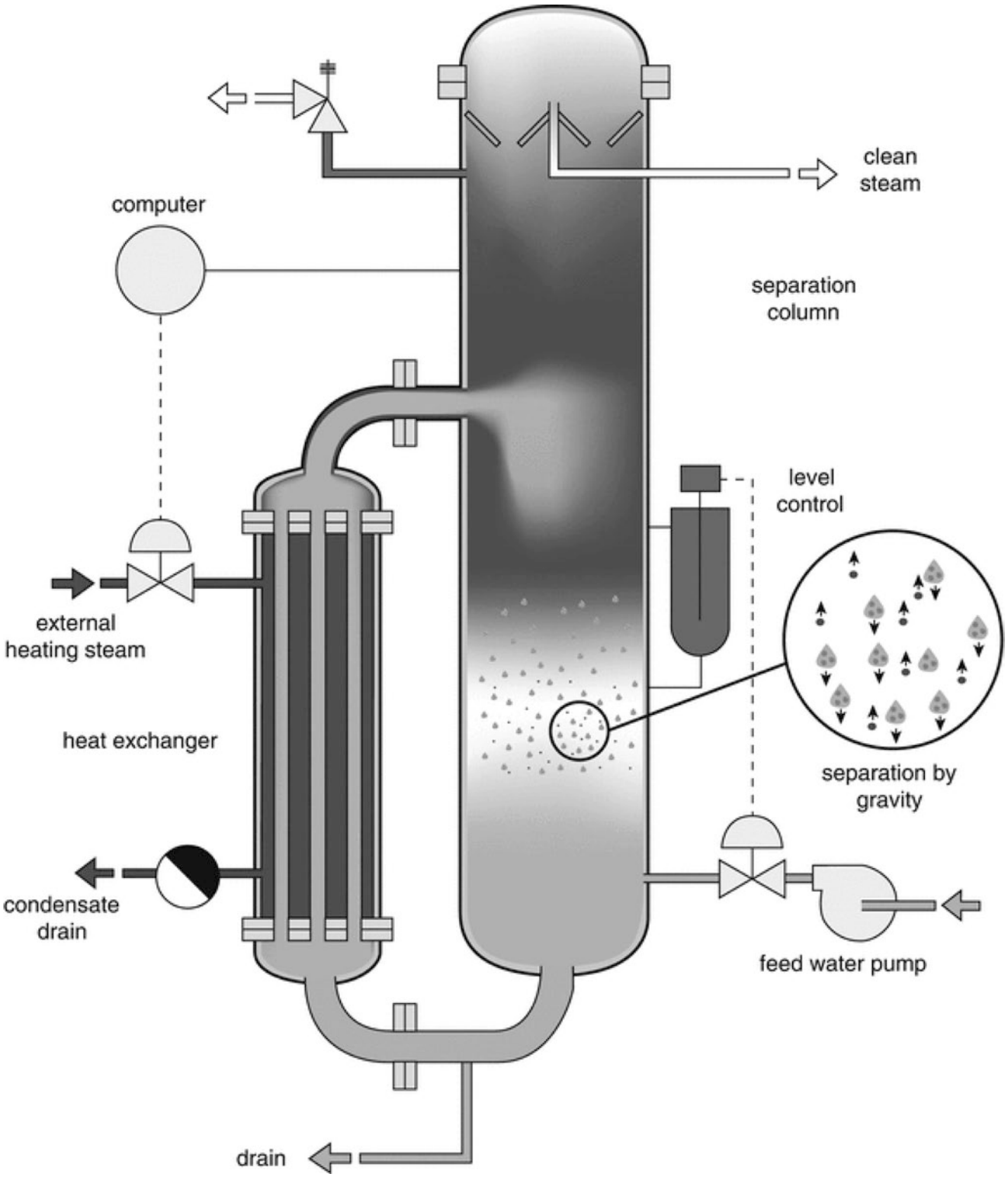


Fig. 28.5 Singular distillation column. (Source: Recepteerkunde 2009, ©KNMP)

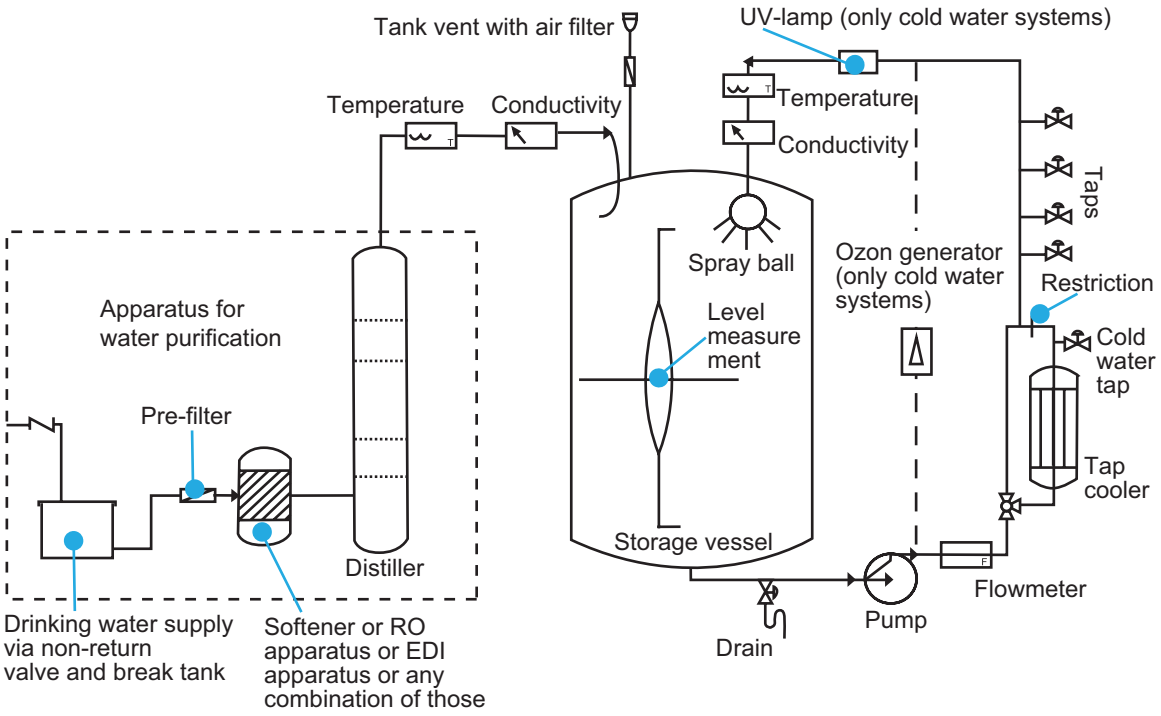


Fig. 28.6 Schematic diagram of water storage and distribution systems

Water for injections in bulk.

The Ph. Eur. specifies that 'water for injections in bulk is obtained from water that complies with the regulations for water intended for human consumption or from purified water by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets.' So the quality of this water is essentially defined by the very specific way it is produced. The reason for this is that there is no reference water quality to compare.

During production and storage adequate measures should be taken to monitor and control the total viable count. This can be measured in freshly tapped water for injections in bulk (maximum 10 CFU/100 ml). Ph. Eur. actually gives this value as an action limit, but to control microbial contamination it is better used as a maximum value. During production by means of distillation, water for injections reaches a temperature between 94 and 99 °C. By maintaining high temperatures in the storage vessel and the loop any growth of microorganisms is prevented. In this way the content of endotoxins) can be kept low (standard: less than 0,25 IU/ml), as well as the total viable count.

The water for injections limit for conductivity is lower than that for purified water. At 80 °C water for injections may have a conductivity of maximal 2,7 microSiemens/cm.

Usually only the storage vessel and not the loop is heated. So during the passage of the loop the water will cool down gradually. Additionally any inadvertent leakage of a valve (e.g. the one that provides a washing machine with water for injections) may impair the quality of the water in the system. These facts underline the choice of the most critical spot for all measurements being the place where the water runs back into the storage vessel.

Design criteria for the quality of water.

For the chemical specifications of pharmaceutical water see Chap. 7. A sufficient low conductivity, specified in the Ph. Eur., warrants that any metals, ions and inorganic contaminants will be practically absent. During the production, storage and distribution Water for Injections in bulk is tested continuously at conductivity, temperature and at TOC content. TOC can be measured either in-line, involving a metering sensor that is permanently mounted into the loop, or off-line, implying periodical measurement in tapped water samples [12]. Water samples should be tested off-line periodically on nitrates, aluminium (especially in water intended for dialysis applications), heavy metals and bacterial endotoxins. Purified water in bulk should be monitored at the same parameters. The (expensive) TOC assay might be partly replaced by periodical testing on oxidisable substances. Bacterial endotoxins in purified water should be monitored, especially when the water is used in haemodialysis. In purified water additional monitoring might be indicated, e.g. of ozone (during and after disinfection), the hardness of the feeding water and the luminosity of the UV source (decaying ozone).

Suppliers of equipment usually use American terminology in their documentations, including the term "sanitisation" referring to disinfection methods that are known to be effective to sterilisation processes, however in which (formally defined) sterility as a final result will not be proven.

Measuring conductivity

Measurement of conductivity during production, storage and distribution of (highly) purified water and water for injections is indispensable. One conductivity sensor usually will be mounted into the pipe that carries the hot, freshly distilled water from the distiller into the storage vessel. Usually this sensor is combined with a temperature sensor. Additionally a conductivity and temperature sensor must be mounted into the return flow of the loop. This is necessary to prove that the water that runs back into the vessel still has adequate quality.

Total organic carbon (TOC)

TOC is an indicator for any existent (decayed) organic material in the water, often originating from living or dead micro-organisms. A low TOC (less than 0,5 mg/ml) may be interpreted as a useful indicator that the water has a proper microbiological quality [9, 12]. This assay can be performed easily and immediately before use.

Microbiological quality of water

Operations, storage and transport methods all can influence the growth of microorganisms.

In practice microbiological quality of water is monitored by action and alert levels. Thus the user will be early notified about any deviation of critical parameters. For instance an alert level might be put at a factor 10 below an action level. To determine these levels a good set of total viable aerobic counts, endotoxin assay results and TOC assay results should be available. For the collection of these results, particularly in the start-up phase very frequent measurements must be executed.

The development of a biofilm in the water production system has to be prevented. The rougher the surface the easier a biofilm will develop. Nevertheless even onto polished metal, synthetic materials, glass and in streaming water it may develop, therefore the micro-biological quality of the water has to be controlled frequently. In demineralised water the growth proceeds faster than in distilled water as a consequence of more available nutrients. As soon as a biofilm causes contamination the term biofouling is used. The best way to eliminate a once formed biofilm is mechanical cleaning, which is becoming more and more common in industry.

However, when the surface is not accessible for mechanical cleaning, other cleaning methods must be applied, such as flushing with hot alkaline followed by hot acetic acid or flushing with concentrated sodium chloride solution followed by hot acid solution or hot alkaline. The microbiological safety of the installation thus not only depends on the application of heat but on the (im-)possibilities to dispose of any formed biofilm as well. Risky surfaces are demineralisation resin, tubes, transport pipes made of stainless steel or synthetic materials, the inner side of storage vessels, taps and membranes in valves.

28.4.6.1 Equipment (Systems) for the Storage of Pharmaceutical Water

At the design of the pharmaceutical water installation the capacity of the storage vessel should be determined based on the maximum daily consumption, the average consumption and the maximum peak consumption per product batch. The water consumption by sterilisers and washing / disinfection machines should also be taken into account.

The higher the peak water consumption, the larger the storage vessel. If the demand for water has a more steady character then the vessel can be smaller. In case of a large vessel the available floor area and its load capacity must be accounted for. Continuous production implies that one or more tanks are being filled and drained continuously. Quality control should take place in a continuous way, completed with intermittent additional tests. After maintenance and also periodically the system should be disinfected. The frequency of the disinfection depends on the results of the process validation [13, 14]. Further specifications of the system follow the required water quality.

The required storage temperature also plays a role:

- Cold storage implies storage conditions between 4 and 10 °C at which micro-organisms grow very slowly. Cold storage renders the system effective and reliable. Disinfection occurs only occasionally and can be performed with hot water. Drawbacks

(continued)

are the expense of a cooling installation and its considerable energy consumption. Stainless steel, PVDF, polypropylene and polyethylene cross-linked (PEX) all are suitable as a material for the storage of purified water at low temperatures. The design of the vessel should be aimed at the lowest possible total viable aerobic count. This implies that all surfaces, pipe holes, valves, etc. should be accessible and made of very smooth material.

- Storage and distribution at ambient temperatures (15–30 °C) is reasonably effective and reliable and the investment and operation is comparatively cheap. However the risk of building up a biofilm is substantial. Therefore, non-cooled storage systems should be disinfected frequently by flushing with hot water or by adding ozone. Materials for loop and storage vessels are similar as for cold storage [13, 14] however the method of disinfecting can limit the choice. More aggressive methods such as treatment with steam are preferable, but require expensive materials such as stainless steel.
- Hot storage and distribution means storage and distribution at a temperature continuously kept over 70 °C. In practice an ample safety margin is implemented and usually the actual storage and distribution temperature is well above 85 °C. Hot storage is the most effective and reliable way to prevent growth of microorganisms. With the aid of well mounted isolation material in the heating mantle a storage vessel can be kept at high temperature at low expense. The loop piping should also, preferably, be insulated. Taps should be placed at short distances from the loop. Before use the tap has to be flushed with hot water. Hot storage involves relatively high investment costs and moderate running costs. It introduces a specific risk of rouging. Hot storage does not diminish the content of endotoxins. The distribution loop can be combined with taps equipped with sanitary coolers to deliver the pharmaceutical water at ambient temperature.

Rouging

At sustained exposure to very pure hot water or steam a thin red, reddish brown, orange, light blue or black deposit (tarnish) might build up. This is seen particularly at less polished spots, e.g. burrs, scratches, sharp edges, material transition areas or bad welds and is called rouging. In fact rouging is an oxidation process. When metal ions in micro-caves dissolve into the water potential differences might occur at a microscopic scale leading to hydrolysis and oxidation. The coloured material consists of iron oxide, iron carbonate or iron hydroxide or any combination of these. Rouging itself doesn't yield any immediate hazard. However once rouging has been built up it might expand and eventually lead to development of rust in which case the smoothness of the texture is affected and the risk of biofilm formation increases. Therefore, highly polished stainless steel constitutes a barrier both against rouging and biofilm formation. Removal of rouging is a very expensive process involving experts [14, 15].

The water level in the storage vessel has to be controlled continuously, preferably with the aid of a building control system. Thus a low level signals to restart the production, however a very low level should produce an alarm signal shutting down the complete installation to prevent, among other things, the circulation pump running dry. A high level will stop the production and an extra high level should give an alarm signal to alert the risk of overflow through the vent filter.

The storage vessel and the loop for water for injections is preferably made of stainless steel AISI 316L and polished to a roughness grade of 0.4–0.6 micrometer mean pore diameter [13, 14]. The water should return from the loop into the vessel through a (rotating) spray ball. By this means the empty upper part of the vessel will be kept hot and germ free. The vessel or at least the lowest point in the loop should be equipped with a sanitary bottom valve ensuring that after complete draining (e.g. for maintenance purpose) no tainting water will stay behind in the system [14].

Tank vent.

A level control system can only be used if the system has been designed according to GMP. Tapping of water from the storage vessel will lower the level in the tank. The sucked-in air entering the vessel has to be filtered through a 0,2 micrometre hydrophobic membrane filter that can be tested and which should be mounted in a stainless steel casing onto the vessel. A pressure safety provision is mounted to safeguard against any possible overpressure in the vessel. The filter has to be replaced at least once yearly as a preventive measure. During the hot storage of pharmaceutical water the filter also has to be kept at a high temperature to prevent the occurrence of condensate. This condensate would provide an ideal substrate for microorganisms which might grow through the filter.

28.4.6.2 Distribution of Pharmaceutical Water

A system for transport or distribution of pharmaceutical water should meet at least four requirements:

- It should deliver water that meets all quality requirements;
- The water should always flow at the required flow rate, especially at the instance of drawing off;
- The water should be delivered at the temperature required for the process at hand;
- The system should function at acceptable investment and running costs.

Piping

Micro-organisms, corrosion, (hidden) construction flaws and ageing can all affect a loop system.

Distribution of water runs to and from the storage vessel. By means of a sanitary pump and a flow rate meter showing the flow rate, the water flows into a sanitary (hygienic, well-disinfectable) piping system. Unused water runs back into the storage vessel. The loop should not contain any branches in which water is stationary. For this purpose specific calculation schemes exist. Generally the length of any branch in the loop never should exceed 6× D (diameter of the loop pipe) but in practice 3× D or even 2× D is to be preferred. Also purified water as feeding water for a distiller installation should recirculate when nothing is drawn off.

The support and mounting of the piping should be constructed in such a way that no sagging occurs, a risk that is more prominent with synthetic materials at higher temperatures than with stainless steel. Preferably the piping is mounted at a slight slope with the bottom valve at its lowest point. The usual angle of the slope of horizontal piping at short distances is advised at 2% and at 0.5–1% for greater lengths.

Joints must never be mounted at a residual strain because that could cause leakages, which can lead to considerable damage. The support system for the piping must not cause any galvanic corrosion. The distribution system must be immune to ozone or the heat of steam. It has to resist a specified water pressure and turbulence as well. The interior of the piping should have a surface as smooth as possible to prevent corrosion and formation of a biofilm. Stainless steel piping must be polished at the inside for this reason. Piping of synthetic materials used for the distribution of pharmaceutical water are smooth plastics like PVDF, polypropylene or PEX. The piping may not release any substances or (metal) ions and should be corrosion resistant [13, 14].

Pump

A circulation pump should have a highly polished finish and should be well cleanable. It must resist any disinfecting process, preferably steaming. Also the pump must allow complete drainage. The latter implies that no water residue must stay behind when the complete loop is drained during maintenance.

The pump should be able to generate a flow rate of 1-2,5 meter per second in the loop, still achieving an acceptable water pressure. The pressure depends also on the loop resistance. Usually a restriction disk mounted in the loop serves to prevent a major pressure drop when water is withdrawn by opening a tap. The flow rate causes the flow to be turbulent and thus prevents the risk at (almost) stationary water e.g. near valves and other small bulges in the loop. After all, any stationary water would substantially increase the risk of building up biofilm [13, 14].

Tapping points.

Membrane valves must be completely drainable and disinfectable, preferably by steam. The membrane made of plastic should be replaced 1–2 × per year. Sometimes globe valves are used to shut off steam pipes, because they are more wear-resistant.

A sufficient number of sample tapping points should be available. The tapping of water during any dysfunction (e.g. deviation of temperature, deviation of conductivity or low level) of the water installation must be prevented. This can be done by automatically blocking all tapping points at the basis of any alarm signal originating from the installation [13, 14].

28.4.6.3 Maintenance and Disinfecting Water Storage and Distribution Systems

Biofilm will emerge especially fast on ion exchange resins, Reverse Osmosis (RO) -membranes and piping made of stainless steel or plastics. Therefore, systems for pharmaceutical water should not contain stationary water and should be disinfected at start-up and after each maintenance process. Even systems for the preliminary treatment of feed water have to be constructed as a recirculating system [14].

Cold water systems usually cannot be steamed. Instead chemical disinfection or disinfection using ozone is customary. An important benefit of ozone treatment compared to other chemical methods is that it can be executed automatically.

Frequent hot water disinfection is a good alternative as a preventive measure, provided that all materials are sufficiently heat-resistant. It is carried out at a temperature of 90–95 °C during at least 2 h of exposure. This process must be validated [14]. The problems to remove a once formed biofilm is discussed above.

RO membranes may not be exposed to ozone. The producer of the membrane should indicate how to treat and disinfect it in a correct way.

Chemical disinfection

If the equipment is provided with adequate connection systems a chemical disinfection is possible. Commonly a solution of hydrogen peroxide and per-acetic acid is diluted to 8–10% and then flushed through the equipment. The system must be thoroughly rinsed afterwards.. The method is quite effective, however it involves the additional efforts of purchasing, storage and handling of the disinfecting agent.

Ozonisation.

Ozonisation is a specific means of chemical disinfection as the active agent (ozone) is generated in the equipment itself. Ozone is used for the periodical disinfection of pharmaceutical water installations when disinfection by steaming or with hot water is not possible. Ozone is a strong oxidising agent and kills microorganisms in water. To obtain sufficient disinfecting power ozone should be present in the water for a sufficient time and in an adequate concentration, according to the guidance of the producer of the ozonisation apparatus. Concentrations with a maximum of 10–50 ppm (sometimes even less) are most common. The ozone generator that is mounted in the loop produces the ozone gas. However after ozonisation the utilised pharmaceutical water must be freed of ozone again. Therefore, UV lamps are included in the loop at a spot that is transparent to UV light. UV light of 254 nm degrades ozone turning it into oxygen. Thus quality control of the lamp is necessary; it usually consists of continuously monitoring the intensity of the UV light. An alarm signal should indicate when the lamp has to be replaced [13, 14].

UV-light for germ reduction.

UV-light with a wavelength of 200–300 nm not only degrades ozone but also reduces the total viable aerobic count in pharmaceutical water, especially in systems with cold storage and distribution. UV-light disrupts the DNA of microorganisms and thus obstructs their growth. Irradiation with UV light is not intended to replace any disinfection method. The effectiveness of the irradiation process depends on water quality, light intensity, flow rate of the water, duration of the irradiation and the identity of the micro-organisms in the water and thus is difficult to validate [13, 15].

28.5 Ultrasonic Baths and Heaters

28.5.1 Orientation

Heaters and ultrasonic baths are mainly used to increase dissolution of substances. The most generally used heaters are: the gas stove and gas burner, electric heating plate, heating lamp, water bath and microwave. Table 28.1 summarises the qualities of various heaters.

Heating is based on three different physical principles: radiation, conduction, and convection. All principles are to a higher or lesser extent present in the various heaters. In an ultrasonic bath, convection is promoted by means of high frequency sound waves instead of heat.

Other important characteristics of the heating equipment are the option of keeping the temperature of the object at a constant level, the option of simultaneous stirring, the heating velocity and the space that the apparatus occupies.

The energy costs are determined by the efficiency and the heat transfer to and into the product. In general, lower efficiency apparatus use more (electric) energy to transfer a given amount of heat into the product compared to higher efficiency apparatus. Alternatively, a lower efficiency may also be the result of energy usage for other processes than heating the product, such as an in-build magnetic stirrer or water bath pump to circulate the heated water in the unit. Compared to the energy that is required for heating and lighting of the premises, the energy usage of the heaters in the pharmacy is however quite modest. Differences in efficiency are therefore only described qualitatively.

Table 28.1 Qualities of various different heaters

Heater	Investment	Energy consumption	Speed	Use space	Thermostating	Built-in stirring
Gas stove	+	–	–	–	–	–
Electric heating plate	±	±	±	+	±	+
Heating lamp	±	±	–	±	–	–
Water bath	±	±	±	±	+	–
Microwave	–	±	–	–	±	–

+ favourable, ± moderate, – unfavourable

Table 28.2 Thermal conductivity of some materials

Material	Thermal conductivity coefficient ($W.m^{-1}.K^{-1}$)
Copper	380
Iron	50
Stainless steel	20
Glass	1
Water	0.6
Air	0.02

Differences in thermal conductivity of various materials may play a role in the choice of a heater and the choice of the material of a heating vessel as well. A high thermal conductivity coefficient means a high conductivity, see Table 28.2.

28.5.2 Ultrasonic Baths

28.5.2.1 Application

Ultrasonic baths are used to increase the dissolution rate of slowly dissolving substances, especially when a substance is not very heat resistant. However, it should be considered that the product intended to be used in the ultrasonic bath should not be sensitive for sonochemical and sonomechinal alterations and/or degradation, which might be an issue for macromolecules with complex three-dimensional structures such as proteins.

28.5.2.2 Description

An ultrasonic bath contains water and creates waves from its walls with a frequency of more than 20,000 Hz. A container (usually glass) with solvent and the substance to be dissolved is placed in the water. The sound waves amplify in the water and pass, via the container wall, into the solvent. The powerful vibrations of the liquid increase the movement of dissolved molecules from the surface of the crystals into the solvent. This increase occurs at the micro level and does not lead automatically to a homogeneous solution. Therefore, the bulk of the solution should be stirred from time to time. The ultrasonic bath may include a bath that may be equilibrated at a fixed temperature by means of an electric heating source and thermostat.

28.5.2.3 Procedure

The same precautions about the water quality should be taken with an ultrasonic bath as with a water bath for heating purposes (see Sect. 28.5.5). Although ultrasound is not audible to the human ear, resonance tones are created within the audible range, which may be perceived as annoying. Therefore, ear protection and placement in a separate room might be advisable.

28.5.3 Gas Stove and Gas Burner

28.5.3.1 Application

Gas stoves and Bunsen burners are used for quickly bringing to the boil water or aqueous solutions. However, accurate adjustment of the heat input is difficult and it is not possible to set the temperature. Both a gas stove and Bunsen burner do not take up a lot of space, but a gas supply is required. The room should be well ventilated because of the open fire, and no flammable liquids, vapours or gases should be present.

28.5.3.2 Description

The gas stove or Bunsen burner mixes natural gas with air to an optimally burning mixture. The tips of the flame reach temperatures of 1500 °C. The produced heat is directed towards the container wall using a diffuser. Through the wall, conduction to the product occurs, in which the heat spreads by conduction and convection. Domestic gas stoves or a Bunsen burner usually are combined with a tripod. On top of the tripod, a metal gauze is used, sometimes with a pressed ceramic core or ceramic plate. The latter is the easiest to clean. The container should have a flat bottom for the proper conduction of the heat from the gauze or plate.

28.5.4 Electric Heating Plate, Immersion Heater and Heating Mantle

28.5.4.1 Application

Electric heaters can be applied in the same way as gas stoves or Bunsen burners. Since these heaters have no open fire, they are generally safer. A negative aspect is that they operate more slowly and have a lower efficiency. In general, electric heaters can be better controlled than gas burners, which means that overheating can be prevented more easily.

28.5.4.2 Description

An electric heating plate converts an electric current largely directed through resistance wires into heat. A cast iron, stainless steel, or ceramic plate conducts this heat to the container with the mass that should be heated. Ceramic has a few advantages since it is lighter, heats faster and can be cleaned more easily compared to cast iron. Compared to stainless steel, it conducts heat better. However, heating the plate requires time. The container should have a flat bottom for optimal conduction of the heat. Most heating plates can be adjusted to various levels of heating, which allows control of the temperature within certain limits. The heating plate can be combined with a magnetic stirrer and a functionality to stir the product with the desired speed (low, moderate or high speed). A heating plate uses little space, but requires an electricity connection.

An immersion heater consists of resistance wires embedded in ceramic material and mounted in a stainless steel spiral. The immersion heater should be placed in the liquid to be heated and is often connected to an immersion thermostat. For the heating of larger volumes, the use of a container with a heating mantle is more efficient. The resistance wires are embedded in the mantle, and thus, the mantle conducts the heat to the product. Another option is the use of a heating tape or blanket that can be wrapped around the container.

28.5.5 Water Bath

28.5.5.1 Application

The most important reason to choose a water bath for heating purposes, is the controllability of the temperature, since this cannot exceed 100 °C. Using a thermostat, the temperature can be controlled at any temperature between room temperature and 100 °C. With a cooling unit, lower temperatures are also possible.

28.5.5.2 Description

A water bath consists of a tank that is equipped with heating spirals with resistance wires, in which electricity is converted into heat. The tank is filled with water. The heated water conducts the heat to the container with the product, either by direct contact or through generated steam ('boiling water bath'). In principle, a water bath is equipped with a thermostat. The welds of the tank should be of good quality, otherwise leakage may occur as a result of calcification. The heating spirals are best embedded in the wall of the tank for the same reason. Tanks that consist of stainless steel can be used with purified water, which eliminates the risk of calcification. Purified water is too corrosive for less resistant metals. The shape of the container that needs to be heated is not important, since both water and steam can cover non-flat surfaces well.

28.5.5.3 Procedure

The water bath should be filled to approximately two thirds of the volume with water. After incidental use, the bath should be emptied and subsequently dried to prevent microbiological growth. When used daily, the water bath should be brought to 100 °C half an hour before use, and subsequently brought to the desired temperature to reduce the risk of microbial contamination of the water. Moreover, the bath must be emptied and dried at least once in 2 weeks for the same reason.

28.5.6 Heating Lamp

28.5.6.1 Application

A heating lamp may be applied for melting fats. Its advantage compared to a water bath is that a heating lamp bears no risk of bacterial contamination and contamination with water droplets. However, the surface of the fats is exposed to intensive radiation, to which the fat should be resistant. Moreover, the heat transfer is not controllable and the risk of overheating exists.

28.5.6.2 Description

A heating lamp converts electricity through a resistance filament into electromagnetic waves. These waves produce radiation heat that is absorbed by objects. The lamp is placed above the substance to be heated; a wide container is preferred for optimal heat transfer. The amount of heat cannot be regulated and depends highly on the distance from the lamp to the product. It is therefore advisable to place a thermostat near the heated product to check whether the temperature is sufficient or too high. The lamp heats quickly after it is switched on.

28.5.7 Microwave

28.5.7.1 Application

Microwaves can be used to heat polar substances directly without the use of a medium such as air or water vapour to conduct the heat. Therefore, no energy is lost to the heating of the heat source itself and only little to the container with the substance to be heated; the latter only heats up from heat coming from the content. Especially small quantities can thus be heated more quickly than with other methods. Its main application in pharmacies is selective heating of water or another polar solvent when heating of the other compounds or phase is undesirable, such as:

- Drying of herbs and eradication of vermin that may be present
- Drying and hardening of coatings
- Drying of granulates
- Regeneration of saturated silica gel being part of a container
- Quick heating of small volumes
- Quick defrosting of small volumes

A short heating time may be advantageous and meaningful because of a minimal temperature burden on the product.

28.5.7.2 Description

A microwave converts electricity into electromagnetic waves. The altering electromagnetic field sets molecules with a dipole, such as water, in motion. During this process, friction heat is produced. The electromagnetic waves have a frequency range of 100 to 1 million MHz, which corresponds to a wavelength of 0.03–300 cm. The efficiency of the conversion of electricity into electromagnetic waves is approximately 50%. The energy source (microwave) is placed in a space (oven) with walls that are made of e.g. stainless steel, enamel or aluminium, which reverberate the waves. Most ovens contain a

metal fan as well. This fan is not only meant to move the air in the oven, but also to mix the electromagnetic fields, in order to reduce the occurrence of nodes and antinodes. These hot spots may nevertheless occur as a result of the shape of the vessel in which it is heated, especially due to curved surfaces.

28.5.7.3 Procedure

For justified use of this heating method, the next points should be considered:

- The material that has to be heated and the container that is being used should be permeable to electromagnetic waves. Glass and many plastics are, but metal (e.g. aluminium foil) and melamine resin are not.
- The amount of energy that is required to heat the material depends on the polarity of the substance. Heating of less polar materials (such as paraffins) requires more energy (thus for a fixed setting of the microwave: more time) than polar materials.
- Microwaves penetrate about 3 cm into an object. Therefore, within larger masses the heat must be spread by conduction, which requires time.
- Heating or defrosting of small volumes may result in inhomogeneous heat transfer to the solution. This may result in hotspots that may negatively impact the container (e.g. plastic infusion bag) or drug stability of thermolabile drugs and excipients.
- The inside of the oven must be kept clean, in order for the surfaces to remain reflective. To prevent leakage of radiation the door must be kept clean as well and the closure must be checked.

28.6 Grinding, Mixing and Dispersing Apparatus

Mixing, dispersing and milling are three of the most used preparation methods, see also Chap. 29. By mixing a heterogeneous physical system is transferred into a more homogeneous one (examples|: liquid-liquid; gas-gas; solid-solid; liquid-solid). When particles of one material are distributed in a continuous phase of another it is a dispersion. By grinding/milling particles size is reduced. Mixing is achieved by axial, tangential or radial flow. These concepts are clarified in Fig. 28.7 and applied in the description of the apparatus. Blending substances without reducing the particle size during the process characterizes so-called low-shear mixing. High-shear mixing is used to disperse one phase or ingredient into the main continuous phase (liquid) with which it would normally be immiscible (e.g. emulsions and suspensions). See Chap. 29 for the terminology of mixing, dispersing and grinding.

This section discusses subsequently the mortar with pestle, the Stephan® mixer, the rotor-stator mixer, the planetary mixer, the beaker mixer/blender, the three roll mill, the coffee grinder, the Topitec® mixer and Unguator® mixers.

28.6.1 Mortar with Pestle

28.6.1.1 Application

The mortar with pestle are the basic tools of the pharmacist. They form a hand operated milling (pulverising), mixing and dispersing apparatus. The mortar is used for the preparation of ointments, creams, emulsions, suspensions, gels, pastes, solutions, triturations and granulates up to a scale that reasonably can be processed by hand. The brass of bronze mortar is also used for crushing plant materials.

28.6.1.2 Description

A mortar with pestle is a vessel widening to the upper side and a thick rod with a club form at the end, the pestle, see Fig. 28.8. A scrape card used for wiping off the mass of the wall is an essential attribute. A brass or bronze mortar distinguishes itself from the standard mortar in that the vessel usually is higher.

By shoving the pestle against the wall of the mortar a milling and dispersing effect results. Mixing takes place in a

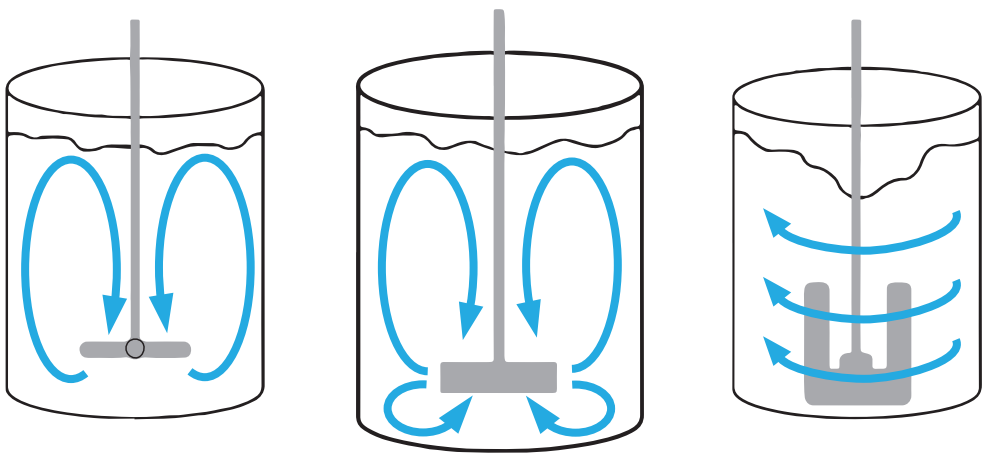


Fig. 28.7 Axial, radial or tangential flow

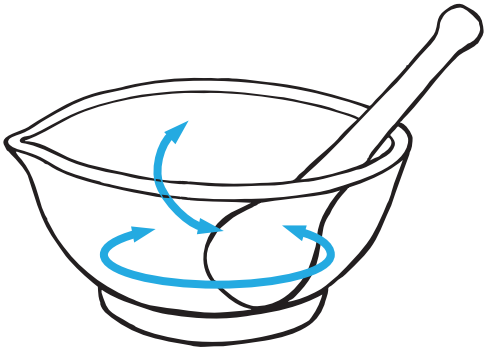


Fig. 28.8 Mortar with pestle

primarily tangential direction. In semisolid and dry mixtures a more or less axial movement results from ladling the mass with a scrape card. This is hardly possible in fluid mixtures. Triturations should regularly be released from the wall and shovelled around with a scrape card. Additionally it is useful to tap the mortar, held a little slantwise, against the table top to recollect the powder.

Material

The mortar is usually made of porcelain ('stone' mortar'), melamine resin ('plastic mortar') or stainless steel ('metal mortar'). The pestle is made of smooth or rough porcelain or of smooth melamine resin. When a pharmaceutical substance is ground in a mortar some losses may result from 'sticking' to the wall of the mortar and the pestle or by being electrostatically charged and subsequently being drawn away by the air of any dust suction installation. Sticking to the wall is most pronounced in rough porcelain mortars. Electrostatic charging is expected to be most substantial in melamine resin mortars.

Traditionally, a porcelain mortar has either a smooth or a rough inner wall. A rough inner wall facilitates a more forceful rubbing, resulting in more friction; shearing forces then will be larger so a rough mortar is expected to be more suitable for pulverising than a smooth one. On the other hand pharmaceutical substances appear to stick more effectively to a rough wall ('into the pores'). Therefore, a general distinction in the effect of preparation in either a rough or a smooth mortar cannot easily be determined in practice. As a rule of thumb a rough mortar is used for pulverising pharmaceutical substances. A smooth one is more suitable for mixing and the breaking up of agglomerates.

A melamine resin mortar is suitable for mixing and breaking up agglomerates, but not for pulverising. Additionally this kind of mortar should never be heated over 100 °C. Moreover coloured substances may give rise to difficult to remove smudges. A supplier suggests that stains may be removed by immersing the mortar in hot perborate solution at 80–90 °C.

A stainless steel mortar is suitable for mixing, not for pulverising. Additionally a stainless steel mortar lends itself for melting Hard fat for suppositories and fatty substances for ointments and creams. If necessary this mortar can withstand rather high temperatures. As a pestle only a melamine resin one should be used as a porcelain pestle might scrape off metal particles from the wall.

Furthermore plastic mortars and pestles are commercially available as a sterilised set. Disinfection and sterilisation of these kinds of materials on a small scale takes validation and thus is inefficient.

The material of the mortar has a substantial impact on the outcome of the preparation. An example is the preparation of Prednisone capsules 10–75 mg. In a rough porcelain mortar more substance 'sticks' to the wall (3–5%) than in a smooth one (2%). Moreover it has been shown that preparation in a melamine resin mortar causes losses resulting from electrostatic charging [16]. Using a stainless steel mortar results in no charging whatsoever.

However, any general conclusions on the relationship between the material of the mortar and the attainable mixing quality are not possible.

28.6.1.3 Operating Procedure

For pulverising, a rough porcelain mortar with a rough pestle is necessary; an excess of pharmaceutical substance is pulverised and subsequently the prescribed amount should be weighed. Mixing usually is done with a smooth porcelain, melamine resin or stainless steel mortar. For mixing, the mortar should be sufficiently wide to facilitate scraping the sides and turning around the mixture. However, if the mortar is too wide it will result in a higher rate of loss. It is obvious that the total amount of constituents to mix will have an impact on the mixing time. However no suitable practical data on this issue are available.

If low dosed pharmaceutical substances, coloured substances or easily electrostatically chargeable substances are to be mixed in a mortar it is best practice to primarily transfer a layer of bulking substance into the mortar, put the critical substance on top of that and finally cover it with another layer of bulking substance: the so-called wrapping method, see Chap. 12. If a porcelain mortar is rough and has large pores, the wall can be rubbed with an excipient first, to block the pores. This is not necessary when a mortar with a smooth wall is used.

Mixing is achieved by stirring around the mass with the pestle. The stirring should be interrupted regularly to scrape the material from the wall with a scrape card. Powder mixtures should be shovelled around regularly and also the mortar should be tapped on the table slantwise too loosen the

powder. Agglomerates are being broken up by vigorously rubbing by a suitable means (see Chap. 29). This should always imply small amounts, because otherwise vigorous rubbing is not possible.

28.6.2 Stephan Mixer

28.6.2.1 Application

The Stephan mixer is a combined mixing and dispersing apparatus. The brand name Stephan is used because of its specific construction and qualities. The apparatus can be used for the preparation of ointments, creams, emulsions, suspensions, gels, pastes, solutions, powder mixtures and granulates. The apparatus was originally developed for food processing.

The mixer is not suitable for grinding crystalline substances. However, lumps and not too strong, large agglomerates can be broken up. For the mixing of powders it should be taken into account that the shearing forces are relatively weak compared to a mortar and pestle; they frequently fail to break up agglomerates.

28.6.2.2 Description

The Stephan mixer is available in different sizes, varying from 5 to 40 L for small scale preparations. The choice for the size will, not taking into consideration the available space in the pharmacy, depend on the volume of the batches. The vacuum version with a mantle is only a standard option for the smallest model; for the larger sizes it can be ordered as an optional feature. The larger sizes can be tipped over to facilitate the emptying of the bowl.

At maximum speed the mixer produces shearing forces at such an extent that they emulsify mixtures of water and oil. Only the rotor-stator mixer generates a higher shear force in fluids. During mixing an appreciable rise in temperature will occur, especially at higher speeds. If a mantle is available the contents of the bowl can be heated or cooled. The application of vacuum is relevant if air must be prevented from being whipped into the mixture.

The centrally mounted shaft is provided either with two stainless steel knives mounted in propeller position or with a mixing vane. The high rotation speed of the knives or the mixing vane down in the bowl results in an intensive mixing. The mixing vane provides a tangential and radial flow and additionally turbulence, See Fig. 28.9.

A plastic scraper, placed inside the bowl, facilitates scraping down the mass from the wall of the bowl, resulting in even better mixing.

The Stephan mixer requires a 380 V (3 phase) socket. The vacuum is realised with a small built-in vacuum pump. For the mantle a connection with a cooling water supply (usually tap water) and a drain is required.

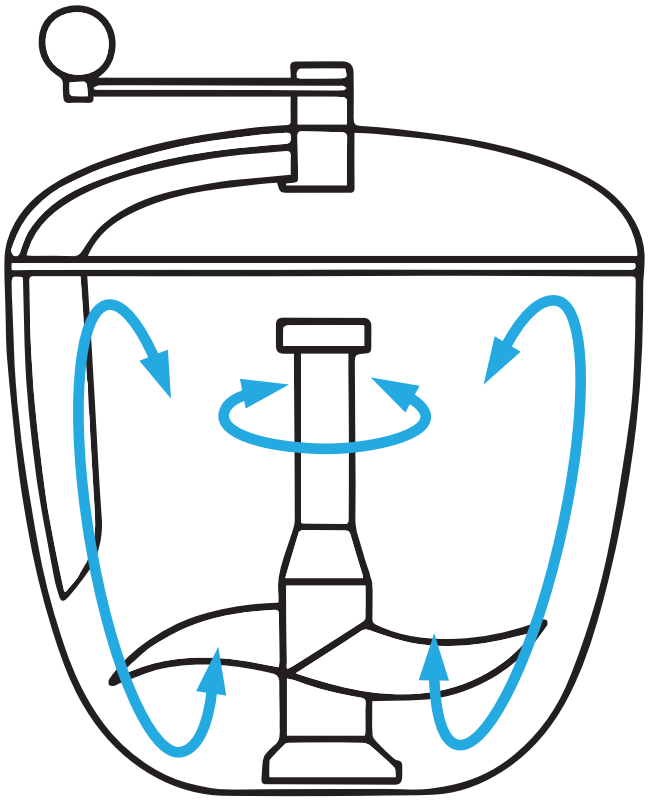


Fig. 28.9 Stephan mixer

28.6.2.3 Operating Procedure

The constituents to be mixed are being fed into the bowl with the mixing vane or the knives. When mixing fluids, the fluid with the least density is preferably fed in at the bottom. A fluid with a higher density, fed in on top of a fluid with low density will generate a beginning of mixing as the heavier fluid will sink through the lighter one to the bottom. The mixing bowl is closed with the lid, not only to shield from splashing but also to be able to pull a vacuum as well as to fix the scraper that is mounted in the lid. If possible and desirable vacuum is applied subsequently. Mixing should start at low speed to prevent splattering of unmixed constituents against the inner side of the lid. Subsequently a higher speed is applied step by step. Depending on the consistency of the mass and the rate of filling it may be necessary to stir the mass in between by hand with a spatula. Be aware that insufficiently mixed mass may splatter onto the inner side of the lid. If emulsification is the objective the mixing vane should run at maximum speed for at least one minute. The precise adjustment of the apparatus depends on the nature of the preparation, the size of the batch and from the required sequence of adding the individual constituents. These adjustments have to be validated.

The shaft with the mixing vane should be greased regularly with a little soft paraffin. Additionally it is advisable to mount a non-return vessel between the bowl and the vacuum

pump. This non-return vessel will collect any fluid that inadvertently could be sucked out of the bowl, keeping the vacuum pump dry and clean. Should, however, some fluid enter the pump, at least the pump should run a couple of minutes 'dry' to prevent erosion. However in this case it is better to demount the pump and clean and dry all its parts.

Cleaning of the mixer seems to be easy, however this must be done quite meticulously. Almost all parts can be demounted and cleaned separately. In any case extra attention is necessary for several connection points, the thermometer, the inner side of the pressure gauge and the inner side because they are provided with a rubber ring or contain a difficult cleanable screw thread. The apparatus does not contain its own drain, therefore the cleaning with soap water and the rinsing of the inner side requires a considerable amount of time.

The apparatus requires relatively little maintenance. For periodical servicing of the engine, the bearings, the vacuum pump and the seals of the shaft a specialised mechanic is necessary.

28.6.3 Rotor-Stator Mixer

28.6.3.1 Application

The rotor-stator mixer is used for the preparation of suspensions, emulsions and solutions. The apparatus is not suitable for mixing high viscosity fluids nor for grinding of crystalline particles. For dissolving relatively easily soluble substances it is easier to apply a mixer with a mixing vane or a magnet stirrer instead. Keeping a suspension homogeneous during filling is better achieved with a stirrer with a well-designed mixing vane than with a rotor-stator mixer. The rotor-stator mixer is a dispersing apparatus in the first place, also suitable for breaking up agglomerates. Rotor-stator mixers may be suitable for the preparation of suppositories. For conditions see Chap. 19.

28.6.3.2 Description

The rotor-stator mixer is a mixing and dispersing apparatus consisting of an engine with an axis on which a rotor is mounted. The rotor comprises a series of vertically placed knives. The rotor turns with a very small tolerance inside the stator consisting of a cylinder with slits. The rotor, spinning at high speed, pumps the product through the slits of the stator, see Fig. 28.10.

The mixer causes a tangential, a radial and an axial flow. The mixing and dispersive effects are very intensive at the moment that the product passes the mixing head. High shearing forces that are required for dispersing, result from the narrow slits of the stator, the friction among the particles in the fluid and from the reduced space between rotor and stator.

The high shearing forces occurring during mixing cause a considerable amount of heat, and thus cooling may be necessary. However this heat can also be used for improving the rate of dissolution.

Optimal Speed and Mixing Effect

Increasing the spinning rate will raise the tangential flow rate and thus extending the chance at creating a vortex. Air will be sucked into the product and part of the added energy is lost in establishing the vortex. At a lower speed the chance of insufficient dispersive action and mixing exists. So the optimal spinning speed is the one where a vortex just evolves. This could imply that the mixing effect in the body of the product might be less intensive. Therefore, the volume of mass determines the size of the rotor-stator mixer. The supplier gives rough outlines for this. As a rule of thumb the rotor-stator mixer can run effectively if one third of the shaft is submerged in the product. If the shaft is inserted too deep into the fluid the product might be too close to the upper bearing with the risk of contamination and damage to the engine. Some models are provided with an overflow opening in the upper part of the shaft. The fluid should not discharge from this opening. Anyhow the determination of the relation between amounts of mass to produce, the size and form of the mixing vessel and the choice

(continued)

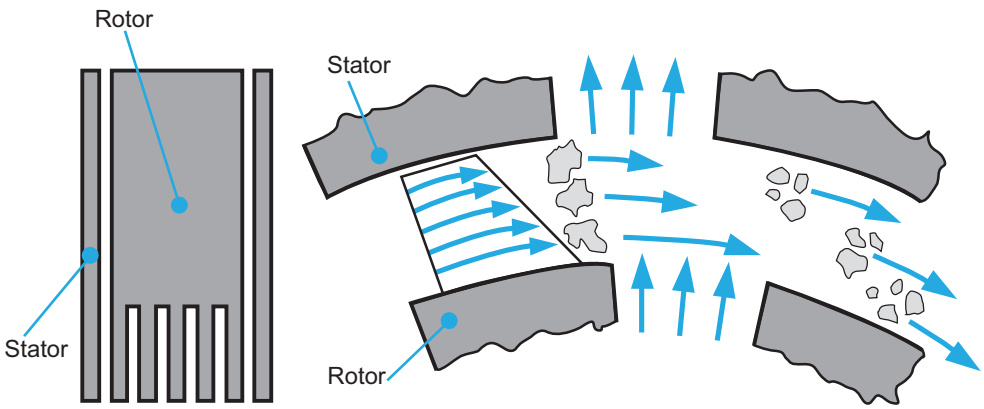


Fig. 28.10 Rotor-stator mixer, lengthwise section (**a**) and part of cross section (**b**)

of a rotor-stator mixer can only be achieved by validation of the mixing procedure. Additionally it could be considered to place the shaft slightly slanted or eccentrically in the vessel, or to move the vessel and its contents up and down under the rotor-stator mixer.

28.6.3.3 Operating Procedure

To control the possible noise nuisance the rotor-stator mixer should be placed in a separate area ('noise room'). The operator should bear ear protection.

Noise levels are expressed in dB(A), an abbreviation for decibel-A. This sound level is adjusted for the frequency of the sound, because the ear is more sensitive for high than for low tones. Damage to hearing can occur from 80 dB(A). From this level the employer is required to provide hearing protection. Starting from 85 dB(A) employees are required to wear hearing protection. There are five types of hearing protection equipment. In increasing degree of effectiveness, these are: cotton wool, earplugs, earplugs, earmuffs and ear plastics. In the pharmacy equipment can be present at which hearing protection is mandatory: some rotor-stator mixers and tube closing machines. In the room where this equipment is used, there should be as few as possible people present during the preparation.

Large rotor-stator mixers and the accompanying vessels should be solidly mounted.

The rotor-stator mixer must never run dry. Without fluid, overheating occurs with risk of short circuits or affecting the dispersing head. The rotor-stator mixer generates a relatively high level of aerosols. To prevent the operator from exposure to those aerosols, the upper side of the vessel could be covered or placed under an exhaust.

Fill the vessel with the fluid in which other fluids or solid substances are to be dispersed. Place the shaft at the correct height (e.g. 1 cm above the bottom) in the vessel. Switch on the engine and gradually turn up the running speed. Be aware that switching on immediately at full power will raise strong reaction forces that might destabilise the placing. The fluid that is pumped by the rotor through the stator will be replenished at the down side of the head by hydrostatic pressure. Sometimes, the fluid that is sucked up can carry along the vessel which then might be sucked onto the dispersing head. Therefore, the vessel should be kept steady with a firm grip with the free hand. Glass vessels might easily break when being touched by the spinning mixer.

Next, the solid substances or fluids to be dispersed can be added; during this process the required speed might vary. Dispersing or mixing should be continued as long as it is determined by the validation process.

Products that are difficult to disperse or to moisturise should be moistened in advance with a small amount of fluid; after dispersing the remaining fluid should be added.

When the mass is dispersed homogeneously the rotor-stator mixer should be turned off. Subsequently the shaft is pulled out and held above the product to drip dry. If necessary the shaft is wiped with a scrap card.

28.6.3.4 Cleaning

To enable adequate cleaning the stator has to be removed from the rotor. Larger rotor-stator mixers are equipped with an extra bearing near the dispersing head to prevent the long axis from swaying. A seal, e.g. a ring that cuts off any fluid from penetrating past the rotating axis, protects the bearing against the product. Seals are made from graphite or ceramic material. Seals made of graphite are preferred in blocking fluid penetration; however, they are more vulnerable. Ceramic seals are much more expensive. The seal is the most critical part as any product leakage, e.g. caused by an impairment during the cleaning process, will affect the bearing. Moreover, serious contamination of the product itself will occur from bearing grease, mixed with rusty product remnants, entering the product mass, past the seal.

Cleaning should be done immediately after use by allowing the mixer to run in warm purified water with a small amount of detergent. Subsequently the mixer should run at least twice in a portion of fresh lukewarm purified water, until the rinsing water is clear and clean. This method is preferred if the rotor axis is equipped with an extra bearing near the dispersing head.

After each cleaning process the adequate function of the seal should be checked, e.g. using a piece of filter paper to test leakage on the axis past the seal. Additionally a shaft of this type should be demounted periodically by a qualified mechanic to check on any leakage traces. Parts that cannot be dried thoroughly after cleaning, e.g. because it is not suitable to demount the dispersing head, might be flushed with alcohol 70%. Finally all parts should dry in the air. Drying in a stove or warm drying cabinet is not advisable because this will also dry the bearing grease.

Depending on manufacturers instructions an operator could demount the shaft. In that case all separate parts are cleaned with soapsuds prepared from soap and hot water. However, soap entering the parts with bearings should be avoided at any cost. Subsequently the parts are well rinsed with purified water and dried with absorption paper.

28.6.4 Planetary Mixer

28.6.4.1 Application

The planetary mixer is used for the preparation of creams, ointments, emulsions, suspensions, gels and light viscous fluids. The planetary mixer is developed primarily for the food preparation and thus not especially designed for pharmaceutical preparations. The shearing forces during mixing are considerably less than those of the rotor-stator mixer (see Sect. 28.6.3) and those of the Stephan mixer (see Sect. 28.6.2). This mixer therefore is not suitable for grinding particles or to break up agglomerates.

28.6.4.2 Description

The eccentrically placed stirring mechanism rotates around its own axis. The axis also makes a rotating movement in the vessel. Therefore, movement of the stirring vane is the same as a planet that rotates around its own axis as well as around the sun, hence the name planetary mixer, see Fig. 28.11. The mixer causes mainly a tangential and a radial flow. The mixing is very intensive.

There are mixers available with a mantle to heat, cool or isolate the contents of the bowl. The choice of the vane depends on the kind of product that is prepared. Most products will be prepared using the vane with the anchor form (also called "K-arm"). The so-called whisk vane is less suitable for fluid or semisolid products as this vane will easily beat in too much air. To prevent splashing product from the bowl during mixing some apparatus are equipped with a lid or splashboard that will completely or partly close off the upper side of the bowl.

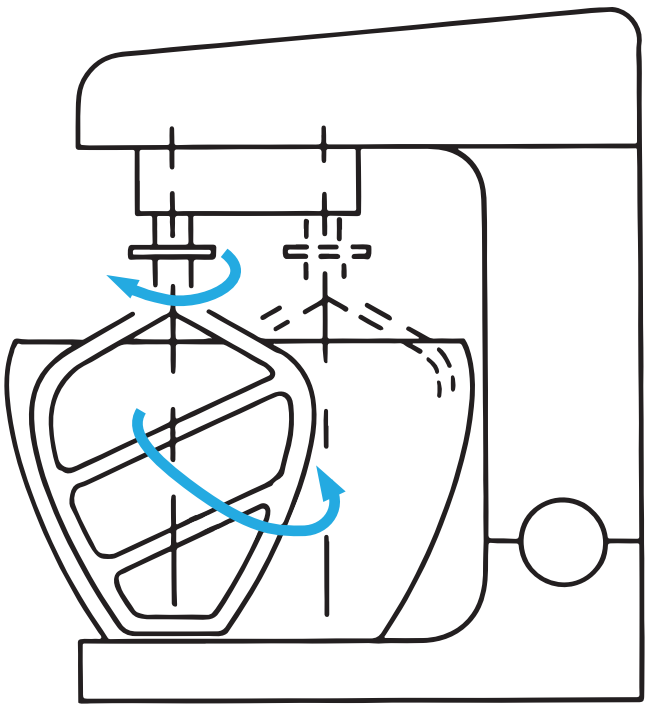


Fig. 28.11 Planetary mixer

Planetary mixers are available in different sizes, from kitchen apparatus to small industrial machines. The choice for the format of the mixer will, except from available space in the pharmacy, depend on the batch volumes. The apparatus can be cleaned easily, because both bowl and stirring vane can be detached from the apparatus. A maintenance agreement should be concluded, especially concerning larger mixers.

A relative disadvantage of planetary mixers is that they cannot run under vacuum. However, a good closing lid has advantages because it reduces the risk of microbiological contamination and of evaporation of water.

28.6.4.3 Operating Procedure

The stirring vane is attached to the apparatus and a part of the constituents to mix are transferred into the bowl. Fluids with the lowest density are preferably placed at the bottom of the bowl. When another fluid with higher density is placed on top, its gravity will already start the mixing process. Subsequently the mixer is switched on at low speed. The speed should then gradually be increased until the desired one. During mixing other constituents could be added. The speed never should be turned up to such a level that air is whipped in or the mass could spill over the rim of the bowl. This risk can be limited by placing a lid or splashboard.

In the case of viscous products the contents should be released from the wall with a scraper by hand, because in the immediate vicinity of the wall hardly any mixing takes place.

The mixing bowl and the stirring vane are usually cleaned by placing them in a washing machine.

28.6.5 Beaker Mixer/Blender

The blender may be used for small scale preparation of emulsions, suspensions and solutions. The apparatus is not suitable for grinding crystalline substances.

28.6.5.1 Description

The blender is a mixing and dispersing apparatus. At the bottom of the mixing beaker a mixing cross is situated consisting of four knives; two of them lying horizontally or are placed slantwise to the bottom; a second pair are placed slantwise upwards, see Fig. 28.12.

The mixing cross also causes a tangential and a radial flow and turbulence. During mixing a lot of air is whipped into the mass and after long mixing the temperature will increase.

Sometimes mixing cross and mixing beaker are one entity; in other cases the mixing cross is permanently attached to the engine block. Apparatus in which the mixing cross part can be detached from the engine are preferred because of the easier cleaning of the mixing cross.

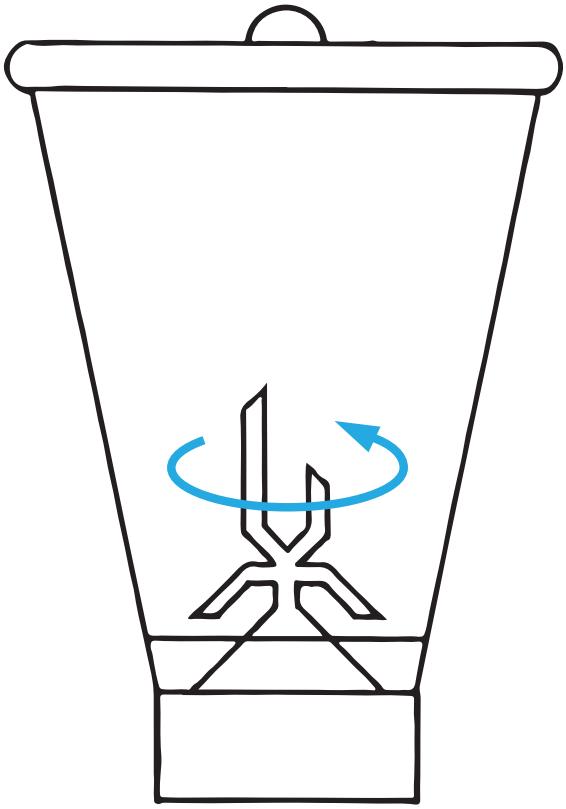


Fig. 28.12 Blender

28.6.5.2 Operating Procedure

The mixing cross part is attached to the engine. Subsequently the beaker is screwed on top of it. The constituents to mix are transferred into the beaker. The beaker may only be filled up to half its volume as otherwise insufficient mixing will result.

To prevent splashing contents from the beaker it should always be covered with a lid. Subsequently the mixer is turned on. Sometimes it may be necessary to release the mass from the wall with a scraper. When the mixing beaker is detached from the engine block it is obvious that the mixing cross part should stay in place to prevent the contents from pouring out from the bottom. When the mixing cross part is one entity with the engine block the contents must be poured out before the beaker is detached. Extra attention should be paid to the mixing cross and the duct and the bearings of the axis during the cleaning process.

28.6.6 Three Roll Mill

28.6.6.1 Application

A three roll mill (or ointment mill) is used to disperse solid substances in a semi solid or thick fluid base. The constituents themselves should be mixed homogeneously in advance.

A three roll mill may be used:

- When the product mass is too bulky to be handled in a mortar.
- When the raw materials have ultra fine particles, such as zinc oxide, precipitated sulfur and substances indicated as 'micronised' (see Chap. 7). These powders have a strong inclination to form agglomerates. The three roll mill disperses those agglomerates in the semi solid base into the primary particles. After transferring through the three roll mill the mass should be mixed again (by hand or in a mixer) to distribute the particles evenly over the whole mass.
- To clear away whipped-in air. During the mixing of semi solid masses air is usually whipped in to some degree. This might result in the inability to fit the required mass into a tube. With the three roll mill the whipped in air is pressed out again from the mass.

If the transfer of a cream through a three roll mill is considered, it should be shown that the emulsion will not break.

28.6.6.2 Description

The three roll mill has, as its name already depicts, three rollers, usually made of ceramic material, having adjustable mutual clearances, see Fig. 28.13.

The mutual rotation speed of the rolls is, independent of the adjustments of their position, always different. Thus when a semi solid mass with incorporated agglomerates are transferred between the rolls and subsequently are transported from the slower to the faster roll, shearing forces are being exerted on the agglomerates, breaking them up into the primary particles.

The distance between the rolls can be reduced up to a minimum of 20 µm, thus principally enabling the grinding of crystalline particles to this size. Whether this is appropriate should be determined for each individual product. Commonly, preparations in the pharmacy will use raw materials with the required particle size.

At the end of the milling process the mass is removed from the last roll with the mounted scraper. The scraper (drain board) is made of stainless steel or plastic.

28.6.6.3 Operating Procedure

In case of processing creams and other products that contain volatile substances evaporation should be considered. This evaporation might occur in an irregular way, thus necessitating final mixing. The degree of evaporation will depend on the duration of the process and thus from the batch volume.

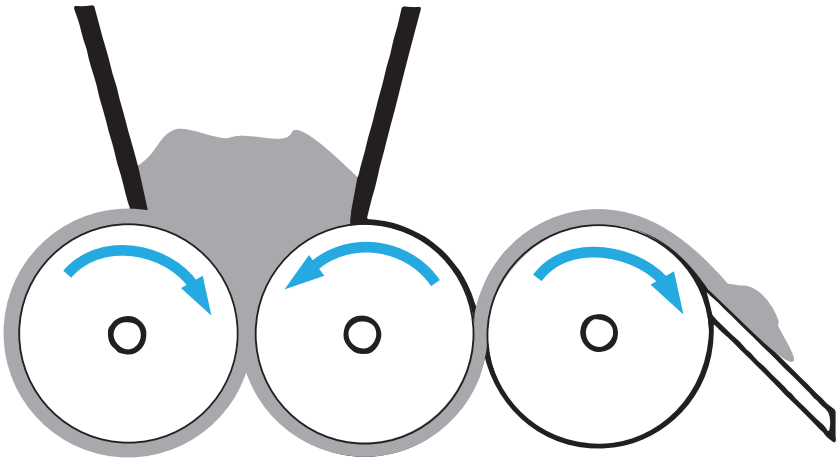


Fig. 28.13 Three roll mill

Transferring a product through a three roll mill will cause losses. So if the resulting mass is an intermediary product used in another preparation process, this loss should be taken into account.

Description Three Roll Mill Exakt®, Type 35 Resp. 50
Shiftable guides are used to adjust the working width if small volumes are to be processed.

The rollers are subsequently adjusted to their smallest slit width (position I). A small volume of product is then transferred between the back and the centre roller. If the mass is not or difficult to transport the slit width is increased until the mass appears on the scraper plate. Subsequently the slit width is narrowed again as far as possible to maintain a minimum of transport. This procedure will attain the highest possible shearing forces. With rotating rollers the rest of the mass is transferred either with a scrape card or a spatula onto the back roller by wiping off in the opposite rotation direction of the roller, or the mass is transferred into the loading funnel.

The processed mass is collected in a mortar and then again meticulously mixed.

To check the mass for any agglomerates, a couple of samples are randomly taken from the mass, flattened between two glass slides and then assessed by examining it against light. If agglomerates are still visible the mass is transferred once more through the three roll mill.

28.6.6.4 Cleaning

The apparatus should be cleaned immediately after use. The cleaning procedure has to be validated with a well designed procedure based on a worst case situation. If cleaning of a specific product or substance appears to be notoriously difficult, the product may play a role in the cleaning validation. Cleaning starts with pulling the plug from the socket. Also the funnel (if applicable) the guides and the scraper are removed. All parts are cleaned (using detergent and lukewarm water) and well dried. Subsequently the rollers are adjusted to their greatest slit width (position III). The rollers can be rotated by hand by means of a knob at the left side. Never run the rollers, engine-driven, during cleaning. The main part of remaining mass is then removed using a tissue.

The cleaning of the rollers is done with a tissue drenched with water in case of a water-soluble mass, or with a tissue drenched with liquid paraffin in case of a fatty mass. The flanks of the rollers and the places just below them must not be forgotten.

Finally the rollers should be wiped off and dried thoroughly with another tissue.

Ether or other inflammable organic solvents should never be used for cleaning; Switching on the motor may elicit a spark and cause a fire.

After cleaning the guides, the scraper and if applicable the funnel, are mounted again. All parts should be completely dry. Finally the apparatus should be covered with a dust cover.

At least once a year maintenance is required.

28.6.7 Topitec and Unguator

28.6.7.1 Application

The Unguator and the Topitec are mixing apparatus for semi-solid preparations. Mixing is executed inside the final container, see Fig. 28.14. The mixing process can be programmed after validation. During the mixing process the operator will hardly be exposed to substances.

28.6.7.2 Description

A mixing disc or propeller is mounted to a bar driven by a stirring engine. The bar is guided through the lid of the container or through the movable bottom. When placed inside

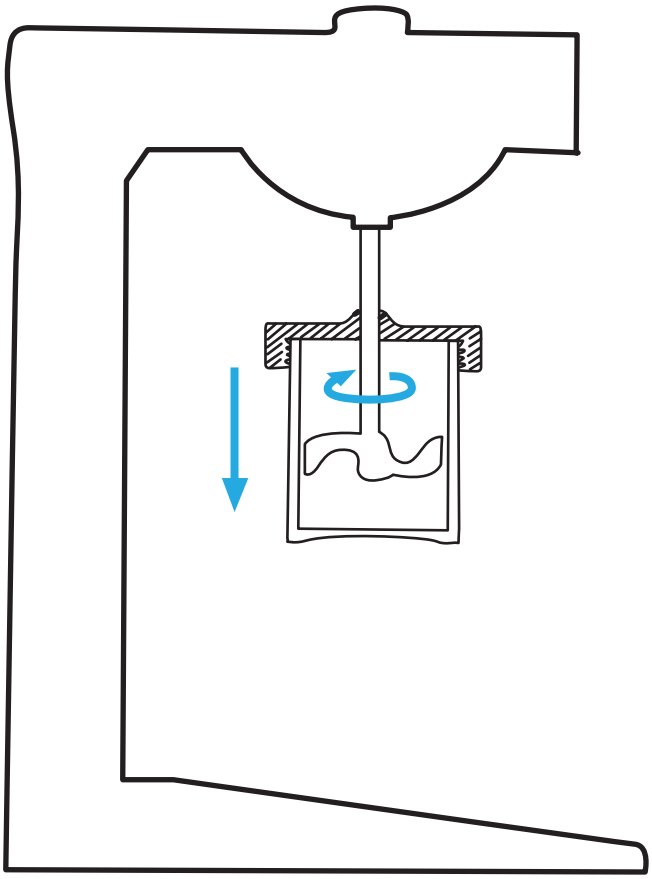


Fig. 28.14 Unguator, schematic

the mixing vessel (final container) this mixer causes, predominantly, a radial flow. Axial and tangential flow should be created by moving the vessel up and down.

28.6.7.3 Topitec

Three types of the Topitec are available. The most simple one is the Basic. The mixing vessel should be moved up and down by hand, which precludes standardisation of the preparation method.

The vertical movement in the type Automatic is executed automatically. The preparation programs (rotational speed and mixing time) are adjustable and can be stored in a memory. With the Automatic amounts up to 1 kg can be produced and the apparatus can be cleaned easily. The movement in the type Touch is also executed automatically.

28.6.7.4 Unguator

Of the Unguator three types are available: B/R; e/s and 2100. The B/R model requires moving the mixing vessel up and down by hand, which precludes standardisation of the preparation method.

The vertical movement in the type e/s is executed automatically. Rotational speed and mixing time are adjustable and programmable. With this type up to 500 g can be produced in one process. In the type 2100 up to 1 kg can be prepared and numerous preparation processes can be stored and reproduced for repeated execution.

28.6.7.5 Preparation Method

The suitability of the apparatus should be validated for each formulation and batch size. The following points of attention can be given, with reference to dispersion and mixing by hand with mortar and pestle (see Sect. 28.6.1, see also Chap. 29 on the basic operations on dispersing and mixing):

- Control of the product is not possible during processing. The visual control of homogeneity in the final product (and for instance the surface of the mixing disc or propeller) requires more attention.
- Physical stability may be challenged because of the high rotational speed of the mixing disc or propeller.
- Heating may occur due to mixing which may increase degradation of heat labile substances and may cause supersaturation.

The Deutscher Arzneimittel-Codex®/Neues Rezeptur-Formularium® (DAC/NRF) [17] issues following guidelines:

- Never mix any coarse or fine crystalline substances with the cream or ointment; just very fine pulverised, preferably micronised, solids or suitable concentrates should be used.
- Stir, if necessary, the active substance intensely with a small amount of base as a premix, comparable to the first step in geometric dilution using mortar and pestle.
- Apply the wrapping method: first transfer half of the base into the container, then add the active pharmaceutical substance and finally introduce the rest of the base.
- Remove enclosed air as far as possible before mixing.
- If heating is involved, stir gently and repeatedly within the cooling-off time.
- Don't process heat labile preparations.

Premixing in the container may be advantageous if insufficient homogeneity is obtained, especially when processing of low concentrations. The active substance is at first mixed with 5–10% of the base and subsequently the rest of the base is introduced. Another option is mixing at different rotational speeds: first at about 500 rpm and then at a higher speed.

Some creams are known to lose viscosity by mixing with this type of apparatus.

28.6.7.6 Testing and Validation

Validation has been described in [18]. The risk of inhomogeneity is most prominent with more viscous bases and with low dosed active substances.

Every formulation and batch size should be related to a specific rotational speed and mixing time. These should be documented and their correct application warranted. Samples should be taken from the most critical places in

the container: near the nozzle, at the bottom and in the centre of the mixing disc or propeller. The centre of the mass is a critical place as well: the mixing effect of the mixing disc or propeller sometimes fails at that particular place.

Validation is best started with a limited number of typical preparations. With experience from the results the range of products can be expanded gradually. Colouring agents may be used to indicate homogeneity, however it cannot replace the analytical assay of content regarding active substances with a variety of particle sizes or other properties. The Topitec and the Unguator are mainly used for individual preparations; a small overproduction could be used for continuous validation.

28.6.7.7 Packaging and Shelf Life

The mixing vessel is the container in which the product is dispensed to the patient. This container is not air and light tight which has to be taken into account. Substances that are vulnerable to oxygen or light may degrade. Products containing dithranol, tretinoin or isosorbide dinitrate, therefore should be packed in aluminium tubes immediately after the mixing process.

A series of container sizes are available. For the Unguator type containers several attachments can be supplied, i.e. cannulas for more accurate dosing. To push or screw in the bottom of the container requires quite some force: this will not work for all patients. The solution is then to pack in aluminium tubes instead.

28.6.8 Grinders

28.6.8.1 Application

In some instances a "coffee" grinder might be used in the pharmacy to pulverise (coated) tablets to process them into capsules. The application is contentious because the milling process cannot be controlled very well and the cleaning process needs attention (by validation). The apparatus is discussed as in pharmacy practice applications for the coffee grinder do exist. The only small scale alternative for milling of powders is the mortar, having the drawback that fragments might spill from the mortar and the result might not be fine enough; this is especially applicable for hard (coated) tablets.

Electronic grinders are primarily designated for the professional environment, such as hospitals. Important applications include: (1) pulverising tablets for the production of capsules with a personalised dose and (2) pulverising tablets for drug administration via an enteral feeding tube. A powder mixture for capsules should consist of particles <180 μm, and the size of all particles should be approximately equal to avoid segregation during preparation. This applies to the tablet powder as well as to other constituents of the capsule formulation. The particle size of powders to be administered via a feeding tube should not exceed 180 μm, to prevent blockage. Today, there are dedicated "coffee" grinders available (e.g. Severo 3.0 medicine grinder; IKA Tube MIll 100 control). These electric grinders were able to produce powders from tablets that meet the above-mentioned requirements. The homogeneity of the powders, in terms of particle size distribution, was good, while the size of 90% of the particles was [19].

When pulverising tablets, the cleaning of the device and the risk of cross-contamination have to be taken into consideration. If a coffee grinder is used for one of the purposes described it must be validated that this way of processing will actually yield a product that meets all requirements.

28.6.8.2 Description

In principle the "coffee" grinder is a beating mill. Grinding is realised by strokes of the knives that spin with high speed down in the milling space. A fine powder with a narrow particle size distribution is provided.

28.6.8.3 Operating Procedure

Reproducible milling and thorough cleaning are major points of attention. The efficacy of milling depends on the filling rate and the duration of milling, so this should be determined and documented for each individual substance. Variations in starting material properties, losses by atomised ultra fine particles and temperature increase should be considered. If mixing is aimed at, it should be assessed if the grinding and the temperature increase are acceptable and if a homogeneous blend will result.

Additionally the possibility of dust explosions should be considered. This is of special concern in a mixture of high concentrations of substances with elevated explosion risk. Usually substances of this type in the pharmacy are being offered as 'phlegmatised', which means that they are premixed with excipients that extinguish their explosion risk (such as benzoyl peroxide hydrated 25% water and nitroglycerin with 40% lactose).

28.6.8.4 Cleaning

The apparatus should be cleaned thoroughly to prevent any cross contamination. This procedure should be validated. Substances which dissolve slowly may play a role. A suitable procedure could consist of the following steps:

- Wipe the empty mill (including the knives) with tissues drenched in water.
- Repeat this with tissues drenched in ethanol 70–96%.
- Then let the grinder run with microcrystalline cellulose. The cellulose acts in this situation as a pharmaceutical inertial cleaning powder.

The Severo applies so-called rondels: thin round pieces of plastic that separate the turning crushing pestle from the tablet in the plastic cup. The use of rondels keeps the

Severo clean and eliminates cross-contamination risk. After grinding, water or a swallowing gel can be added to the cup, making intake by the patient very easy. One has to be sure, however, that no particles stick to the wall of the cup. The disposable attachments with knives of the IKA mill yield considerable waste. Recycling (with adequate cleaning following a validated cleaning procedure) should be possible but after a certain amount of time, the knives will get blunt.

28.6.9 Three-Dimensional Mixer

28.6.9.1 Application

The three-dimensional mixer is used for homogeneous mixing of powdery substances with different specific weights and particle sizes. Producing dry-to-wet and wet-to-wet mixtures is also possible. The mixing container turns in a three dimensional motion and the efficiency of this method comes from the use of rotation, translation and inversion according to the Schatz geometric theory [20] The mixing container is set into three-dimensional movement that exposes the product to always changing and rhythmically pulsing motion.

28.6.9.2 Description

A three-dimensional mixer consists of a mixing basket that can hold any form of container. The container is fastened in place in the basket which is moved. The basket's movement is driven by drive belts and an eccentric drive gear. The speed can be adjusted see Fig. 28.15.

28.6.9.3 Operating Procedure

Powders are transferred to a suitable container which is fitted in the mixer. According to validation results the mixing parameters are set and the mixing program is started. The advantages of this process are the dust free processing (closed container), minimum shear forces and no product separation.

28.6.9.4 Cleaning

As the mixer uses a closed container, claning is relatively easy. In principle only the container needs (validated) cleaning manually or in a dedicated cleaning apparatus.

28.7 Filling and Apportioning Apparatus

When the bulk mass is ready it has to be divided into portions with the quantity of one dose (capsules, suppositories or powders) or one dispensing unit (bottles or tubes).

This section will discuss subsequently:

- Filling apparatus for fluids
- Suppository molding apparatus
- Capsule filling and closing apparatus
- Tubes filling apparatus

28.7.1 Small Scale Filling Apparatus for Fluids

28.7.1.1 Application

Devices that are used to deliver a fixed volume per container are called dispensers or filling pumps. Apart from these, pumps are used e.g. to transfer the product from one vessel to the other.

Fluids that are portioned out in a pharmacy usually are solutions for external use and oral liquids. However, emulsions, suspensions and light viscous fluids are also being portioned out with dispensers or filling apparatus. Apportioning of suspensions and emulsions should always be executed under continuous stirring.

Fig. 28.15 Turbula Shaker Mixer

28.7.1.2 Description

The filling apparatus in the pharmacy usually is a dispenser or a peristaltic tube pump, see Figs. 28.16 and 28.17. For filling very tiny batches an injection syringe may be suitable as well.

Requirements for a dispenser or pump are:

- The dosing must be accurate, correct and reproducible.
- The apparatus or tubing should not discharge any foreign substances or particles (this should be validated and documented for each apparatus).
- The apparatus, tubing or the filling process should not be a source of microbiological contamination.
- The material that has immediate contact with the filled product should neither adsorb or absorb any substance.
- Parts that are in direct contact with the product should be designed for easy cleaning and drying and if necessary should be autoclavable (if tubes are used, common practice is to use disposable (sterile) tubing as cleaning(validation) is complicated).
- Consumables such as tubes should be economically efficient in use.

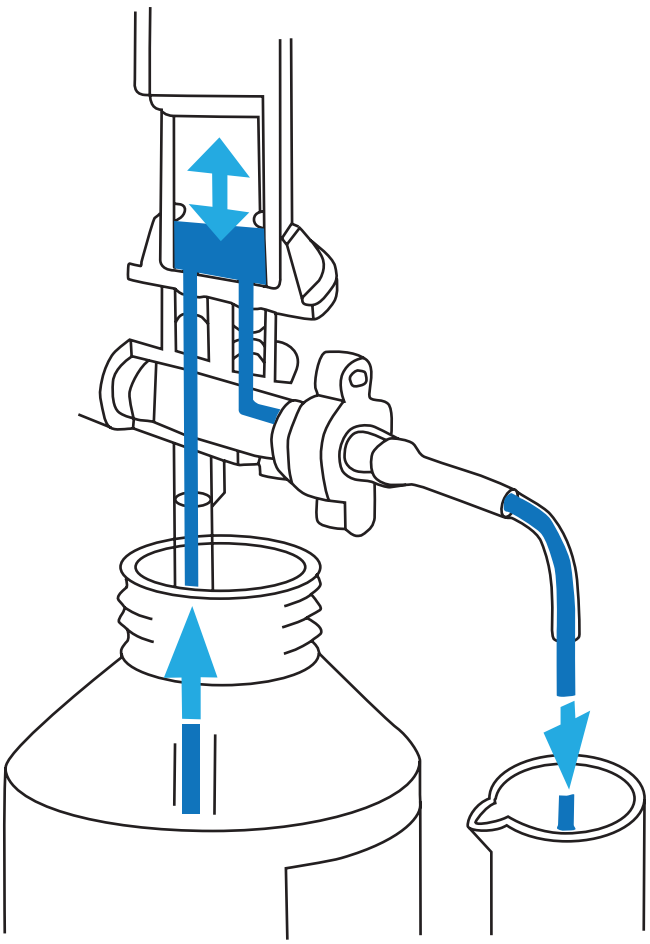


Fig. 28.16 Dispenser

28.7.1.3 Dispenser

A dispenser is a semi-automatic dosing and filling apparatus, allowing fixed volume dosing by hand. The apparatus consists of a glass cylinder, in which a piston is mounted. The piston is moved up and down by hand. The stroke can be adjusted to the desired dosing quantity.

The choice of the size will, apart from available space, depend on the quantities that should be filled per stroke and from the desired filling speed.

Most dispensers may be designed for laboratory use which might involve that general principles of hygienic design are not or insufficiently met. So all parts should be dismounted after use and be cleaned, rinsed and dried. For critical applications a cleaning validation is required.

Maintenance is usually carried out within the department. However, availability of spare parts is required.

Dispensers are available in different dosing ranges, e.g. from (small volume) 0.4–2.0 mL, increasing to (large volume) 300 mL. The material in direct contact with the product usually consists of inertial glass (piston, cylinder) and Teflon® (nozzle, suction tube). Some dispensers are made suitable for the dosing of aggressive fluids by a specific choice of materials.

The product is transferred into a pharmaceutical grade holding flask of which the screw thread fits onto the dispenser from which a Teflon suction tube stretches to the bottom of the flask.

The cylinder is stripped from air bubbles by pumping the piston a number of times.

The empty unit to be filled is placed under the plastic nozzle. Thereafter, the adjusted volume is dosed by moving the piston up and down by hand.

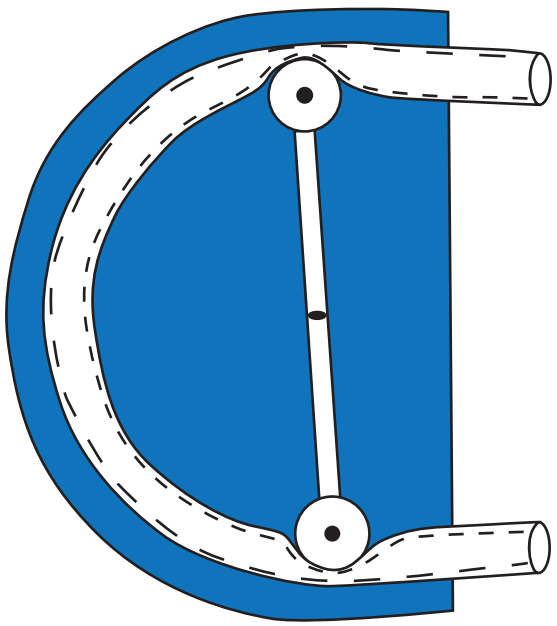


Fig. 28.17 Peristaltic tube pump (principle)

28.7.1.4 Peristaltic Pumps

Apart from the dispenser the peristaltic tube pump is generally used as a filling apparatus for liquids. Peristaltic pumps typically have dry casings and use rollers along with non-reinforced, extruded tubing. Generally, peristaltic pump refers to lower pressure and flow rate, whereas hose pumps refer to higher generated pressure and flow rate. What this part states is "non-inforced tubing and lower pressure" = peristaltic pump, and "higher pressure and reinforced tubing" = hose pump.

This tube pump facilitates the automation of the filling process. The most simple model is actuated by a foot switch. In more automated filling systems the empty container is placed under an electronic eye, actuating the pump, to fill the required volume.

Peristaltic pumps have no valves, seals or glands to leak, clog or replace.

The pumped fluid does not touch the pump itself – it is in contact only with a high-pressure, flexible hose or tubing, thus eliminating the risk of the pump contaminating the fluid, or the fluid contaminating the pump. Maintenance is confined to a periodic tube change, which takes minutes. Peristaltic pumps can run dry, reverse their direction of flow, and are self-priming. A tube pump is an example of a peristaltic pump for accurate dispensing. In pharmacy practice it can be a more or less pulseless, small or medium size bench top pump. It has manual or semi-automatic control. It has the principle of a positive displacement pump, used for dispensing a variety of solutions for oral, parenteral or external use and of different viscosities. They are easy to install and after training simple to operate.

For all pharmaceutical applications a hygienic design of the pump including tubing is very important to prevent microbial growth in the tubing. For parenteral use membrane filtration in the filling line is recommended to prevent foreign particles entering the parenteral finished product (the final sterile filtration should be carried out as close as possible to the filling point.

The heart of a peristaltic pump is the rolling pump head. Usually this will be a precision multi-roller pump head for accurate flows. The fluid is being drawn into the pump, trapped between two shoes or rollers and finally being expelled from the pump. The complete closure of the tubing, which is squeezed between a shoe and the track, gives the pump its positive displacement action, preventing backflow and eliminating the need for check-valves when the pump is not running.

The operator has to place special pump head tubing or special silicone dispensing tubing under the rollers of the pump head. The tubing to be fixed in the pump head can be either a separate short piece of special pump head tubing or it can be the tubing itself (in one piece). The pump head section divides the tubing in a suction part and a dispensing part. Fixating points in the pump head prevent the tubing in the pump head from sliding and moving during pump action. The pump head itself consists of several hard tube rollers that revolve within a C-shaped recess in which the silicon pump tube tightly fits. The rollers squeeze the tubing by rolling over, resulting in a peristaltic pump action with a suction effect. The rolling speed can be chosen by the operator. At the suction side an extension tube made of a pharmaceutical grade rubber might be attached to the silicon tube to dip into the stock vessel. This extension tube should be rigid to prevent it from collapsing during suction. The rubber material should be compatible with the product. That extension tube must be autoclavable as well. This tube should have a stainless steel notch at its end to prevent the suction tube from sticking to the wall of the vessel during suction. At the dosing side of the pump a compatible and autoclavable tube is mounted with, at its end, a filling needle (nozzle) made of stainless steel, to be fixed in a holder above the package to be filled. The filling needle can be sterilised or cleaned and stored dry.

Some special peristaltic pumps are equipped with a double pump head. This is to buffer the pulsing action by synchronising both pump heads in such a way that a more steady flow arises at the filling process. A drawback is that the assembling of such a pump configuration requires a lot of training of the operator and a good management of the (sterilised) materials as well.

Per product the specific pump (tubing) parameters and any other adjustable variables should be well documented, for instance pump speed, pump tubing specifications, type of pump head and specifications of extension tubings for the suction side and for the dosing side.

28.7.1.5 Pump Tubing

Both the inner diameter and the wall thickness of the pump tubing are of great importance. The manufacturer supplies obligatory guidelines. The supplier should deliver the tubing in a well labelled box, with a clear description about diameters and application purpose. Per pump model a set of tubing formats should be introduced, varying from large to small. The large ones, dose more fluid per unit of time than the small ones.

Only qualified silicone pump tubings should be used. Any tubing, not specifically designed for tubing pumps might have a poor chemical and physical material quality soon resulting in internal abrasion. This could lead to contamination of the product and to inaccurate dosing. For the dosing of parenterals some producers recommend the 'platinum cured' tubing. This rubber quality has a relatively low wearing off of extractable components.

The tubings, mounted on the pump, should be pre-rinsed with the product to be filled. This is to prevent dilution of the

product by retaining condensation water after sterilisation and to saturate any possible adsorption sites.

Pump tubings may easily adsorb substances, which could cause cross contamination or staining of the tubings. This problem may be approached differently:

- By single use tubings
- By using dedicated tubings
- By cleaning the tubings after use

The single use of tubings seems to be quite expensive. However, it may be an acceptable option when put in the perspective of the efforts coming with both other options.

Using dedicated tubings requires:

- Cleaning, rinsing and drying after use (or sterilising as a more reliable process than rinsing and drying). Drying may occur in drying hot air cabinets. The assessment of the correct drying time however is not easy; as a consequence, tubings might stay too long inside the hot drying cabinet. For sterilisation the best practise may be to let the tubing drip dry after the last rinsing phase, as far as possible, subsequently wrapping it into a special sterilisation-laminate pouch and finally steam-sterilise it. The steam will, by means of the vacuum pulses preceding the sterilisation process, penetrate the tubing fully and sterilise it externally and internally. Verify the sterilisation temperature recommended by the producer of the tubing. This should be at least 121 °C. For parenteral production disposable sterile tubing is state of the art.
- Storage of a large pile of laminate pouches with packed, sterilised tubings and filling needles
- Documenting the use of every tubing in order to remain within its shelf life

Cleaning tubes after use requires, in addition, the validation of the cleaning process, which is practically unfeasible.

Needles and nozzles should be cleaned very thoroughly regarding their tiny apertures. The effectiveness of the cleaning should be validated.

- There are several brands of pumps available used in (hospital) pharmacies. E.g. the Baxa pump from Baxter and the PharmAssist™ Dispensing Repeater Pump. For those systems various types of (disposable and presterilized) sets, tubing, and accessories are available

28.7.1.6 Automatic Liquid Filling Machine

The automatic filling machine is a tool for improving the precision of fillings, especially for small volumes, rationalising handling that are not precise enough during manual hospital preparation and saving time of staff. This results in better repeatability and reliability of filling, as well as making this critical process safer. In addition, automatic filling machines allow the transfer of products in a closed system from a sterile container to a final container that is also sterile; sometimes a step of filtration can be added. The risk of microbial contamination is thus greatly reduced. Finally, the automatic filling machines currently available on the European market can be adapted to activities of each hospital pharmacy. They offer the possibility of dispensing volumes of a few milliliters as well as large volumes (up to several liters). Among these automatic filling machines, it is possible to distinguish two main categories of equipment. The first category consists of automates with a pre-established software program and a repetition of the same movements. The second category is formed by robots, which are automates equipped with sensors and effectors allowing them to receive information from the environment in which they operate in order to acquire a certain autonomy.

Among the automated machines in hospital pharmacy, the most common category is liquid filling machines. These can be classified according to the filling technique used: volumetric, gravimetric or a combination,

- Volumetric system: Volumetric automates determine the quantity of liquid to be transferred into container by piston pumps, or by the number of rotations of a rotor, the diameter of the filling tube and its length (peristaltic pump) or by the motorised displacement of a piston (motorised syringe pump). See also 28.7.1.2, 28.7.1.3, and 28.7.1.4
- Gravimetric system: The gravimetric technology multiplies the density by the volume of the raw material in order to determine the weight to be transferred into the container, which is positioned on a scale.
- Volumetric and gravimetric system: These machines deliver the products to be dispensed by a volumetric system (peristaltic pump or syringe pump) associated with a gravimetric control system of the final volume of the container

28.7.1.6.1 Oral Liquids Filling Machine

The automated systems for the preparation of oral doses of liquids are based on the withdrawal of the liquid by a peristaltic pump and a gravimetric weighing control of the prepared container. Each container, presented under the pump which delivers the pre-set volume, is fed by means of a rotating disc. The traceability of all the steps is integrated. (See Fig. 28.18: example Automate Noodis [21]).

28.7.1.6.2 Injectables Filling Machines

Rotating filling machine.

For small scale batch injectable production in sterile vials or ampoules, apparatus based on rotational movement may be implemented in hospital pharmacies. The most widespread technique consists of feeding vials or ampoules or even syringes into a disk. This disk rotates and places the open container under the pump, which delivers the volume

Fig. 28.18 Automate Noodis

using a peristaltic pump. For the vials, the disk comes to deposit the stoppers then to crimp, for the ampoules the disk comes to seal it using a flame and for syringes, a stopper is fixed. Hospital systems are generally of reduced capacity compared to industry, they allow at maximum to fill a few thousand units per hour (examples are Ampoule Filler & Sealer type Rota® or Smartfiller®, AddedPharma).

Filling with pumps

Apart from the rotating filling machine, a number of small scale filling pumps for sterile preparations are available on the market which are based either on peristaltic pumps (see above 28.7.1.4) or volumetric pumps using syringes or piston. Depending on the software driving them, the level of automation may be more or less sophisticated allowing the provider to call their systems as automated compounding devices (ACDs) [22]. As an advantage ACDs can provide admixture preparation in a safer, more efficient, and more accurate manner. However, the benefits of ACDs can be realised only when the technology is used appropriately and depending on the form of automation [23]. The American Society of Health System Pharmacists (ASHP) has published guidelines for the safe use of these devices [24].

The automation with a peristaltic or a volumetric pump will dispense the product, starting from bottles or a master bag with starting material, in a final package like syringes (Smartfiller® Added Pharma) or bags (Exactamix®, Baxter). Other systems, combining several peristaltic pumps, offer the possibility of preparing different final packages like syringes, bags and portable infusion systems (Pharmoduct®, Dedalus). These automates are associated with a control system of the preparation process. Controls can be carried out by gravimetric measurement either during the process or on the finished product depending on the design. The loading and unloading of raw materials and finished products is done manually.

In Figs. 28.19a, 28.19b, 28.19c, and 28.19d some examples of automated preparation devices are shown: (a) MediMix compounder (IMF); (b) Medoc compounder (Icumed); (c) MibMix compounder (Hemedis); (d) Exacta Mix compounder (Baxter).

Fig 28.19a MediMix compounder (IMF)

Fig 28.19b Medoc compounder (Icumed)

Fig 28.19c MibMix compounder (Hemedis)

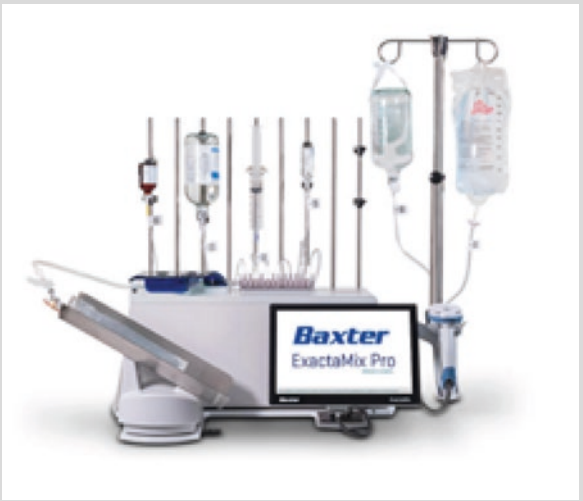


Fig 28.19d Exacta Mix compounder (Baxter)

Robots

Some filling devices may be qualified as robots although the distinction is sometimes arbitrary.

Two different options will be discussed: serial injector automates and automates with robotic arms

- **Serial injector** automates are based on translational movement of an injection head in two dimensions. The automate will transfer the active ingredient solution from a vial to the final package (bag, syringe or elastomeric pumps) using syringes fitted with needles (PharmaHelp V2®, Fresenius) or closed transfer systems (Equashield PRO® Equashield). These automates allow the use of different active ingredients in the same preparation run or the production of the same active ingredient in different final doses.

The currently available serial injector automates cannot or can be used for the reconstitution of the active ingredient as a powder or lyophilisate.

Medicines to be used and the final package are identified by data matrix labels and/or video recognition. Quantitative controls are carried out by gravimetric measurements during the several steps in the preparation process or only on the finished product depending on the equipment. Control software allows alerts in the event of malfunctions or sometimes error correction. Loading and unloading of starting materials and finished products are done manually. These

(continued)

robots might be integrated in a safety cabinet (Pharmahelp® V2 from Fresenius, Equashield Pro from Equashield). The Smartcompounder®, a removable system of limited size, allows installation in a biological safety cabinet or in an isolator. The dimensions and floor load of these automates are relatively small, allowing easier integration into existing production units.

- **Robotic arms.** Robotic arms are mechanised devices able to do complex, programmed and repetitive tasks mimicking human activity without requiring permanent human presence. This type of automation improves safety for the operator by protection and quality of the final products. With regards to operator protection, robots reduce exposure to hazardous substances and the risk for onset of wrist injuries by avoiding repetitive movements. Regarding the safety of final products, this type of automation allows to ensure a great repeatability in complex tasks, limits the risk of occurrence of human error, achieves traceability of each step and performs an « in process » control. This type of robot operates with at least one robotic arm (see Fig. 28.20).

The operation of the arm mimics human handling and the process is entirely computer controlled. This equipment requires a significant investment and close monitoring and maintenance which is balanced by operational profitability because of their potential for improving productivity, improving the quality of preparation and optimization of organisations.

Some examples are shown in Fig. 28.21 (Apoteca Chemo®, Loccioni, KIRO® Robot, Grifols, Smartcompounder from ACS Steriline robotics, RIVA® ARxIUM, IV station Onco®, Omnicell). They may also have an additional arm and peristaltic pumps.

The preparation is done from the transfer of commercial products in a final package (bag, syringe, elastomeric pump) via a syringe. Active ingredients as a powder can be used because reconstitution and controlled agitation are possible with this type of robot. Batch preparation or individual patient preparation is also possible. Quality controls are carried out by identifying commercial starting material and final package using data matrix labels, chips and/or visual recognition. Quantitative controls are carried out by gravimetric measurements throughout the

(continued)

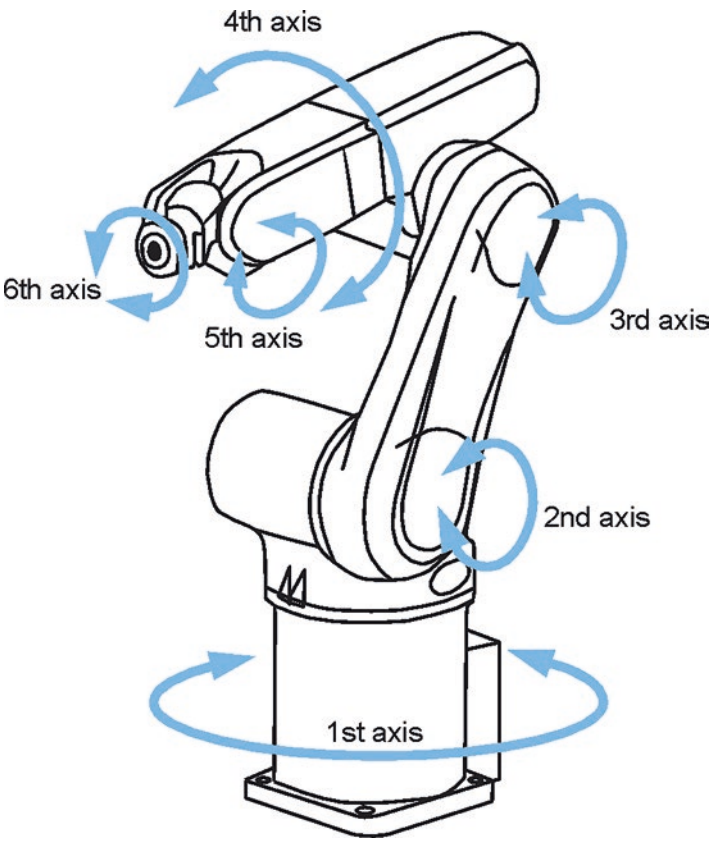


Fig. 28.20 6 axis motorized arm

Fig. 28.21 Some examples of serial injections automates and robots from JD Hecq [25]

preparation process. The final labelling of the preparation can also be automated.

This more complex equipment requires extensive and reliable software management to support the process.

Some of these robots have greater loading capacity and operating autonomy. In that case, less operator involvement is required and productivity is increased. These robots are integrated in safety cabinets, with under- or overpressure, or are integrated in isolators. Disadvantages are associated with the size and weight of these machines, the complex cleaning, the maintenance and the initial qualifications.

There are of course advantages and drawbacks of automation. Automation improves quality in comparison to manual preparation with better accuracy and it decreases the risk of microbiological contamination. It helps to improve productivity and by limiting human repeated handling automation prevents wrist injuries and increases the safe handling limiting direct exposure to toxic drugs. Main drawbacks are the risk of malfunction, the need of software updating, the high investment and maintenance costs, the need for acceptance of the technicians to the new technology and the complex qualifications. Introduction of new processes like automation always has the risk of introducing new errors (see Chap. 36).

28.7.2 Suppository Molding Apparatus

28.7.2.1 Application

Suppository molding apparatus are used to produce comparatively larger batches of suppositories. In the pharmacy this will usually amount to 250–1000 suppositories per batch. The apparatus is denoted as *hand-operated* if the apparatus is just designed to keep a relatively large amount of suppository mass homogeneous and at the right temperature during molding. The actual dosing and placing of suppository molds below the dosing point is hand-operated, in that case. If the dosing is executed automatically the apparatus is denoted as *half-automatic*. With a *fully automated* apparatus also the transport of molds below the dosing point is automated.

For small batches, suppository molds are used that are filled manually directly from the stainless steel mortar in which the mass is prepared.

28.7.2.2 Description

A Suppository molding apparatus (see Fig. 28.22) consists of the following components:

- A double-walled metal or glass vessel in which the suppository mass is contained
- A water reservoir in the casing of the vessel which is kept at the desired temperature by a heating coil and a thermostat
- A stirrer placed inside the vessel to keep the mass homogeneous during molding

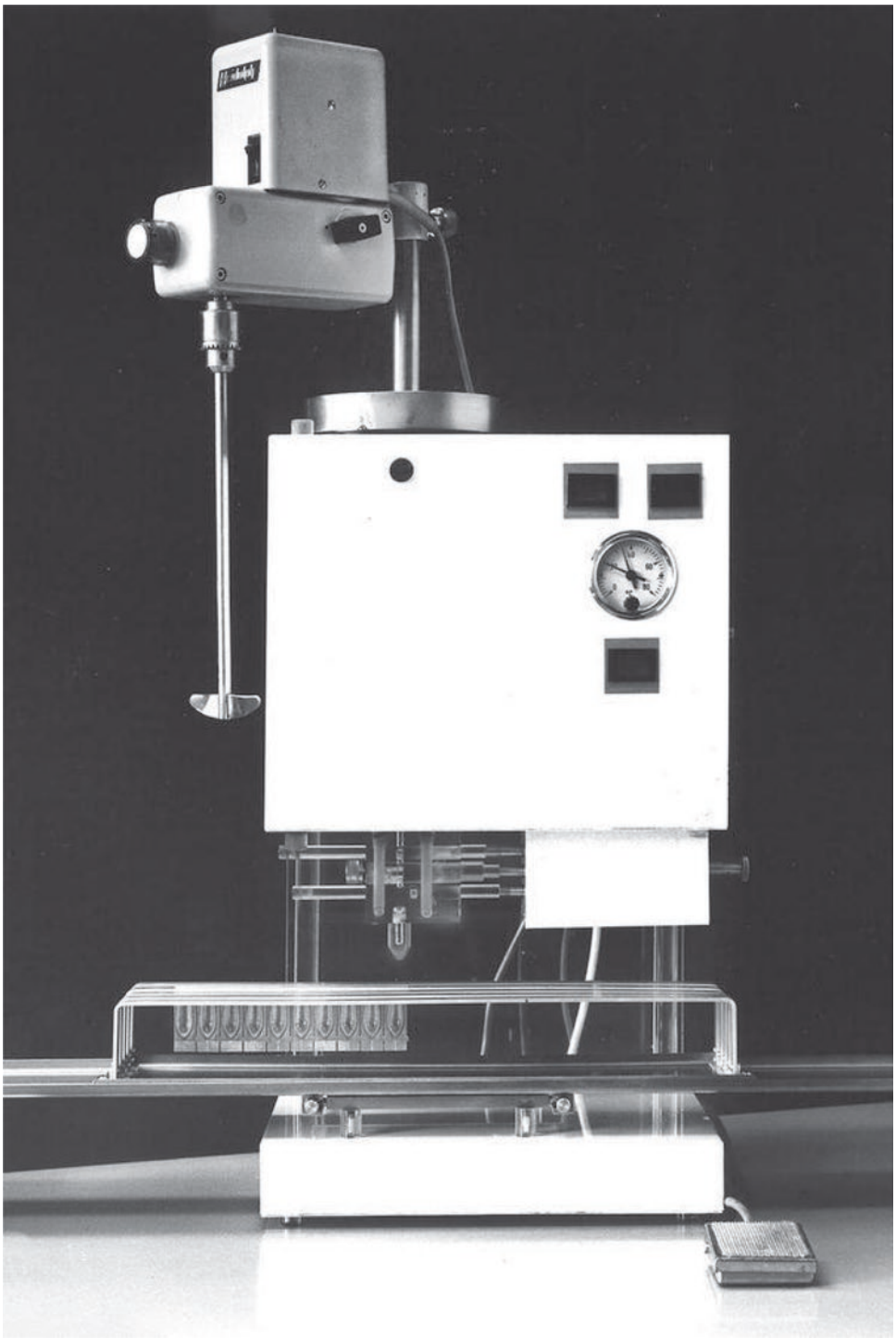


Fig. 28.22 Suppository molding and pouring apparatus. Source: Recepteerkunde 2009, ©KNMP

- A dosing point, equipped with a tap or an automatic dosing mechanism, heated or not
- A number of holders for strips of plastic suppository molds, optionally with an automated transport mechanism and a foot switch

The calibration of the temperature probe and the accuracy of the temperature adjustment of the suppository mass are critical for the process. Additionally the cooling rate near the dosing point is critical as the mass might solidify prematurely.

The water reservoir is at an ideal temperature for microorganisms to grow. Therefore effective measures should be taken to prevent microbiological contamination.

The (half) automated apparatus, in principle, facilitates a more reproducible method of working than hand operated apparatus.

28.7.2.3 Operating Procedure

Either suspension suppositories or suppositories with dissolved active substances can be molded with the suppository molding apparatus. Preparation of suspension suppositories is the most common, however it is also the most critical process, as is discussed elaborately in Chap. 19. Dispersion of larger quantities of active substance is best performed by using a rotor-stator mixer, which cannot be executed within the suppository molding apparatus. An alternative way of dispersing is triturating the powder with molten base in a mortar and adding it to the rest of the molten mass in the apparatus vessel. The blade stirrer of the molding apparatus is only suitable to keep the pre-dispersed suppository mass homogeneously during the phase of molding; no dispersion can be achieved.

The mass should be mixed continuously during molding. A rotor-stator dispersing apparatus is not suitable for this purpose as it whips air into the mass and its mixing is insufficient.

The shape of the stirring blade, the position of the stirrer in the vessel and the stirring speed all have a decisive impact on the efficacy of the mixing process. The stirring blade should be placed as close above the molding drain as possible. The stirrer should be pre-adjusted, and re-adjusted during the molding, at such a speed that no air is whipped into the mass [27–29].

A suppository molding apparatus should be subjected to initial and periodical qualification and the molding process to validation. The precise method to execute the PQ depends on the formulation and batch size. A worst case scenario should always be defined and test processes should be executed with a suitable formulation. The test product should be mainly examined on content uniformity, weight uniformity, and appearance.

28.7.3 Hard Capsule Filling and Closing Apparatus

28.7.3.1 Application

The small scale preparation of hard capsules is performed with hand operated capsule opening, filling and closing apparatus for small batches. The manufacturing of soft gelatin capsules is not discussed as they are not prepared in a pharmacy but only on an industrial scale.

Per single batch a portion of 50, 60 or 100 capsules can be prepared; larger batches can be made by reiterating the filling of the single batches. The production capacity per hour is at maximum about 1000 capsules.

Large scale capsule filling machines are used on a limited scale in pharmacies (e.g. for the production of capsules used in multi-centre clinical trials or for medium scale manufacturing of capsules with specific dosing). They may require a different design of the powder mixture because the way of operating requires a better flowability.

If large batches of oral dosage forms are necessary, usually the production of tablets is considered. Tableting machines for relatively small batches are commercially available, e.g. Korsch XP1, Manesty B4, Optima 3000, Riva-Piccola.

28.7.3.2 Description

A hand-operated capsule opening, filling and closing apparatus consists of a rectangular metal frame with below and above four horizontal plates, see Fig. 28.23.

The lower plate can be moved up and down relative to the frame. The upper plate is mounted with a hinged transparent cover that can be fixed. The upper plate, as well as the middle plates, is perforated with 50–100 holes for the capsules. Apparatus brands that are used frequently are Capsunorm® (plastic type), Feton® (plastic type), Loeco® (polycarbonate), Loetschert® (aluminium), Optima® (aluminium), Profill® (aluminium) and LGA (France; plastic type). The overall width of the holes depends on the capsule size. Each apparatus is dedicated to a fixed capsule size. The holes in the upper plate are tapered to the underside, so only the lower halves of the capsules fall through, see also Fig. 28.24.

The holes in the two middle plates are smaller and have the same size as the smaller lower halves of the capsules. The lower middle plate can be moved slightly in horizontal direction relative to the upper middle plate resulting in slightly displaced holes relative to each other. The lower middle plate can be fixed in its shifted position by means of two clamp screws, thus fixing the lower halves of the capsules and facilitating the separation of the upper halves all at once.

The upper middle plate is equipped with an edge that contains the powder during its spreading over the plate. After filling of the lower half of the capsules the upper half is placed and the capsules are closed.

Issues to consider at the purchase of a capsule filling and closing apparatus are, ease of use and sustainability. However apart from this there are additional issues:

- Material of the plate sets; the plate sets are made of aluminium or plastic; plastic plates are not resistant to hot water cleaning; the plates might warp easily. The process, cleaning instructions and the periodical assessment should be adjusted appropriately.
- The option of using capsules arrayed on card; the efficiency of these cards may outweigh its extra costs.

(continued)

- The option of the use of a capsule sorting apparatus; this is an empty capsule "orienter" to drive the capsules in the right position.
- A tamper, powder spreader or disposable plastic powder spreading card might be practical for powder distribution and filling in some cases; however be careful: the use of these and other devices must always be standardised and validated. Otherwise the process might not be reproducible enough.

28.7.3.3 Operating Procedure

The preparation of hard gelatine capsules covers four steps: insertion, opening, filling and closing, see Fig. 28.23.

If less than the apparatus capacity of 50 or 100 capsules is being prepared, the unused openings of the apparatus should be covered, for instance with tape.

If the insertion of loose capsules is done by hand, gloves (unsterile) should be worn to avoid any contamination of the capsules. Wearing gloves is recommended anyway to avoid exposure of the skin with hazardous substances (see Chap. 26).

Insertion by means of a capsule sorting apparatus is executed, in principle, quicker and more hygienic, although the apparatus does not always function flawlessly. Capsules arrayed on a card can be inserted quickly, hygienically and faultlessly. The card is placed, with or without an adapter, and using a little bar the capsules are pressed out off the card into the holes of the apparatus. A card may have the disadvantage that the choice of the capsule type itself is limited.

28.7.3.4 Cleaning

After use the apparatus must be cleaned thoroughly to prevent cross contamination. The upper plate and both middle plates are removed from the frame. The plates should be cleaned with a soap solution. Plastic type plates may not be resistant to hot water as is the case with the Capsunorm and Feton apparatus: the water temperature should not exceed 40 °C.

All parts are rinsed with clean water subsequently; if the hardness of the water could result in scaling, purified water is to be preferred. Drying should be done using a clean, non-fluffing cloth or piece of tissue paper.

The apparatus should dry further in the air, possibly near a heater or in a stove. The Capsunorm and the Feton apparatus may only dry in air.

The apparatus support is cleaned by means of a moist cloth.

Frequent maintenance is very important for the preparation of good quality capsules. By the frequent tapping of the apparatus onto the worktop or by a too rough (warm) way of cleaning, the apparatus can easily be dislocated or the plates could warp. As a consequence the upper rim of the lower halves of the capsules might not align everywhere with the upside of the upper middle plate. This can be detected by careful visual inspection.

There is also equipment that can be washed and dried in a cleaning apparatus.

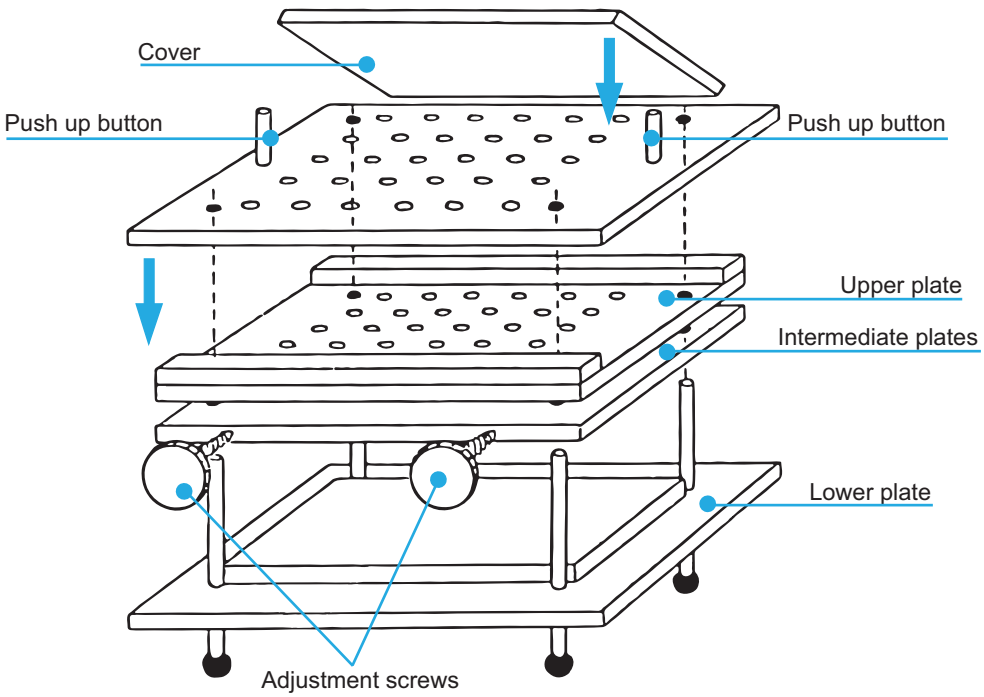
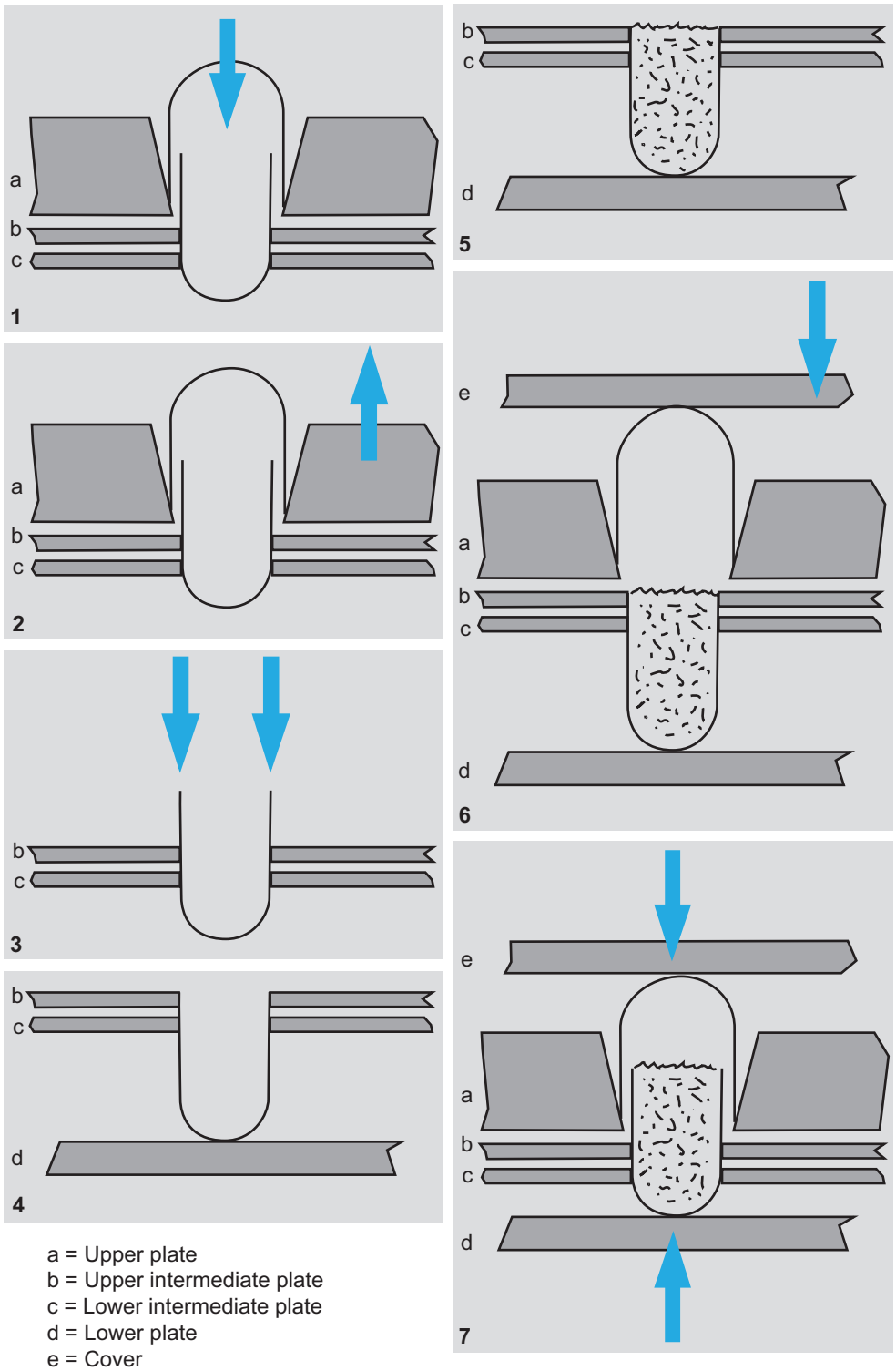


Fig. 28.23 Hand-operated capsule filling and closing apparatus



a = Upper plate
b = Upper intermediate plate
c = Lower intermediate plate
d = Lower plate
e = Cover

Fig. 28.24 Filling of hard gelatine capsules

A regular test to assess whether the capsules apparatus still works correctly is described below:

- Insert empty capsules in the apparatus and remove the upper halves;
- Check if the upper rims of the lower halves level exactly on or at the most a fraction of a millimetre below the upside of the upper middle plate;
- If the alignment is not levelled, e.g. by the frequent tapping of the apparatus onto the worktop, the lower plate should be adjusted. At the Capsunorm and the Loetschert-apparatus this is done by means of set-screws at the legs, using a small key or not. For the Feton-apparatus the legs have to be unscrewed followed by placing extra rings at the hexagonal parts of the legs;
- After adjusting, the apparatus is assessed for its functioning by the preparation of a batch of 60, respectively 100 capsules with, for instance, microcrystalline cellulose. Subsequently the relative standard deviation and the mean of weights of the content of the capsules is determined. If the relative standard deviation exceeds 1.5%, or the deviation of the mean of weights from the theoretical weight exceeds 1.5%, the functioning of the apparatus should be investigated. The variation of weights of the empty capsules should be taken into account;
- Results should be logged on a maintenance card, a logbook or in a journal.

If the apparatus is dislocated, capsules will be filled irregularly and a too large a variation of weights is the result. In that case the position of the lower plate should be readjusted. Subsequently the test should be re-executed.

When examining the test results the outcome not only depends on the quality of the apparatus but also on the experience of the operator.

It is also possible to document the operator qualification for the preparation of capsules using a pre-approved apparatus.

28.7.4 Tube Filling Apparatus

The filling of tubes can be executed by hand, with simple tools and with larger apparatus. The following tools and apparatus are described:

- Poly.propylene film or paraffined weighing paper plus spatula (filling by hand);
- Piston-cylinder apparatus, simple (for a few dozens of tubes);
- Piston-cylinder apparatus with hand wheel (dozens to hundreds of tubes);
- Apparatus with a pumping mechanism (larger batches; not discussed in this Chapter).

28.7.4.1 Polypropylene Film or Weighing Paper

Application

Propylene film or weighing paper is used to fill an amount of ointment or cream into a tube by hand by pushing the substance with a spatula into the tube.

Operating Procedure

The chosen amount of ointment or cream is put onto the film like a sausage. The film is rolled around the 'sausage' subsequently and the whole is slid into the tube. After flattening the open end of the tube firmly with a spatula the film is pulled out of the tube again. Film is preferred over weighing paper with creams and water containing ointments, as paper could attract too much water. For closing the tube neatly a pair of tube squeezing pincers should be used.

Operating Procedure for Aseptic Preparation

Filling of e.g. eye creams should be carried out aseptically.

See Chap. 20 for the preparation method including filling of tubes with a syringe. If the filling has to be done by hand the polypropylene film is preferred as this can be steam sterilised. The drawback of this filling method is the relatively large risk of direct or indirect contact of the product with the hands of the operator. Additionally at the filling of more than one tube each portion must be weighed onto the film. This requires the placement of an electronic balance in the LAF-workbench, with special attention to aseptic working with this in the laminar airstream.

28.7.4.2 Piston-Cylinder Apparatus, Simple

Application

The piston-cylinder apparatus is suitable for the filling of some dozens of tubes, see Fig. 28.25.

Description

The piston pushes the mass through the threaded opening of the cylinder into the empty tube screwed on top of that. The synthetic material is resistant against almost all ointment ingredients, though not against long-lasting contact with most organic solvents. Phenols, tar preparations, alcohol and acetone do not affect the material. The apparatus can be steam-sterilised (15 min at 121 °C).

Operation Procedure

Using this apparatus requires less operator experience and skill than the hand operated method with film or paper, however cleaning requires much attention.

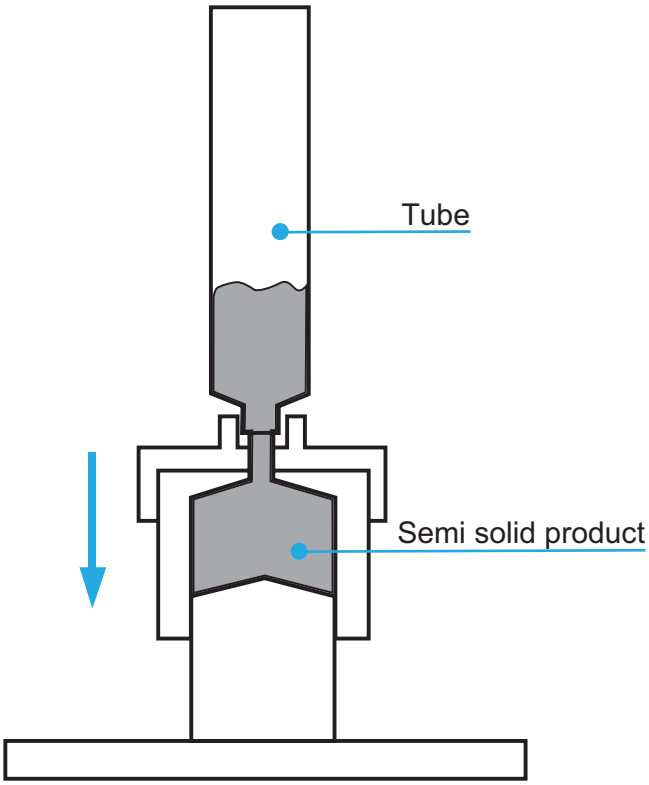


Fig. 28.25 Schematic drawing of a piston-cylinder apparatus

First the right amount of product must be brought into the cylinder. Especially with the handling of thick masses attention should be paid to avoid the introduction of air bubbles during filling, as in that case insufficient ointment will be filled into the tube. This can be achieved by tamping down the cylinder with the mass several times during the filling. While handling masses with a thin consistency, a closing cap should be placed on the cylinder opening during the filling process to prevent leakage. When the consistency is too thick it can be an awkward task to push the mass through the neck of the tube.

The loss remaining after one filling procedure depends on the used amount and the type of mass and usually ranges from 3% to 7%. During stock preparation this should be taken into account by weighing in some 5% excess at the first filling of the cylinder. For this reason the apparatus is less suitable for transferring small quantities (<50 g) into a tube.

For several tube sizes adapters and screw joints are available, however the cannula of an eye cream tube is too narrow to press the cream into the tube. This problem can be solved by mounting a (metal) filling pipe onto the cylinder over which the rear side of the eye cream tube fits. Consequently the tube will be filled from the open end. This kind of filling pipe is available. To monitor how far the eye cream tube can be filled, a mark should be applied.

28.7.4.3 Piston-Cylinder Apparatus with Hand Wheel

Application

The piston-cylinder apparatus with a hand wheel is suitable for some dozens to hundreds of tubes per batch, see Fig. 28.26.

Description

The piston-cylinder apparatus is made of stainless steel. It is available in sizes/volumes of 1–3 L, with tube filling pipes for several tube-opening sizes.

Operation Procedure

The cream or ointment is transferred into the cylinder-shaped vessel. By bringing down the piston using the hand wheel the cream or ointment is pressed into the tube which has been slid over the outflow opening. At the filling pipes ring marks are applied to provide equal filling of the tubes, see Fig. 28.26.

During cleaning the bleeding valve in the piston should always be demounted as well.

28.7.5 Unit Dose Packaging

28.7.5.1 Application

Modern drug distribution systems use single unit packages to a great extent and, in fact, such packages are central to the operation of unit dose systems and other important aspects of pharmacy practice. Many tablets, capsules and injectables are available in a single unit dose package, however, in some cases they are only available in bulk. For these situations small scale unit dose packaging is available.

28.7.5.2 Description

In general there are two options. First, there are compact automated unit-dose packaging machines that allow to form, fill, seal and print blisters. Tablets, capsules, suppositories and liquids can be packed in these blisters. Each unit-dose blister can be labelled with a batch number, the expiry date and bar code. E.g equipment by Pentapack (Belgium).

Secondly there are dedicated systems available for manual blistering using pre-formed blisters and separate printed labels.

28.7.5.3 Operating Procedure

The automated equipment is developed for small scale batches (20–5000 doses). Tablets/capsules (or vials and small syringes) are feeded manually. The product is packed in on-line formed individual blisters. The blisters are identified by (barcode) labels produced in-line with dedicated software.

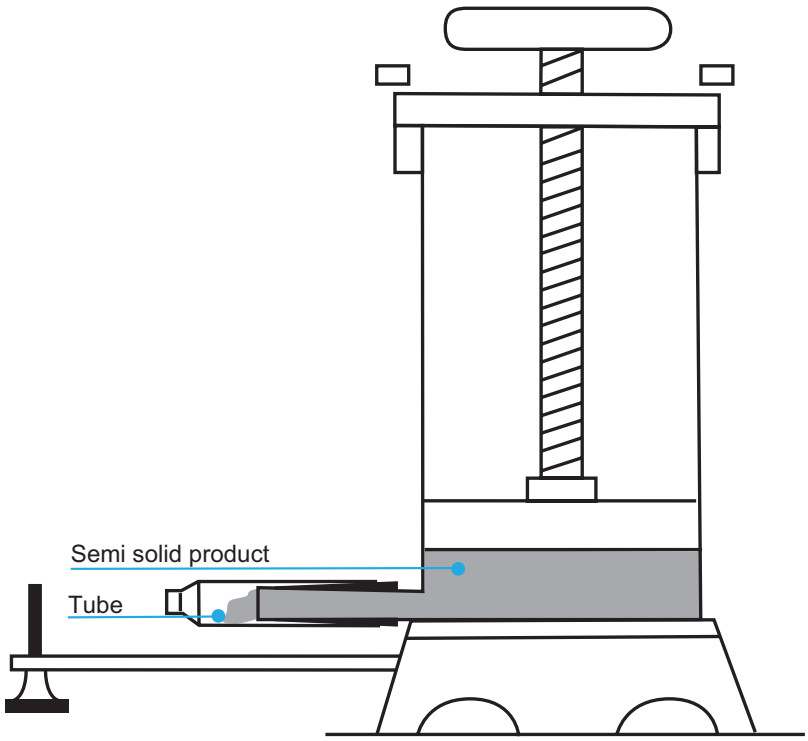


Fig. 28.26 Schematic drawing of a piston-cylinder apparatus with a hand wheel

28.7.5.4 Cleaning

Cleaning of the equipment and a validatied line-clearenprocedure in between batches is an important step especially to prevent mix-up of products.

28.8 Cleaning Apparatus

28.8.1 Application

A washing machine is used to clean all utensils (implements and parts of preparation apparatus) which have such a form and dimension that they fit into the washing-up machine and can be placed in such a way that all surfaces will be reached by the detergent solution during the washing process. Additionally the utensils must be resistant to the treatment, the cleaning temperature and the used detergents.

28.8.2 Description

A professional washing machine will achieve the following:

- Mechanical removal (along with destructive effect of heat) of microorganisms, however this is not a sterilising cycle
- Removal of nutrients for microorganisms
- Removal of remainders of any products
- Deliver dry material

In general mechanically cleaning and rinsing is the preferred method because it is easier to be standardised. Visible product residues are best removed by hand using absorbing paper.

The machine washing-up cycle consists of pre-rinsing, cleaning, post-rinsing (several runs, the last of them preferably using purified water) and drying. A professional washing machine should have a built-in dryer. Furthermore the water temperature of the main program should be 65 °C or higher.

To implement a GMP process flow, double-door equipment in between “dirty” and “clean” environment needs consideration as well as implementing an automated registration of the critical parameters of each t cleaning cycle.

28.8.3 Operating Procedure

The removal of visible product residues should preferably be done immediately after the preparation process and the mechanical cleaning should be done within one day. This so-called ‘pre-cleaning hold time’ should be assessed in advance and be warranted in practice. After all, residues that are left during a longer time might be hard to remove effectively by a standard cleaning process. Additionally micro-organisms may grow.

A load scheme should be available in order to clean the utensils in a standard way. So called rinsing shadows must be prevented: surfaces which aren’t reached during the cleaning process because they are covered by other objects. The load scheme should also prevent placing objects in such a way

that upward situated cavities collect rinsing water that will remain. The load scheme, the chosen washing program and the nature and quantities of detergents and, if applicable, neutralising products, should be documented in advance to guarantee a clean product.

Validation of the cleaning process (and detergent removal) has to be done before operating. As difficult to clean objects utensils contaminated with zinc oxide paste (if desired with 3% brown iron oxide) can be recommended. The validation should be repeated periodically, e.g. yearly, or at any time utensils are not clean after washing up or when new utensils are introduced. Results should be documented.

For adequate cleaning an alkaline detergent is necessary, preferably designed for laboratory use. Household agents will not always clean sufficiently [30]. The detergent must be dosed in accordance with the initial validation tests.

Prior to use, the sieves must be checked on possible residues of the proceeding run. Utensils must be placed in such a way that water from the spray nozzles will effectively hit the dirty parts. In general, this means that the most contaminated part should be directed downward.

Utensils with hollows or cavities should be placed in a slanted position otherwise water cannot drip off. High and narrow utensils should be placed directly over the spray. Loading procedures are necessary to put utensils in the machine that either have difficult to access places or aren't resistant to the temperatures or chemicals in the machine.

Vulnerable utensils should not be placed against other ones.

To guarantee an adequate cleaning the machine should not be overloaded. Neither objects should contain any caked dirt, which should be removed by pre-cleaning any residues directly with absorbing paper and by enforcing the pre-cleaning hold time. This pre-cleaning also prevents the sieves of the machine from clogging.

The correct operation (program choice, dosing of detergents and neutralising agents, logging of runs) should be incorporated in an operating instruction. This should include the instruction that after every run each utensil is checked for its cleanliness and dryness. The washing-up machine should preferably not be started at the end of a Friday afternoon because in that case any water residue will remain in place for a couple of days, increasing the risk for microbial contamination.

28.9 Apparatus for Cooled Storage

28.9.1 Application

Cooled storage (refrigerators, cold stores and freezers) is necessary in every pharmacy. For most medicines, a household refrigerator or freezer is not sufficiently specified since predefined temperature limits need to be in place. The pharmacy refrigerator for licensed products is part of the so-called cold chain, see also Chap. 39. The producer or wholesaler usually will store medicines that should be kept 'cool' in large temperature-controlled cold stores. The cold chain should warrant that storage conditions will be maintained during transport and temporary storage to ensure the stability of the product.

28.9.2 Description

The temperatures of pharmacy refrigerators and freezers are standardized to meet predefined temperature limits. The temperature limits are generally based on international guidelines for drug stability testing, such as the International Council for Harmonisation (ICH) Q1A guideline [31]. Refrigerated and frozen storage are described as 5 °C ± 3 °C and −20 °C ± 5 °C, respectively. Though the guideline does not specifically describe lower storage temperatures, some products may need to be stored at temperatures below −20 °C. The storage units commonly utilised for this objective are ultra-low temperature (ULT) freezers, nitrogen vapor tanks or liquid nitrogen tanks that maintain the product at temperatures of −80 °C ± 10 °C, −150 ± 15 °C and −196 °C, respectively. Temperatures below −20 °C are generally required for the long-term storage of products that contain nucleotides (e.g. DNA or RNA) or cells.

A refrigerator without an internal freezing compartment will best meet the temperature requirement of 2–8 °C. It should be considered that a temperature zone below 0 °C might arise for refrigerators that contain a built in freezing compartment. Automated thawing is undesirable as well if the refrigerator has only one evaporator, because this will raise the temperature every now and then to have frozen moisture thawed and drained away. A good refrigerator is provided with forced air circulation to achieve an even temperature and with a thermostat to control the temperature at 4 °C. Some refrigerators are equipped with specific provisions for monitoring. Others have an external temperature display or a logging function.

Freezers generate a substantial amount of heat and should therefore be installed in well ventilated and low-humidity areas. Sufficient clearance (10–20 cm) in all directions around the freezer for effective heat dissipation should be considered. Furthermore, it should be considered that empty space in a freezer may result in the intrusion of warm and humid air after opening and closing the door. Utilising an efficient inventory system (i.e. racks and drawers) not only aids in quickly retrieving the stored samples, but also aids in minimising door-opening times, and thus, temperature fluctuations.

If there are several storage units placed together in one room it is advised to connect them to different electricity groups to diminish the consequences of any failures. If the stock of cooled products requires considerable space, it should be decided whether several storage units or one bigger cold store is preferred. Several storage units usually are energetically less favourable than a bigger cold store. However, in case of a failure of one storage unit, it might be an advantage to have spare capacity in the others. In a cold store the risk of failure might be abated by installing a redundant pair of compressors. A cold store should be installed, validated and controlled in a similar way as storage units such as a refrigerator or freezer.

Products or samples that need to be stored at temperatures below −130 °C can be stored in nitrogen vapour tanks or in liquid nitrogen. A nitrogen vapour tank is a large closed container that contains at the bottom a layer of liquid nitrogen that evaporates in the chamber of the container. The samples are stored in the nitrogen vapour chamber directly above the liquid layer. Alternatively, lower storage temperatures are achieved if the samples are stored in the liquid nitrogen instead of the nitrogen vapour. Storage in liquid nitrogen provides a stable ultra-low temperature. However, liquid nitrogen intrusion into the stored sample container and the resulting potential contamination issues should be considered for liquid nitrogen storage [31, 32].

28.9.3 Operating Procedure

28.9.3.1 Installation

The instructions of the manufacturer should be followed carefully. Usually this means that a stabilisation time should be observed of 24 h after initial installation or after a removal. Then, after switching on, the temperature and the mutual temperature differences should be measured at a sufficient number of different places in the empty storage unit. Subsequently, these measurements are to be repeated in the storage unit with the maximum loading capacity. The maximum allowed loading capacity of the refrigerator, freezer, or nitrogen tanks should be predefined to ensure that the temperature limits are met and maintained during the installation and the use thereafter in daily practice. As rule of thumb for refrigerators, a maximum allowed loading capacity of three-quarters is generally accepted to ensure adequate air circulation for a homogeneous temperature distribution.

All measurements can be executed with two different temperature sensors:

- Using calibrated minimum/maximum thermometers or
- Using calibrated temperature data loggers.

The use of calibrated electronic temperature data loggers have many advantages over the use of minimum/maximum thermometers as the course of the temperature over time can be measured, recorded and evaluated.

The storage unit can be used after the correct functioning has been established. It is advisable to use a qualification protocol with predefined temperature limits and acceptance criteria to ensure a standardised assessment of the storage unit.

Temperature limits and acceptance criteria to consider are:

- The amount of temperature sensors for the qualification.
- The location of the temperature sensors during the measurements. The measurement points should be evenly distributed throughout the entire storage unit to ensure a homogenous temperature in the storage chamber, i.e. corners and middle of the chamber.
- The duration of the qualification monitoring time to give a representative temperature logging during use in daily practice (i.e. 12–24 h of monitoring time).
- All measured temperatures have to be between the predefined and accepted temperature limits, both in the empty and maximally loaded storage unit.
- Minimum and maximum temperatures, measured at one location, should not vary more than a predefined amount (i.e. 5 °C).
- The measured mean minimal temperature should not differ more than a predefined amount from the measured mean maximum temperature (i.e. 5 °C)
- An open-door study is advised to investigate the temperature change over time and to evaluate the time point at which a temperature excursion is reached.
- If the refrigerator or freezer has a built in thaw-freeze cycle, it is advised to investigate this cycle as well with temperature sensors.

If these criteria are not met, arrangements should be made and subsequently the measurements of temperatures and temperature differences should be repeated. The thermostat adjustment to achieve the correct functioning should be documented.

28.9.3.2 Use

Relevant points in the use are:

- The control of cooling provisions needs continuous attention. Household provisions are not sufficient.
- Current interruptions or a failure in the closing of the door might cause unacceptable deviations of the temperature.
- The refrigerator should never be filled for more than 75–80% of its capacity. This filling rate leaves sufficient

space for an adequate air circulation, providing a homogeneous temperature distribution.
- Product should not be placed against the refrigerator back wall; this disturbs the air circulation and, in case of an automatic thawing refrigerator, ice might build up against the back wall.
- Maintain a ventilated and low humidity environment for freezers.
- Routinely clean and remove ice from the door gasket for a better sealing after closing the door.
- A lot of empty space in a freezer may result in the intrusion of warm and humid air after opening the door.
- Efficient inventory systems minimise door-opening times and temperature fluctuations.
- Non-automated nitrogen vapour tanks require an adequate liquid nitrogen layer on the bottom of the container for the desired storage temperatures. The tank should be refilled periodically and on time.
- Liquid nitrogen intrusion and potential contamination of of samples stored directly in liquid nitrogen might be an issue [32].

28.9.3.3 Cleaning

For the cleaning procedure, no scouring agents or alkaline detergents should be used to minimise damage to the different parts of the unit. Surfaces can be wiped with a soft and sturdy cloth. By cleaning each shelf individually, it is possible to keep the contents of each shelf or drawer cool during cleaning. The contents can be stored temporarily on a different shelf or in another drawer of the storage unit.

Another possibility is the use of a cool box for products stored in a refrigerator. In that case direct contact of the product with the freezer packs should be avoided to prevent any local freezing. The freezer packs belong in the upper part of the box, preferably inside the lid, because otherwise the temperature inside the box will not fall below 15 °C.

28.9.3.4 Thawing (for Non Automatic Fridges)

The timing and frequency of thawing of the refrigerator and freezers is determined by the thickness of the ice built-up onto the cooling elements as well as the general instructions of the manufacturer. With a thick ice sheet it takes considerably more energy to cool. However, thawing and cooling costs energy as well.

A rule of thumb for thawing a refrigerator is to do it when the ice sheet has grown to 1–2 cm. Another possibility is thawing with a closed door. In that case the contents are kept in the refrigerator. Leaking meltwater should be collected in such a way that the products remain dry. A drawback is that cleaning cannot take place at the same time. Finally, it can be considered to remove all products from the refrigerator and stack them in a cool place wrapped in isolating material such as a woollen cloth. The low temperature can be retained for some time in this way.

28.9.3.5 Monitoring

The required temperature should be verified continuously. The temperature can be recorded continuously using temperature sensors. One of these has to be placed in the coldest place and the other in the least cold place, which are determined during qualification of the storage unit. The use of only one moveable temperature sensor can be justified if the temperature differences in the storage unit are almost negligible at the several measurement places.

The temperature sensor used to control and monitor or both is preferably placed in a holder, e.g. in a little cardboard box or better in a vial filled with glycerol. By this method the reaction of the sensor to the opening of the door can be buffered. Electronic data loggers can provide continuous recording.

Pharmacy employees have to check the temperature every time they open the fridge or freezer and proceed in accordance with alert and action levels of the temperature. By this procedure any failure during operating hours can be detected easily. However the connection of a cooling system to a building control system raising an alarm any time the temperature fails to stay within its prescribed boundaries is to be preferred.

Procedure in Case of Failure or Temperature Excursion

Failures can arise by any breakdown of the storage (e.g. power failure). Several causes of failure can be discerned:
- The door does not close well or has been left open for a prolonged time (the most common interruption of the cold chain in community pharmacies seems to be caused by an open door).
- The thermostat is not adjusted correctly.
- A power failure has occurred.
- The storage unit does not function well: e.g. a specific part has broken down (thermostat switch, ventilator, automatic thawing mechanism or compressor failure).
- For liquid nitrogen or nitrogen vapour tanks, the container may not contain a sufficient amount of nitrogen.

A temperature calibration should be executed each time any doubt has risen about the temperature.

The consequences of a power failure or temperature excursion for the product are based on the maximum/minimum temperature reached, the duration of the temperature excursion and the general stability of the product. It is advisable to not only consider the course

(continued)

of the measured temperature inside the storage unit (e.g. temperature logger data), but to also consider (approximate) the course of the product temperature as well. For instance, the gravity of a 10 min temperature excursion at 12 °C is less for an infusion bag containing 1000 ml of an aqueous solution compared to an injection vial containing 1 ml of the same solution since a longer period is needed for the former to reach temperatures above the 8 °C limit. This approximation combined with the stability data of the product aids in assessing the consequences of the temperature excursion.

In case no temperature logger data is available, the duration of a power failure can be retrieved from the energy company. Besides the available stability data in the summary of product characteristics and published literature, some producers of licensed medicines usually have specific information to assess the gravity of the interruption of the cold chain, which can be made available upon request.

It is suggested to investigate the increase of the temperature in some situations in order to have an indication of the possible damage when disturbances have occurred:

- A power interruption of at least 12 h.
- A defective thermostat while the ventilator keeps running.
- Leave the door ajar 1 cm for at least 12 h.

Measurements best be executed in a closed, empty refrigerator as a worst case in relation to the rate of temperature increase.

As a preventive measure the purchase of an emergency power supply might be considered. This could consist of an apparatus with a back-up time of e.g. 8 h, producing 230 V from closed gel batteries, built-in into the refrigerator or installed outside of it.

28.10 3D Printing

28.10.1 Introduction

Additive manufacturing (AM), or more generally known as 3D printing, refers to the production of three-dimensional objects in which the printable material (referred to as "ink") is added layer by layer. The technology was first developed in the 1980s and has ever since been further developed. Currently, a wide range of AM technologies exist that are not only limited to the production of pharmaceutical dosage forms such as (controlled-release) tablets [34], suppositories [35], orodispersible films [36], and even printed nail polish to treat onychomycosis [37]. For instance, AM has been employed in several branches of health care to manufacture prostheses and dentures in dentistry, implant and hearing aids as medical devices, and tissue analogs for implantations [38]. The technique has also been used in engineering to not only manufacture metal objects and tools, but to manufacture entire constructs such as houses [39, 40].

AM can be generally summarised into four steps. First, the object is digitally created from a computer-aided design (CAD) or other imaging techniques such as a magnetic resonance imaging (MRI) or computed tomography (CT) scan. The CAD is then converted into a file (generally a .stl or .obj file) that contains the information regarding the design and geometry of the object. This file is converted into a coding file (.gcode), which is a printer-specific file that contains instructions for the layer-by-layer production of the three-dimensional object. The final step is design optimization using several printed samples and investigated printing parameters to fine-tune and update the printing file. For some printing techniques, post-processing (e.g. curing or polishing) is needed to obtain a printed object with the desired characteristics [41].

The International Organization for Standardization (ISO) and American Society for Testing and Materials (ASTM) recognize seven different categories of AM techniques (ISO/ASTM 52900:2015). The classification is based on the additive shaping principle and how the physical three-dimensional object is built. These seven categories are powder bed fusion, material extrusion, sheet lamination, material jetting, binder jetting, vat photopolymerization, and directed energy deposition. Each category can be further divided into different printing techniques that utilise the same printing principle, but differ in how the printing technique and materials are used. Not all AM categories are relevant for, or utilised to print three-dimensional pharmaceutical dosage forms. Table 28.3 summarises the different AM categories and several printing techniques that are commonly used to manufacture pharmaceutical dosage forms. This section will only focus on the AM categories binder jetting, material extrusion, vat polymerization, powder bed fusion, and material jetting since only these categories are relevant for the production of pharmaceuticals.

Currently, there is no specific guideline on the manufacturing of 3D printed pharmaceuticals. Even though AM has been utilised, investigated, and further developed since the 1980's, at the time of writing only one pharmaceutical dosage form holds a marketing authorization. Spritam (levetiracetam, Aprecia Pharmaceuticals) is a 3D-printed and Food and Drug Administration (FDA)-approved immediate-release orodispersible tablet. Since the approval of Spritam in 2015, regulatory bodies showed a growing interest in the production of pharmaceuticals and medical devices with AM techniques. In 2017, the FDA released the report "Technical Considerations for Additive Manufactured Devices" [42] and in 2021 the

Table 28.3 The seven AM categories according to ISO/ASTM 52900:2015, different printing techniques, advantages, and disadvantages related to the manufacturing of the pharmaceutical dosage forms [38, 44–47]

ASTM/ISO category	Technique	Printing Material (ink)	Mechanism	Advantages	Disadvantages
Material extrusion	Fused deposition modeling (FDM)	Drug-loaded thermoplastic filament	Printing material is forced through a printing nozzle and extruded to build the object	Complex geometries and structures, controlled drug release, little to no post-processing, low cost	Low drug load filament, thermal degradation, drug loaded filament properties, pre-process filament preparation required, supporting structure may be needed for bigger objects
	Pressure assisted microneedle (PAM)	Semi-solid drug mixture (gel or paste)		Multiple printing syringes can be used to print one object (polypill), more suitable for thermolabile drugs, higher drug load, low cost	Semi-solid mixture properties, post-process drying residual (organic) solvents, photodegradation in case photopolymer is used, supporting structure may be needed for bigger objects
	Direct powder extrusion (DPE)	Drug-pellet mixture		Requirements pellet properties, more suitable for thermolabile drugs, higher drug load, single step process, low cost	Relatively new technique, lower printing resolution, weight variation, supporting structure may be needed for bigger objects
Binder jetting	Spritam (Aprecia Pharmaceuticals)	Liquid binding agent	Solid particles are joined together by a liquid binding agent to build the object	Fast drug disintegration profile, wide range of available materials, relatively fast printing time, takes place at room temperature and atmospheric pressure	Wastage of unbonded material, residual organic solvents, post-process curing, dosage structural integrity (fragile)
Vat polymerization	Stereolithography (SLA), digital light processing (DLP), continuous DLP (CDLP)	Liquid photopolymer (resin)	A vat containing a liquid photopolymer and drug mixture is selectively cured by light to solidify and build the object	High precision, relatively fast, high resolution, flexible design in print geometry	Post-processing, photodegradation, limited availability in pharmaceutical grade resins
Material jetting	Continuous inkjet (CIJ) printing Drop-on-demand (DoD) printing	Photopolymer, wax, thermoplastic polymer	Droplets of printing material are deposited and solidified to to build the object	High precision, relatively fast, low cost, minimal material wastage for drop-on-demand technique	Supporting structure may be needed for bigger objects, high shear stress, less suitable for thermolabile drugs in case of thermal print head actuator, material wastage for continuous inkjet printing, photodegradation in case of UV light source
Powder bed fusion	Selective laser sintering (SLS)	Solid polymer particles (powder)	Thermal energy from a laser sinters (fuses) the powder particles to build the object	Solvent free, one step process, relatively fast, high resolution, complex, complex geometries and structures, controlled drug release	Drug degradation due to high laser energy, limited availability of laser absorbing materials, wastage of unsintered material
Directed energy deposition	Not applicable for pharmaceutical dosage forms	Metal wire or powder, ceramic, polymers	Thermal energy is used to fuse the deposited material from the print head to build the object	Not applicable for pharmaceutical dosage forms	
Sheet lamination		Sheets of paper, polymer, or metal	Sheets of material are bonded together to build the object		

"Discussion Paper: 3D Printing Medical Devices at the Point of Care" [43]. Though these documents discuss medical devices and recognize that due to the different AM categories and techniques no universal set of rules can be stated, it highlights specific points to consider in the manufacturing of 3D-printed objects such as the software, hardware, quality control regime, process validation procedures, and patient safety, which are also relevant for the production of 3D-printed pharmaceuticals.

28.10.2 Material Extrusion

In extrusion-based printing, the printable material (solid or semi-solid) is extruded from the print head through a nozzle onto a print platform to create the printed object layer-by-layer. The technology can broadly be divided into three printing techniques, namely fused deposition modelling (FDM), pressure assisted microsyringe (PAM) printing, and direct powder extrusion (DPE) printing. These techniques use drug-loaded polymer filaments, semi-solid materials, or polymeric powder blends, respectively, as the printable material (Fig. 28.27). Since the object is printed and built from scratch, a supporting scaffold structure may be needed and printed simultaneously with the object. This is generally true for bigger printed objects, but may not always be necessary for smaller printed objects such as small dosage forms (e.g tablets) [48].

The drug loaded thermoplastic filaments that are used in FDM can be produced by active substance incorporation into the polymer by hotmelt extrusion (HME) or impregnation. The filament is usually coiled up and unreeled into the printing nozzle, which heats up the filament until the melting point, softens the material, and extrudes the melted material from the nozzle onto the print platform. Rapid cooling solid-

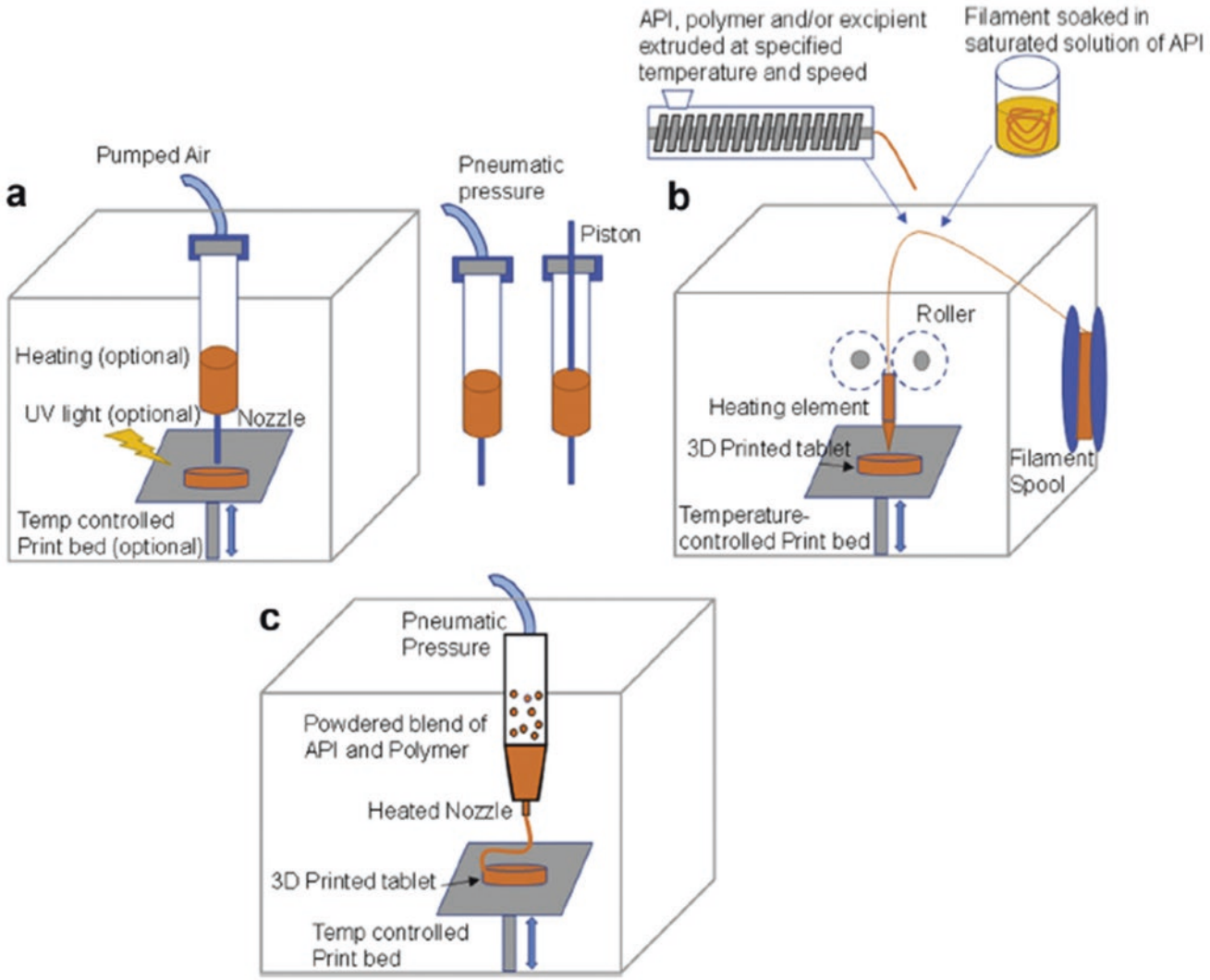


Fig. 28.27 Schematic representation of the three material extrusion-based printing technologies PAM (**a**) FDM (**b**), and DPE (**c**). In case a photopolymer is used for the PAM printing procedure, a UV light source is needed to solidify the extruded semi-solid material [48]

ifies the printed material on which new molten material can be layered to create the three-dimensional object.

The FDM printing technology is suitable to print a wide range of complex structures with different outer and inner geometries. Multi-layer dosage forms can be printed in which each layer contains a different active substance/excipient formulation. By modifying the inner or outer structure of the printed dosage forms, different (controlled) drug release profiles can be obtained. Printing dosage forms with FDM is relatively cheap with little to no post-processing steps. The availability of pharmaceutical grade polymers makes this technique interesting to print dosage forms that are intended for human use.

The required drug loaded polymer filaments should be flexible so that they can be coiled up and unreeled into the printing nozzle. Moreover, a sufficient amount of active substance should be incorporated into the filament. These filament characteristics may not always be achieved for every medicine formulation since the mechanical properties of the filaments are influenced by the constituents of the formulation. High active substance loading may also be challenging, especially when the filament is prepared by substance impregnation, which requires a high concentration of active substance solution and long impregnation times. FDM is also not suitable for thermolabile medicines due to the heat exposure that is needed to prepare the drug loaded filaments by HME and the subsequent heating of the filament by the printing nozzle [49].

Another extrusion based printing technique is PAM printing. Instead of using solid drug-loaded filaments, a semi-solid (gel or paste) material is continuously extruded from the print head that contains one or multiple small syringes. The semi-solid printing material consists of a mixture in which the polymer, active substance, solvents, and excipients are processed. This mixture is slowly extruded from the small syringes in succeeding layers by pneumatic or mechanical pistons to build the three-dimensional object. Evaporation of the present solvent in the printed semi-solid mixtures solidifies the material, on which a new layer can be added to build the object. Alternatively, semi-solid mixtures containing a photopolymer can be used, which solidifies under ultraviolet (UV) light exposure. To utilize photopolymers in the printing process, the printing head should be equipped with a UV light source.

Compared to FDM, no heat is required in PAM printing to fabricate the semi-solid printing mixture. Therefore, thermolabile medicines which cannot be used in FDM printing may be used by PAM printers. Furthermore, the print head of a PAM apparatus can be equipped with multiple printing syringes that contain several active substance formulation mixtures. This makes it possible to print a single object that contains multiple active substances in one dosage from (e.g. a polypill).

The viscosity of the PAM printing mixture is crucial. On the one hand, the printing mixture should be viscous enough to maintain a stable structure during the printing process, whereas on the other hand the viscosity should not be too high so that the mixture cannot be readily extruded from the printing nozzles. Additionally, the printing mixture may contain organic solvents to optimise the rheological characteristics of the formulations. Hence, a post-process drying step is often needed and concerns with regards to residual organic solvent may hamper the applicability of certain printing mixture formulations.

A relatively new extrusion-based printing technique for pharmaceutical preparations is DPE. The printing material that is supplied to the printing nozzles is a dry pellet mixture instead of a filament (as in FDM) or a semi-solid formulation (as in PAM). The pellets are supplied to a single screw extruder, pulverised by the screw, heated and molten by the nozzle head, and directly printed onto the print platform. This technology does not require the preparation of drug-loaded filaments by HME or semi-solid mixtures that must comply with certain mechanical or rheological properties, respectively, which allows to print medicine formulations that are not suitable to be printed with FDM or PAM [50]. Compared to FDM or PAM, however, lower resolution objects with a higher weight variation are printed [48].

28.10.3 Vat Photopolymerization

The vat photopolymerization printing technology consists of a photocurable liquid (often a resin) that is present in a vat in which the printer platform is submerged. The printer is equipped with a light source (e.g. UV light, LED, or a laser beam) that selectively emits light on the printer platform with a predefined pattern that is contained in the uploaded print file. The energy from the printer light induces photocuring, which results in the photopolymerization and/or photocross-linking of the liquid. This reaction solidifies the liquid on the printer platform on which a new layer can be added. The print platform is moved up (or down) and the entire process is repeated until the three-dimensional object is fully printed.

Three vat photopolymerization technologies that are commonly utilised in the production of pharmaceuticals are stereolithography (SLA), digital light processing (DLP), and continuous DLP (CDLP). Typical SLA, DLP, and CDLP printers are illustrated in Fig. 28.28. SLA utilises a laser beam that consecutively, layer-by-layer, follows the pattern and geometry of the uploaded print file. Upon completing a

(continued)

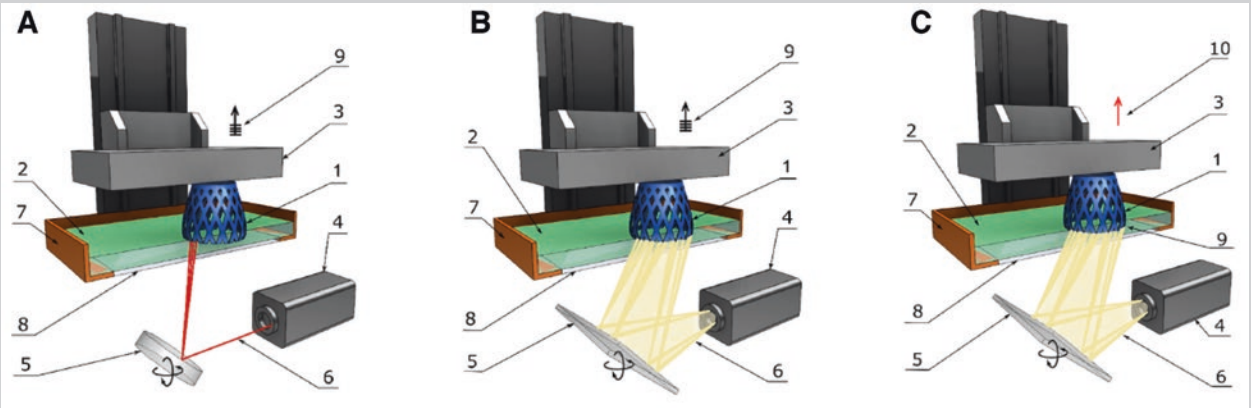


Fig. 28.28 Schematic representation of typical vat polymerization printers. (Reprinted and adjusted from Ref. [51])
(**a**): Typical SLA printer. 1: Printed object; 2: liquid photopolymer; 3: Printing platform; 4: Light/laser source; 5: Mirror; 6: light/laser beam; 7:vat containing liquid photopolymer; 8: clear plate; 9: consecutive and layer-by-layer elevation of the print platform. (**b**) Typical DLP printer. 1: Printed object; 2: liquid photopolymer; 3: Printing platform; 4: Light/laser projector; 5: Mirror; 6: light/laser beam; 7:vat containing liquid photopolymer; 8: clear plate; 9: consecutive and layer-by-layer elevation of the print platform. (**c**) Typical CDLP printer. 1: Printed object; 2: liquid photopolymer; 3: Printing platform; 4: Light/laser projector; 5: Mirror; 6: light/laser beam; 7:vat containing liquid photopolymer; 8: clear plate; 9: Object building front; 10: continuous elevation of the print platform

printed layer, the print platform moves up (or down) and the next layer is added to the previously created layer. DLP utilises a similar process but instead of a laser light that follows a specific pattern, a light projector emits an entire cross-sectional image of the to-be-printed object on the print platform. Subsequently, just like in SLA, the print platform is consecutively moved layer-by-layer until the object is fully printed. The principle of CDLP is similar to DLP, but the difference is that the print platform is moving continuously, and therefore, the projector also emits the cross-sectional images in a continuous manner instead of a layer-by-layer by fashion. For all three printing techniques, post-process photocuring of the printed object is often needed to increase the mechanical strength and structural integrity [51].

Vat photopolymerization printing times are relatively fast and printed objects with complex structures can be obtained, which makes it a flexible printing technique for high-resolution pharmaceutical dosage forms. However, the main disadvantage of the technique is photodegradation, especially for light-sensitive active substances and excipients. Photodegradation does not only result in a formulation with a lower active substance content, but also in a formulation with a higher content of (potentially toxic) degradation products upon completion of the printing process. The flexibility of this technology is also hindered due to the limited availability of pharmaceutical-grade and non-toxic photocurable liquid resins.

28.10.4 Binder Jetting

The binder jetting printing technology consists of a thin powder bed layer that is present on a print platform. A liquid binder solution is selectively applied by the printer nozzle onto the powder bed layer. The printer nozzle follows the print instructions of the print file, which contains the information about the size and geometry of the printed object. The evaporation of the binder solution (by air) results in the coalescence of the wetted and dried powder. Subsequently, the print platform is lowered and a new succeeding powder bed is swept over the previous layer by a roller/sled. The entire process is repeated until the three-dimensional object is fully printed (Fig. 28.29). After the unbonded powder that surrounds the printed object is removed, a final curing step of the object may be needed to harden and increase the mechanical strength of the object [52].

An advantage of binder jetting is that the printing time is relatively short and no additional supporting materials are required during the printing process of bigger objects. Furthermore, the entire printing procedure takes place at room temperature and atmospheric pressure, which makes it possible to print medicines with low thermal and oxidative stability. Additionally, porous dosage forms with a high active substance load can be printed. These formulation characteristics can yield fast-dissolving and immediate-release formulations, a prime example being the first ever and only FDA-approved 3D-printed oral dosage form Spritam (levetiracetam, Aprecia Pharmaceuticals).

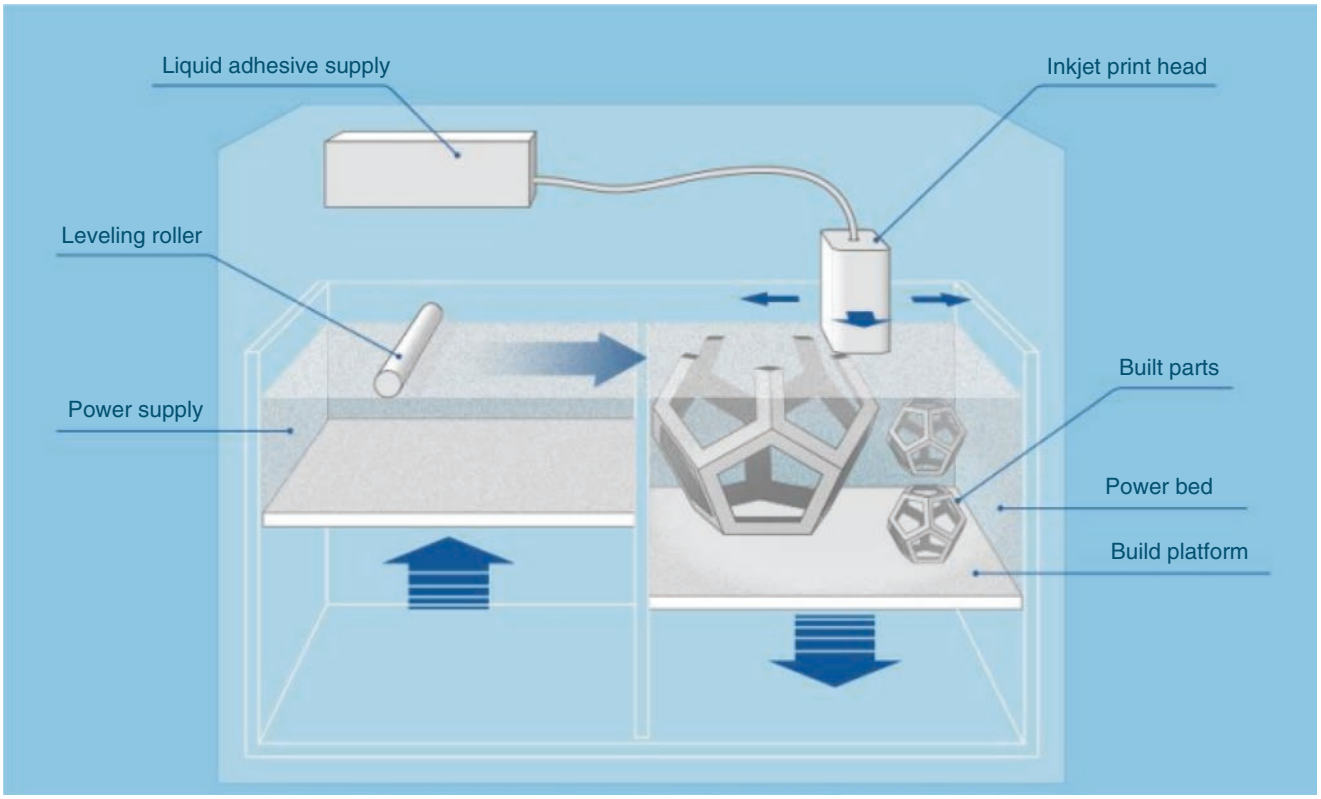


Fig. 28.29 Schematic representation of a typical binder jetting printer. (Reprinted from Additively.com)

Post-process production steps such as the removal of the unbonded powder as well as the object curing procedure makes the entire manufacturing process time consuming, whereas unbound material wastage adds to the printing costs of the technique. Even after a curing procedure, the structural integrity of a printed object may be low. The tensile strength, friability, and hardness of printed pharmaceutical dosage forms may therefore be suboptimal. Finally, if the liquid binder solution contains organic solvents, a drying step should be in place to ensure that no residual solvent is present in the printed dosage form.

28.10.5 Powder Bed Fusion

Selective laser sintering (SLS) is a powder bed fusion printing technology that is utilised to print pharmaceutical dosage forms (Fig. 28.30). Similar to the binder jetting technique discussed above, the powder bed fusion technology also consists of a thin powder bed layer that is present on a print platform. However, in powder bed fusion a laser beam instead of binder solution is used to bind the powder together. The laser beam selectively follows a specific pattern on the powder bed, for which the pattern instructions are contained in the uploaded printing file. The energy of the laser sinters (fuses) the powder particles on the print platform and thereby creates a printed and solid layer.

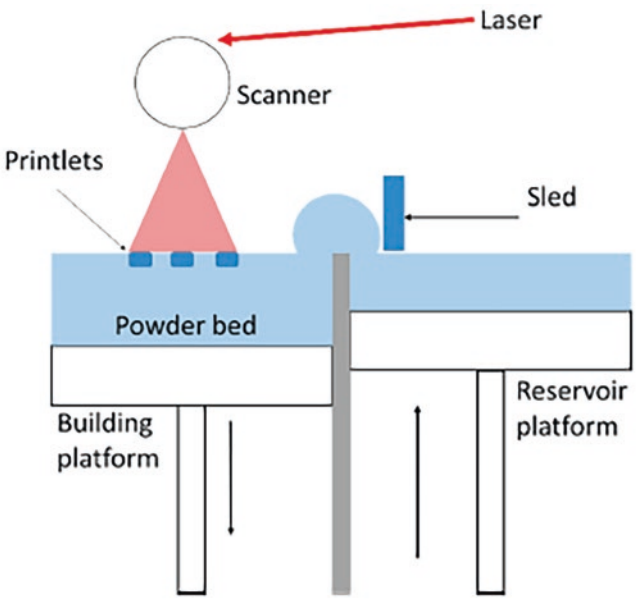


Fig. 28.30 Schematic representation of a typical SLS printer. (Reprinted from Ref. [54])

Subsequently, the print platform is lowered and a new powder layer is spread on the previous layer by a roller/sled. This process is repeated until the three-dimensional object is fully printed. As a final process step, the unsintered pow-

der that surrounds the printed object is removed to obtain the final product [53].

SLS is suitable to manufacture complex structures with varying porosity in a one-step process, which can produce medicine formulations with different release profile characteristics. The technology is also solvent-free since no liquid binding solution is needed. Because no additional supporting materials are needed during the printing process, fast and low-cost printing can be achieved. However, the energy of the laser beam that is needed to sinter the powder is not compatible with photosensitive and thermolabile active substances. The flexibility of the technology is also hampered due to the limited choice in pharmaceutical-grade and non-toxic powder blends that are suitable for SLS.

28.10.6 Material Jetting

The material jetting technology has similarities with two-dimension printing (printing ink on paper) and the other three-dimensional printing technologies that are discussed above in this section. The technology consists of a print head that jets the printing material drop-by-drop onto a platform in a specific pattern contained in the print file, similar to two-dimensional ink printing on paper. The jetted ink solidifies on the platform, the platform is lowered, and another layer of jetted ink is added to the printed object. This process is repeated until the object is fully printed [45].

The ink commonly consists of a liquid mixture that contains a wax or photopolymer in which the active and/or excipients are processed. Photopolymer ink solutions solidify under UV lighting and therefore a UV light source is typically attached to the print head of these printers, which solidifies the ink as soon as it is printed onto the print platform [55].

Several techniques can be used to jet the ink from the ink reservoir via the print head onto the print platform. In continuous inkjet printing (CIJ), a continuous stream of ink droplets is ejected from the print head, whereas in drop-on-demand (DoD) ink droplets are only ejected from the print head when an ink drop is required. Pneumatic pressure, thermal energy, or a piezoelectric actuator in the print head can be used to generate the required force (pressure) to eject the ink out of the print head (Fig. 28.31).

Similar to the material extrusion technology (Section 2), the object is printed and built from scratch, and thus, a supporting scaffold structure may be needed for bigger objects (Fig. 28.32). Material jetting differs from binder jetting technology (Section 4) since the ink itself is the building material of the object instead of the adhesive that is dispersed from the print head, whereas it also differs from vat polymerization, a technique which also uses UV light to solidify the printed material, since no vat that contains the photopolymer is used during the printing process (Section 3).

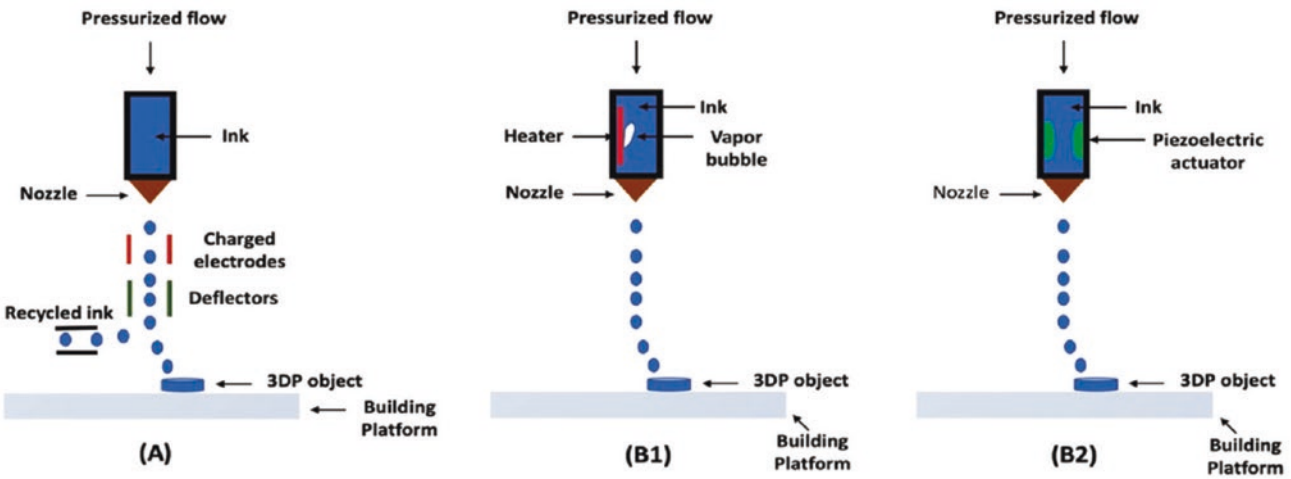


Fig. 28.31 Schematic representation of a typical material jetting printer (inkjet printer). (**a**) CIJ printer whereby pneumatic pressure in the ink reservoir continuously jets the printing material onto the print platform. (**b1**) DoD inkjet printer whereby thermal energy is used to jet drops on demand onto the print platform. (**b2**) DoD inkjet printer whereby a piezoelectric actuator is used to jet drops on demand onto the print platform. (Reprinted from Ref. [45])

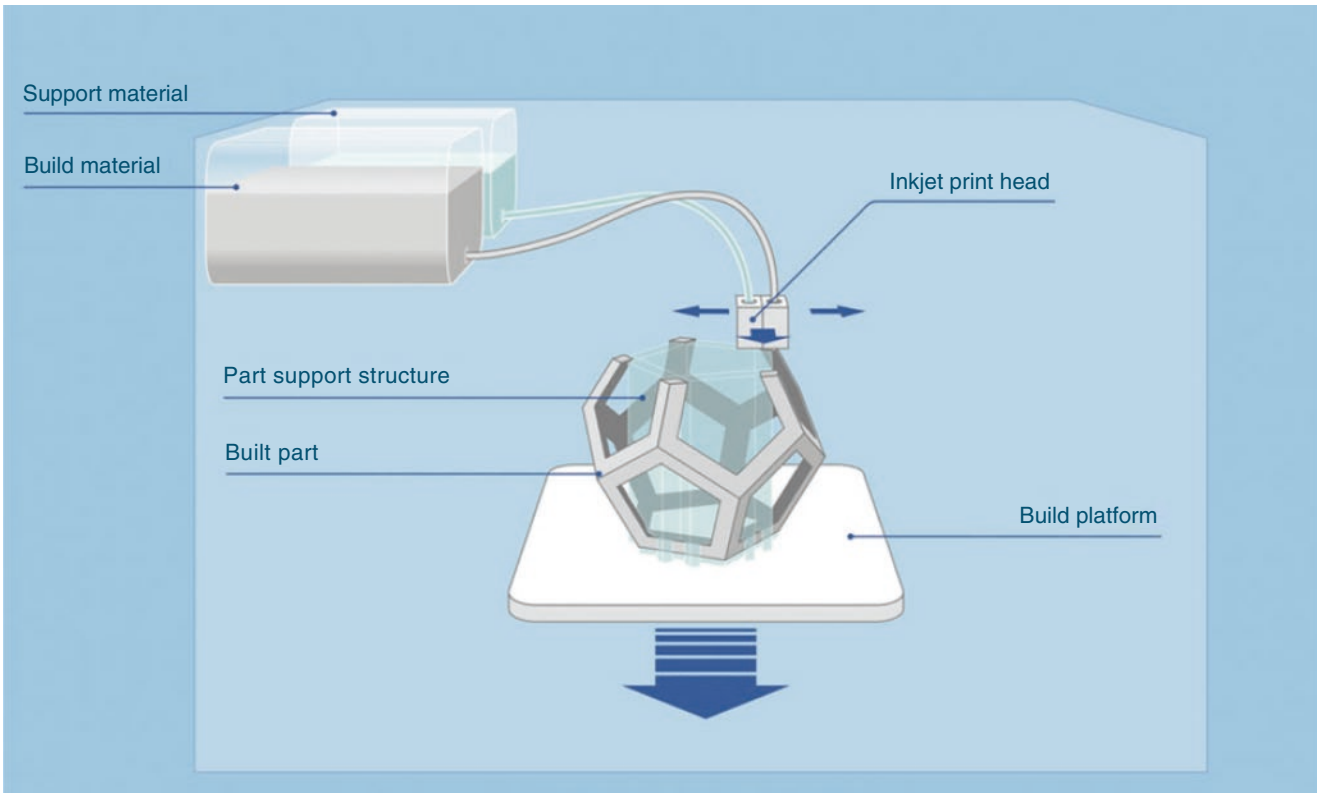


Fig. 28.32 Schematic representation of a typical material jetting printer (inkjet printer) that prints a bigger object for which a supporting structure is required. (Reprinted from Additively.com)

Multiple printing heads may be used that each print a different ink formulation. The different inks can selectively be added to the object to create an object that consists of different materials (e.g. multi-active substance object). In addition, the technique is relatively accurate, precise, reproducible, and cheap. However, it is less suitable to print objects with a high active substance load. Printing photosensitive or thermolabile active substances is also hampered in case a photopolymer ink solution or thermal inkjet printing head, respectively, is used. Another drawback of the technique is that the ink should comply with certain fluid characteristics (e.g. viscosity, surface tension, rheology) for the formation of the desired ink stream or droplets, which is not always possible for every medicine formulation.

References

1. Health and Safety Executive (2017) Controlling airborne contaminants at work. A guide to local exhaust ventilation, 3rd edn. http://www.hse.gov.uk/pubns/hsg258.pdf
2. Health and Safety Executive (2022) Control of Substances Hazardous to Health (COSHH). Controlling exposure to chemicals – a simple control banding approach. https://www.hse.gov.uk/pubns/guidance/coshh-technical-basis.pdf
3. Health and Safety Executive (2021) COSHH Fume cupboard, engineering control, sheet 201. http://coshh-tool.hse.gov.uk/assets/live/G201.pdf
4. EN 14175-4 Fume cupboards on site test methods
5. EN 12469 Biotechnology – performance criteria for microbiological safety cabinets
6. Eudralex. Volume 4. Guide to good manufacturing practices for medicinal products. http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm
7. General Chapter <800> Hazardous drugs – handling in healthcare settings. 2019. http://www.usp.org/usp-nf/notices/compounding-notice
8. Midcalf B, Mitchell PW, Neiger JS, Coles TJ (eds) (2004) Pharmaceutical isolators a guide to their application, design and control. Pharmaceutical Press, London
9. Collentro WV (2007) Pharmaceutical water, system design, operation and validation. Informa Healthcare, Richmond
10. ISPE Water and steam systems Baseline guide. ISPE (2011)
11. Note for Guidance on quality of water for Pharmaceutical use. EMEA (2002)
12. Bader K, Hyde J, Watler P, Lane A (2009) Online Total Organic Carbon (TOC) as a process analytical technology for cleaning validation risk management. Pharm Eng 29(1):8–21
13. ISPE baseline guide vol 4. 2019. Water & steam systems, 3rd edn.
14. Mathiesen T, Rau J, Frantsen JE, Terävä J, Björnstedt P-A, Henkel B (2002) Using exposure tests to examine rouging of stainless steel. Pharm Eng 22:90–97
15. ISPE good practice guide: commissioning and qualification of pharmaceutical water and steam systems, 2nd edn. ISPE (2014)
16. van de Poll MAPC, Jelsma RBH, Lukkien M, Boeke AW (1992) Mortier dichtwrijven, een mythe? Pharm Weekbl 127:258–259
17. I.6. Dermatika – Zubereitungen zur kutanen Anwendung. I.6.3.2.1. Alternative Herstellungstechniken. Halb- und vollau-

tomatische Rührsysteme. Fassung 2014/1. Deutscher Arzneimittel-Codex/Neues Rezeptur-Formularium (NRF). Govi-Verlag Pharmazeutischer Verlag GmbH Eschborn. Deutscher Apotheker-Verlag, Stuttgart
18. Wagenaar HWG, Dessing WS, Joosten AAM (2008) Mengapparaten Topitec en Unguator vergeleken met handmatige bereiding van dermatica met hydrocortisonacetaat. PW Wetenschappelijk Platform 2(8):170–174
19. Woerdenbag HJ, Visser JC, Leferink Op Reinink MPAM, van Orsoy RR, Eissens AC, Hagedoorn P, Dijkstra H, Allersma DP, Ng SW, Smeets OSNM et al (2022) Performance of tablet splitters, crushers, and grinders in relation to personalised medication with tablets. Pharmaceutics 14. https://doi.org/10.3390/pharmaceutics14020320
20. Bhoite K, Kakandikar GM, Nandedkar VM (2015) Schatz mechanism with 3D-motion mixer- a review. Mater Today 2:1700–1706. https://doi.org/10.1016/j.matpr.2015.07.003
21. NOODDIS France. Available via URL: https://nooddis.fr/. Accessed 17 March 2023.
22. Soumoy L, Hecq J-D (2019) Automated compounding of intravenous therapy in European countries: a review in 2019. Pharm Technol Hosp Pharm 4(2):51–57.
23. Batson S et al (2020) Automated compounding technology and workflow solutions for the preparation of chemotherapy: a systematic review. Eur J Hosp Pharm 27:330–336
24. Iredell B et al (2022) ASHP guidelines on the safe use of automated compounding devices for the preparation of parenteral nutrition admixtures. Am J Health-Syst Pharm 79:730–735
25. Hecq JD (2018) Review of manual and automated compounding of intravenous drugs: an update in 2018. https://doi.org/10.13140/RG.2.2.21942.60480
26. https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/safe-use-automated-compounding-devices-preparation-parenteral-nutrition-admixtures.pdf
27. Cox HLM, De Kind LAP, Vink-Stephan JJ (1979) Onderzoek naar gelijkmatigheid van de verdeling van het geneesmiddel over zetpillen bij gebruik van een zetpillengietapparaat IV. Het ROWA zetpillengietapparaat. Pharm Weekbl 114:811–815
28. Cox HLM, De Kind LAP (1978) Onderzoek naar gelijkmatigheid van de verdeling van het geneesmiddel over zetpillen bij gebruik van een zetpillengietapparaat I. Pharm Weekbl 113:364–368
29. Cox HLM, Holthuis JJM, De Kind LAP (1981) Onderzoek naar gelijkmatigheid van de verdeling van het geneesmiddel over zetpillen bij gebruik van een zetpillengietapparaat V. Het GPI type H250 zetpillengietapparaat. Pharm Weekbl 116:1101–1104
30. Cabaleiro J (2004) Automatic dishwashers and detergents in the pharmacy: the basics. Int J Comp 8:200–202
31. Stability testing of new drug substances and drug products. ICH Q1A guideline 2003
32. Hawkins AE, Zuckerman MA, Briggs M, Gilson RJ, Goldstone AH, Brink NS, Tedder RS (1996) Hepatitis B nucleotide sequence analysis: linking an outbreak of acute hepatitis B to contamination of a cryopreservation tank. J Virol Methods 60:81–88. https://doi.org/10.1016/0166-0934(96)02048-4
33. Hunt CJ (2019) Technical considerations in the freezing, low-temperature storage and thawing of stem cells for cellular therapies. Transfus Med Hemother 46:134–150. https://doi.org/10.1159/000497289
34. Karalia D, Siamidi A, Karalis V, Vlachou M (2021) 3D-printed oral dosage forms: mechanical properties, computational approaches and applications. Pharmaceutics 13. https://doi.org/10.3390/pharmaceutics13091401
35. Seoane-Viaño I, Ong JJ, Luzardo-Álvarez A, González-Barcia M, Basit AW, Otero-Espinar FJ, Goyanes A (2021) 3D printed tacrolimus suppositories for the treatment of ulcerative colitis. Asian J Pharm Sci 16:110–119. https://doi.org/10.1016/j.ajps.2020.06.003
36. Gupta MS, Kumar TP, Davidson R, Kuppu GR, Pathak K, Gowda DV (2021) Printing methods in the production of orodispersible films. AAPS PharmSciTech 22:129. https://doi.org/10.1208/s12249-021-01990-3
37. Pollard TD, Bonetti M, Day A, Gaisford S, Orlu M, Basit AW, Murdan S, Goyanes A (2022) Printing drugs onto nails for effective treatment of onychomycosis. Pharmaceutics 14:448. https://doi.org/10.3390/pharmaceutics14020448
38. Trenfield SJ, Awad A, Madla CM, Hatton GB, Firth J, Goyanes A, Gaisford S, Basit AW (2019) Shaping the future: recent advances of 3D printing in drug delivery and healthcare. Expert Opin Drug Deliv 16:1081–1094. https://doi.org/10.1080/17425247.2019.1660318
39. Kanyilmaz A, Demir AG, Chierici M, Berto F, Gardner L, Kandukuri SY, Kassabian P, Kinoshita T, Laurenti A, Paoletti I et al (2022) Role of metal 3D printing to increase quality and resource-efficiency in the construction sector. Addit Manuf 50:102541. https://doi.org/10.1016/j.addma.2021.102541
40. Kreiger EL, Kreiger MA, Case MP (2019) Development of the construction processes for reinforced additively constructed concrete. Addit Manuf 28:39–49. https://doi.org/10.1016/j.addma.2019.02.015
41. Jamróz W, Szafraniec J, Kurek M, Jachowicz R (2018) 3D printing in pharmaceutical and medical applications – recent achievements and challenges. Pharm Res 35:176. https://doi.org/10.1007/s11095-018-2454-x
42. Guidance for Industry and Food and Drug Administration Staff Technical Considerations for Additive Manufactured Medical Devices. 2017
43. Food and Drug Administration Discussion Paper: 3D Printing Medical Devices at the Point of Care. 2021
44. Salmi M (2021) Additive manufacturing processes in medical applications. Materials (Basel, Switzerland) 14. https://doi.org/10.3390/ma14010191
45. Pitzanti G, Mathew E, Andrews GP, Jones DS, Lamprou DA (2022) 3D printing: an appealing technology for the manufacturing of solid oral dosage forms. J Pharm Pharmacol XX:1–22. https://doi.org/10.1093/jpp/rgab136
46. Vaz VM, Kumar L (2021) 3D printing as a promising tool in personalized medicine. AAPS PharmSciTech 22:49. https://doi.org/10.1208/s12249-020-01905-8
47. Gonzalez-Gutierrez J, Cano S, Schuschnigg S, Kukla C, Sapkota J, Holzer C (2018) Additive manufacturing of metallic and ceramic components by the material extrusion of highly-filled polymers: a review and future perspectives. Materials (Basel, Switzerland) 11. https://doi.org/10.3390/ma11050840
48. Annaji M, Ramesh S, Poudel I, Govindarajulu M, Arnold RD, Dhanasekaran M, Babu RJ (2020) Application of extrusion-based 3D printed dosage forms in the treatment of chronic diseases. J Pharm Sci 109:3551–3568. https://doi.org/10.1016/j.xphs.2020.09.042
49. Araújo MRP, Sa-Barreto LL, Gratieri T, Gelfuso GM, Cunha-Filho M (2019) The digital pharmacies era: how 3D printing technology using fused deposition modeling can become a reality. Pharmaceutics 11. https://doi.org/10.3390/pharmaceutics11030128
50. Goyanes A, Allahham N, Trenfield SJ, Stoyanov E, Gaisford S, Basit AW (2019) Direct powder extrusion 3D printing: fabrication of drug products using a novel single-step process. Int J Pharm 567:118471. https://doi.org/10.1016/j.ijpharm.2019.118471
51. Pagac M, Hajnys J, Ma Q-P, Jancar L, Jansa J, Stefek P, Mesicek J (2021) A review of Vat photopolymerization technology: materials, applications, challenges, and future trends of 3D printing. Polymers (Basel) 13. https://doi.org/10.3390/polym13040598

52. Sen K, Mehta T, Sansare S, Sharifi L, Ma AWK, Chaudhuri B (2021) Pharmaceutical applications of powder-based binder jet 3D printing process – a review. Adv Drug Deliv Rev 177:113943. https://doi.org/10.1016/j.addr.2021.113943
53. Awad A, Fina F, Goyanes A, Gaisford S, Basit AW (2020) 3D printing: principles and pharmaceutical applications of selective laser sintering. Int J Pharm 586:119594. https://doi.org/10.1016/j.ijpharm.2020.119594
54. Gueche YA, Sanchez-Ballester NM, Cailleaux S, Bataille B, Soulairol I (2021) Selective Laser Sintering (SLS), a new chapter in the production of Solid Oral Forms (SOFs) by 3D printing. Pharmaceutics 13. https://doi.org/10.3390/pharmaceutics13081212
55. Clark EA, Alexander MR, Irvine DJ, Roberts CJ, Wallace MJ, Sharpe S, Yoo J, Hague RJM, Tuck CJ, Wildman RD (2017) 3D printing of tablets using inkjet with UV photoinitiation. Int J Pharm 529:523–530. https://doi.org/10.1016/j.ijpharm.2017.06.085