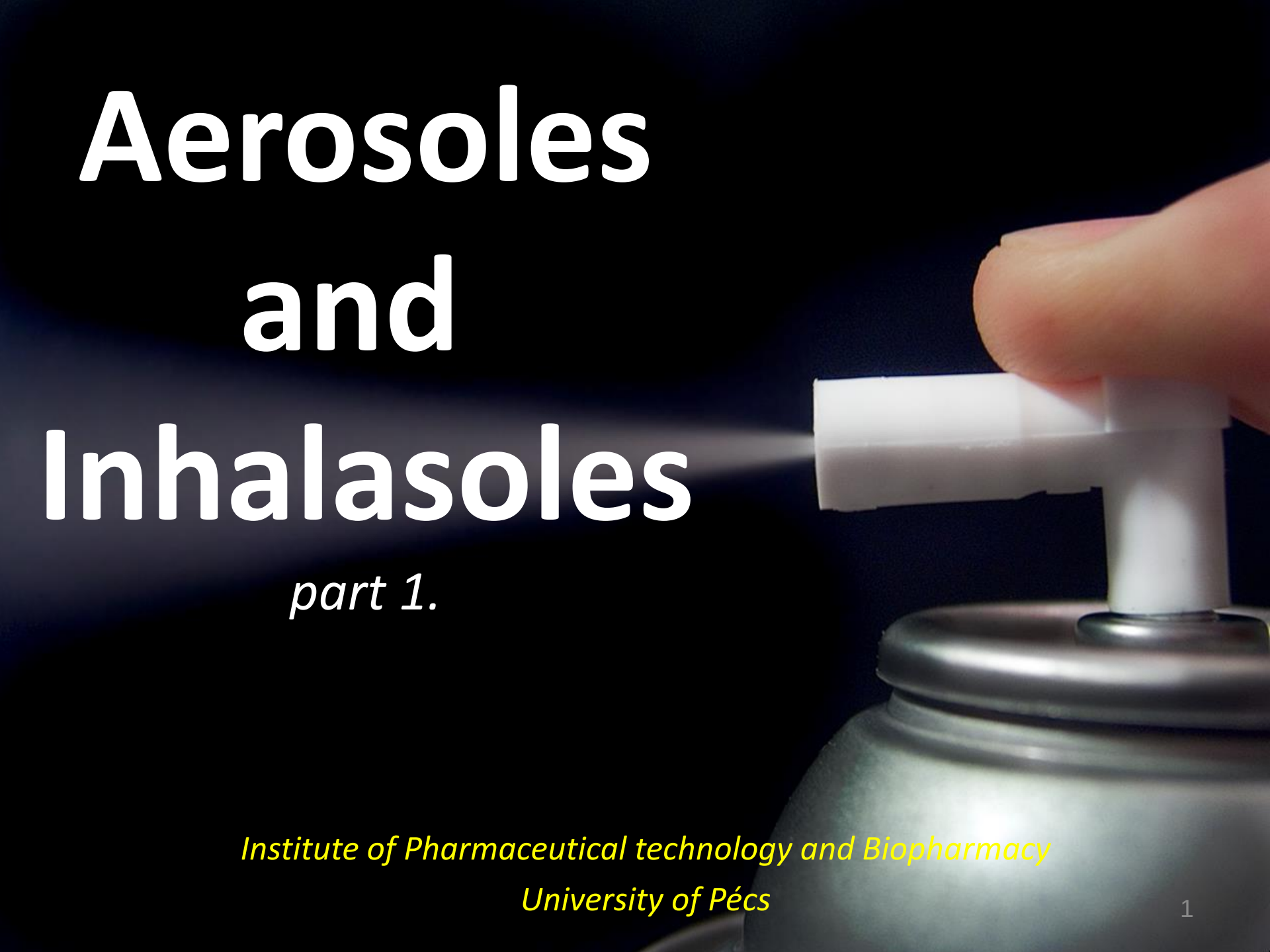
Aerosoles and Inhalasoles

part 1.



Institute of Pharmaceutical technology and Biopharmacy

University of Pécs

Topics

- Definition
- Devices
- Excipients
- Manufacturing of aerosols
- Quality controls
- Packaging of aerosols

Important dates!

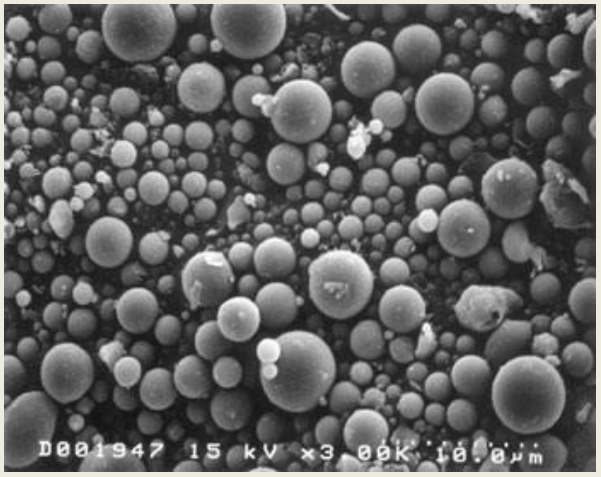
Aerosoles

Definition

Aerosols are **disperse systems** - fine solid particles or liquid droplets in air or another gas.

The aerosol (spray) are used to deliver drugs for organism and skin.

Technological applications of aerosols include medical treatment of **respiratory illnesses**, **skin** or other surfaces (eg. ear, nasal mucosa).



Photomicrograph made with a Scanning Electron Microscope (SEM) Fly ash particles at 2,000x magnification.

Most of the particles in this aerosol are nearly spherical.

Pressurised pharmaceutical preparations

Definition

Pressurised pharmaceutical preparations are presented in special containers under pressure of a gas and contain one or more active substances.

The preparations are released from the container, upon actuation of an appropriate valve, in the form of an **aerosol** (dispersion of solid or liquid particles in a gas, the size of the particles being adapted to the intended use) or of a liquid or semisolid jet such as a **foam**.

Pressurised pharmaceutical preparations

Preparations

Additional requirements for preparations presented in pressurised containers may be found, where appropriate, in other general monographs, for example:

- Preparations for **inhalation**,
- **Liquid** preparations for **cutaneous** application,
- **Powders** for **cutaneous** application,
- **Nasal** preparations and
- **Ear** preparations .

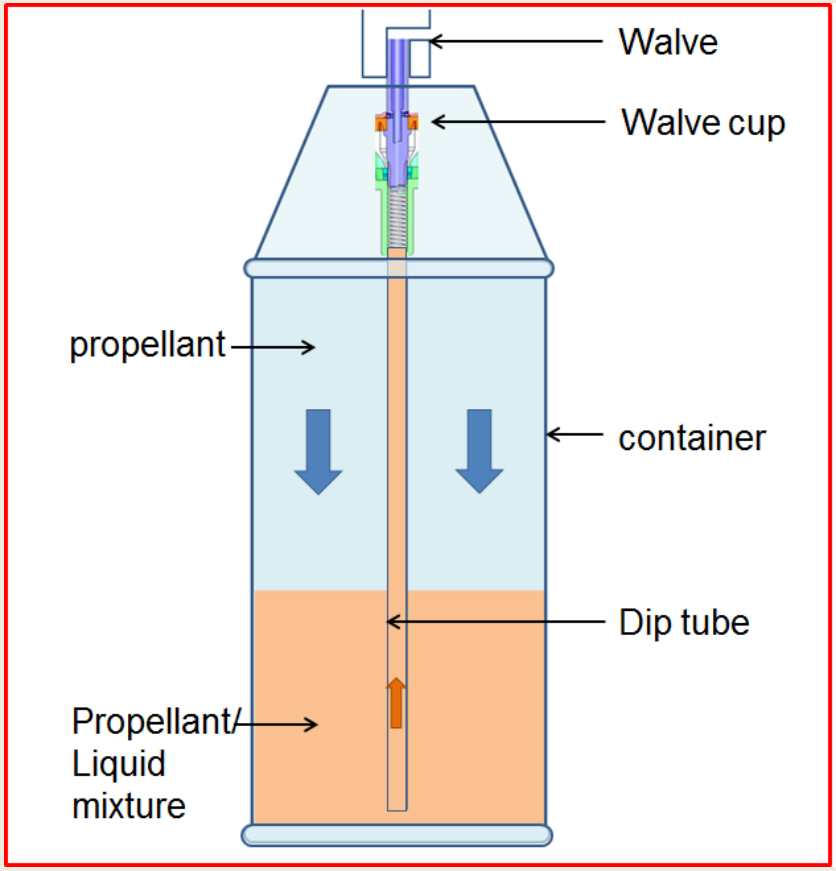
Aerosols

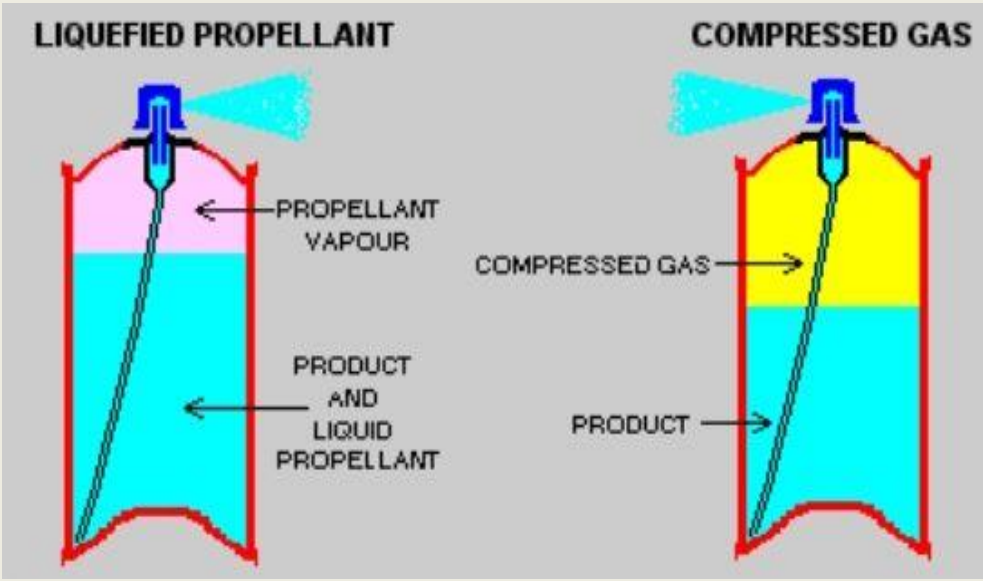
Steps of atomizing

1. The atomizing head disintegrates the droplets.
2. Droplets dispersed in the air resistance.
3. The solvent evaporates from the droplets – solid particles.
4. Transfer kinetic energy of flowing particles a portion of the air as a result of airflow speeds.

Aerosol devices

Aerosol devices





Aerosol devices

Container

The containers are tight and resistant to the internal pressure.

They must be stand at pressure as high as 140 to 180 psig (pounds per sq. inch gauge) at 1300 F. (9.6-12.4 bar at 700 °C)

Materails of containers are compatible with their contents.

Aerosol devices

Container

Containers may be made of

Metals

1. **Tinplated steel**
   a. Side-seam (three pieces)
   b. Two-piece or drawn
   c. Tin free steel

2. **Alunimium**
   a. Two-piece
   b. One-piece (extruded or drawn)

3. **Stainless steel**

Glass

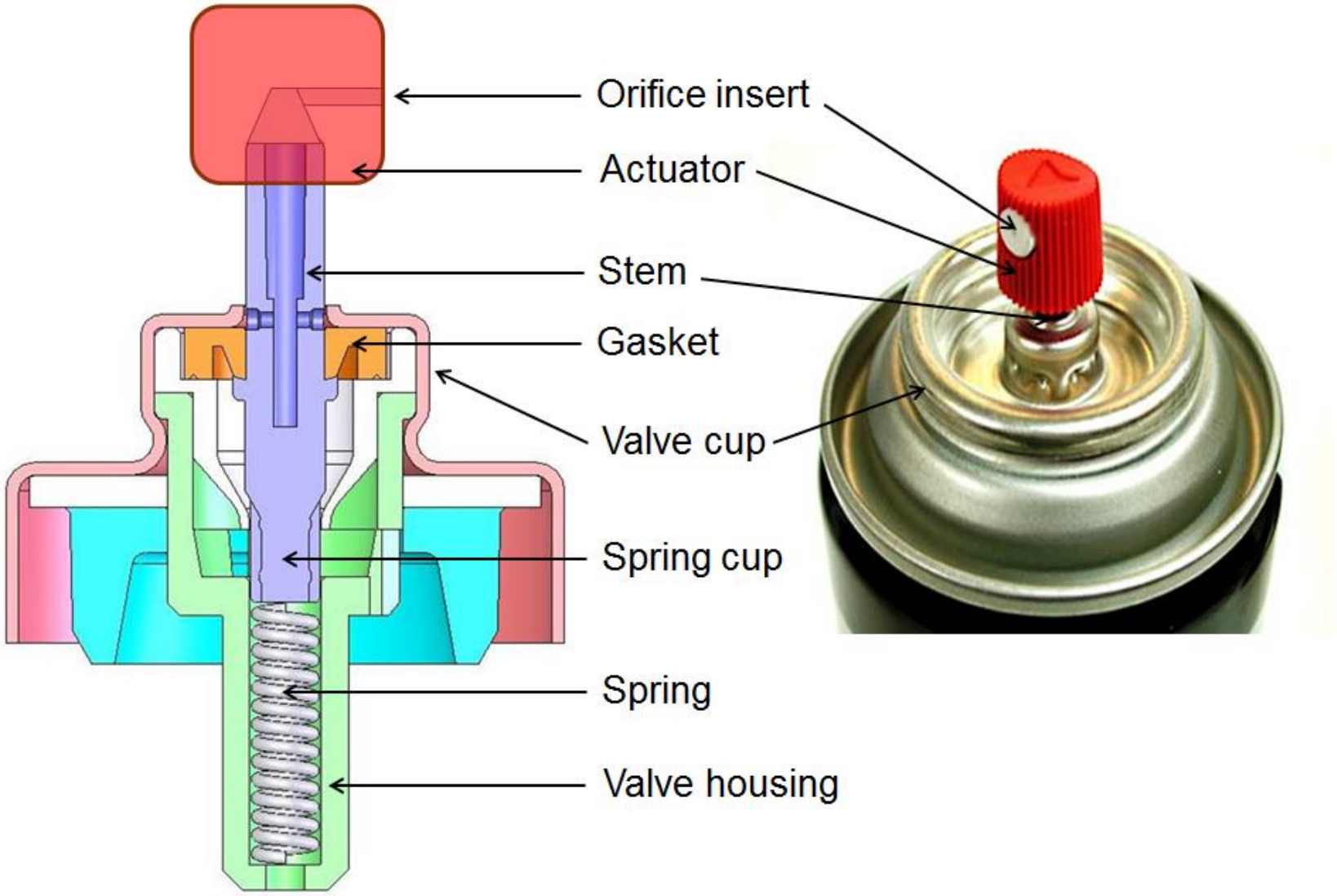
a. Uncoated glass
b. Plastic coated glass

Plastic

Aerosol devices

Container

Aerosol devices



Aerosol devices

Definition

Valves are

- To **deliver the drug** in desired form,
- To give **proper amount** of medication.

Types of valves

- **Continuous** spray valve,
- **Metering dose** valves deliver a defined quantity of product upon each valve actuation,
- **High speed** production technique.

Aerosol devices

Definition

The valve keeps the container tightly closed when not in use and regulates the delivery of the contents during use.

The **spray characteristics** are **influenced** by the **type** of spraying device, in particular by the **dimensions**, **number** and **location** of orifices.

Some valves provide a **continuous release**, others („**metering dose valves**") deliver a **defined quantity** of product upon each valve actuation.

The various valve materials in contact with the contents are compatible with them.

Dispersing of potent medication at proper dispersion/spray approximately 50 to 150 mg ±10 % of liquid materials at one time use of same valve.

Aerosol devices

Definition

Actuators are for ensuring that aerosol product is delivered in the proper and desired form.

Different types of actuators:

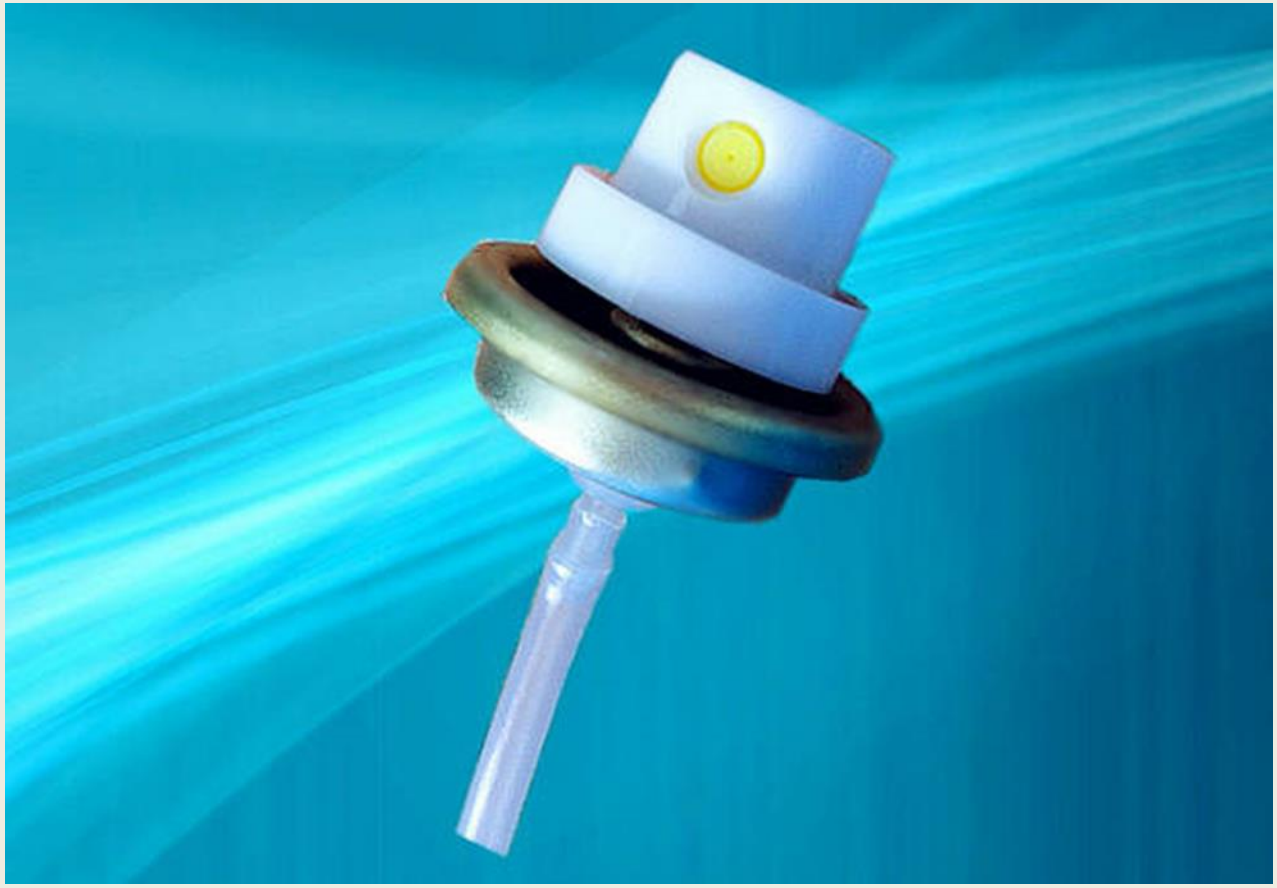
- **Spray** actuators,
- **Powder** actuators,
- **Foam** actuators,
- **Special actuators.**

Aerosol devices

Valves and actuators and tubes

Aerosol devices

Valves and actuators



Normal actuator for general purposes

Aerosol devices

Valves and actuators

Actuator with nebulizing insert suitable for **oral** and **otic** applications

Aerosol devices

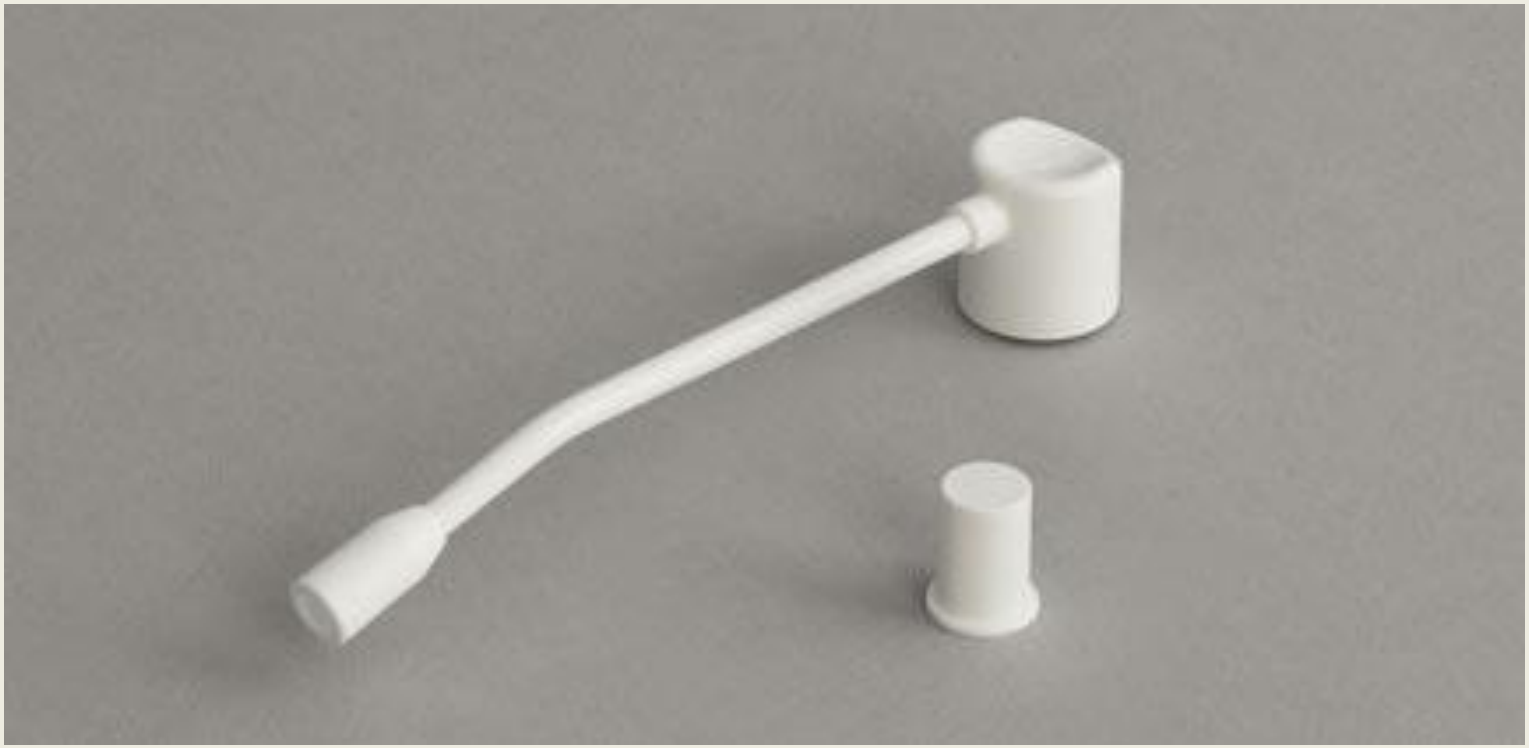
Actuator

Suitable for **nasal** use by adults and children

Special nebulizing insert ensures correct spray pattern

Aerosol devices

Actuator



Angled tube incorporates a nebulizing insert
Suitable for **oral** applications

Aerosol devices

Actuator

Aerosol Foaming Soap Pump

Excipients

Excipients

The preparations consist of a **solution**, an **emulsion** or a **suspension** and are intended for **local application** to the **skin** or to **mucous membranes** of various body orifices, or for **inhalation**.

Suitable excipients are

- propellants,
- solvents,
- solubilizers,
- antioxidants,
- emulsifying agents,
- suspending agents and
- lubricants for the valve to prevent clogging.

Organic liquids exhibit a **strong interaction** with most of the **rubber** and **polymeric** materials used in the manufacture of the valve.
Therefore, potential leaching of compounds from these rubber components, as well as from all other polymeric materials, into the drug formulation is considered as a very serious concern that should be addressed.

Excipients

Propellants

The pressure for the release is generated by suitable propellants.

The **propellants** are either **gases liquefied** under pressure or **compressed gases** or **low-boiling liquids**.

Liquefied gases are, for example, **fluorinated hydrocarbons** and **low-molecular-mass hydrocarbons** (such as propane and butane).

Compressed gases are for example, **carbon dioxide**, **nitrogen** and **nitrous oxide**.

Mixtures of these propellants may be used to obtain optimal solution properties and desirable pressure, delivery and spray characteristics.

Excipients

Propellants

Propellant is responsible for developing the power pressure with in the container and also expel the product when the valve is opened and in the atomization or foam production of the product.

For oral and inhalation eg.

Fluorinated hydrocarbons,
Dichlorodifluromethane (propellent 12),
Dichlorotetrafluromethane (propellent 114)

For topical preparation

Propane,
Butane,
Isobutane,
Compound gases (Nitrogen, Carbon di oxide, Nitrous oxide)

Excipients

Propellants

Chlorofluorocarbons (CFCs)

In the early days of MDIs the most commonly used propellants were the chlorofluorocarbons CFC-11, CFC-12 and CFC-114.

Transition to **hydrofluoroalkane** (HFA) propellants

In 2008 the **Food and Drug Administration** announced that inhalers using **chlorofluorocarbons** as a propellant, such as Primatene Mist, could **no longer be manufactured or sold as of 2012**. This followed from the U.S. decision to agree to the 1987 Montreal Protocol on Substances that Deplete the Ozone Layer.

In addition, inhalation aerosol formulations typically include organic liquids as the propellant (chlorofluorocarbons, hydrofluorocarbons) or as the vehicle (alcohols).

Excipients

Propellants

Physicochemial properties of propellants

- Vapor presure,
- Density,
- Solubility,
- Boiling point.

Chlorofluorocarbons (CFCs) (***Freon***)

Advantages

- Inhalation - low toxicity
- Odorless
- High chemical stability
- High purity
- CFC-11 is a good solvent

Disadvantages

- The ozone layer is damaged
- Their "greenhouse effect" is significant
- Internal pressure decreases when applied
- Expensive

Chlorofluorocarbons (CFCs) (***Freon***)

Physiological effect:

Single long-term use (few minutes) with strong cooling

Dose Effect (Practically 1000 ppm

-- light disturbance - 30 minutes, approx. 12,000 ppm)

No evidence of hepatic impairment

(as carbon tetrachloride, chloroform)

Less toxic than chlorine hydrocarbons,

Reason: high chemical stability, low bonding between F - C is strong

Chlorofluorocarbons (CFCs)
(***Freon***)

Disadvantages:
reduces ozone in the stratosphere - reduces the ozone layer thickness (about 6-7% of the drugs for freonic propellant products)

Biofarmacy studies

They are bound to plasma proteins, therefore higher solubility, as isotonic saline solution.

Freon 11 solubility in water is higher, absorption rate is also higher.

Freon's 114 distribution ratios are the largest.

Due to dissolution lipoid tissue has a high half-life.

Hydrofluorocarbons

Advantages

- Inhalation - low toxicity
- High purity
- High chemical stability
- Not ozone depleting

Disadvantages

- Bad solvents
- Small „greenhouse” effect
- Expensive

Hydrocarbons

Advantages

- Cheap
- The ozone layer is not (minimally) damaged
- There is no „greenhouse effect”
- Good solvents
- Mixture:
  33% propane + 67% butane
- Today:
  99% Butane (Extremely Clean!)

Disadvantages

- Internal pressure decreases when applied
- Flammable,
- Explosive
- Odorous
- Inhalation - their toxicity is unknown
- Low flux density

Compressed gases

application, the spray characteristic is not a critical requirement, not a decisive parameter

Advantages

- Inhalation - low toxicity
- High purity
- High chemical stability
- Not flammable
- Not environmental pollutants

Disadvantages

- Necessary non-volatile solvent
- May be a drop during application
- Pressure decreasing during application

Compressed gases

Nitrogen

- Physiological and chemical indifference
- Inhibits oxidation
- Temperature does not affect the pressure
- Cheap
- High internal starting pressure
- Not miscible (non-foaming, non-fine spray)

Compressed gases

Carbon dioxide

Advantages

- Non-toxic
- Cheap
- Not flammable
- Not explosive
- Not environmentally hazardous
- Oxidation
- Little cooling effect
- In dissolved form - temperature rise - small change

Disadvantages

- Soluble in weak acids
- Special valves - multiple impacts - fine spray
- Higher solvent fraction - flammability increases
- Bottles can not be used in reverse direction

Compressed gases

Nitrous oxide

Advantages

- Well soluble in water, in organic solvents
- Not flammable
- Economical

Disadvantages

- Does not spill in itself
- Dispersing with small amounts of freon

Argon

Disadvantages

- noble gas
- expensive

Excipients

Roles of excipients:

- valve **lubrication**,
- to ensure a homogeneous **distribution** of the solid phase in the liquid or in the propellant,
- the structural **stabilization** of the „foam aerosols”,
- **emulsifying** the propellant and the aqueous phase,
- **increase the solubility** of the active substance in the propellant and in the liquid system.

- Anionic - eg. oleic acid
- Cationic - eg. cetylpyridinium chloride
- Amphoto - eg. phosphatidylcholine
- Nonionic - eg. sorbitan trioleate

Manufacturing of aerosols

Manufacturing of aerosols

Manufacturing

The filling apparatus can be:

- Pressure filling,
- Cold filling,
- Compressed gas filling apparatus.

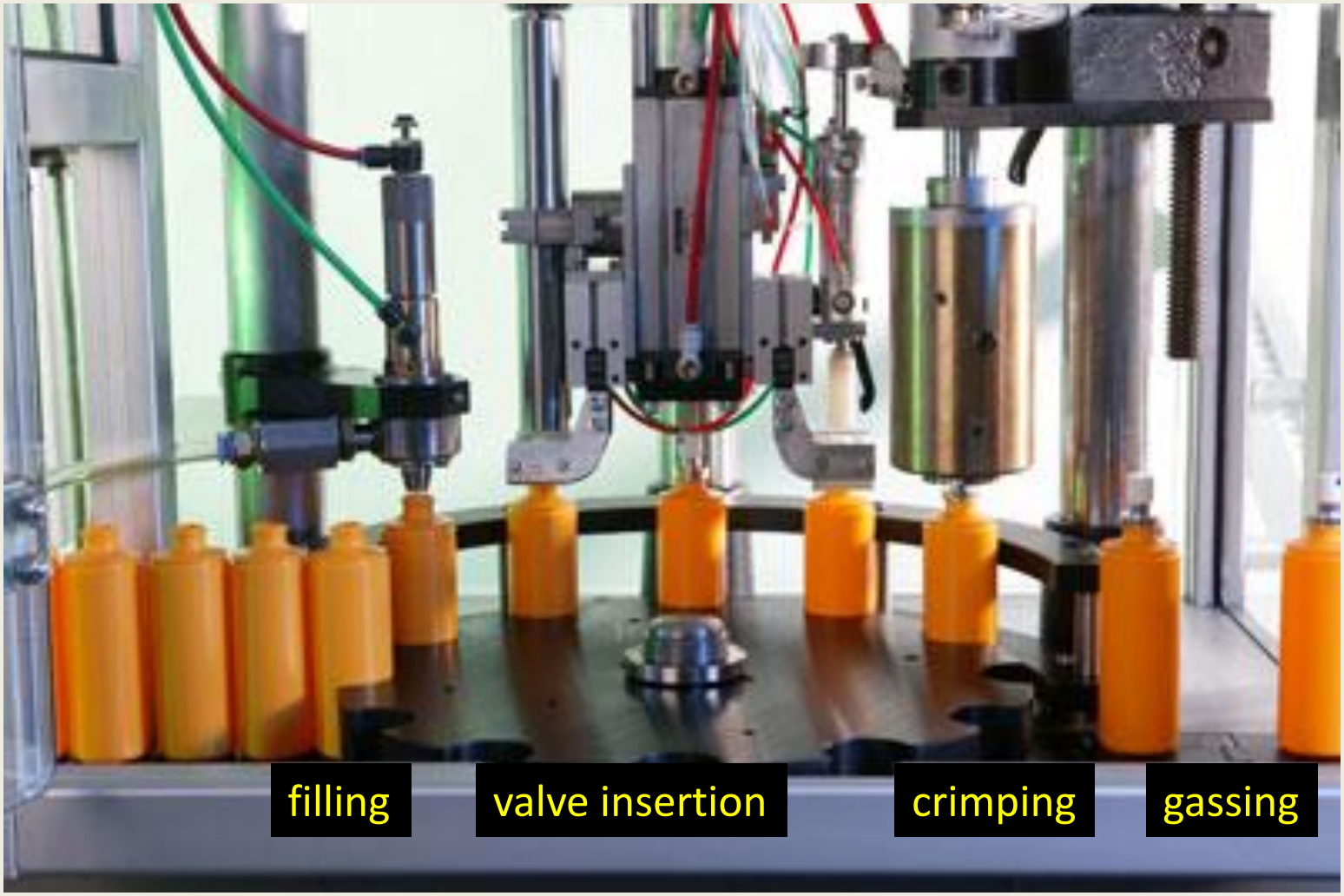
Manufacturing of aerosols

Manufacturing

Hand-powered device

Manufacturing of aerosols

Industrial manufacturing



Manufacturing of aerosols

Industrial manufacturing

Manufacturing of aerosols

Industrial manufacturing

valve insertion

Manufacturing of aerosols

Industrial manufacturing

Machine has three functions:

- filling liquid,
- valve putting,
- valve capping.

To avoid corrosion the position pump will be made by silicon rubber, Teflon, ceramics and other corrosion resistance materials.
Capacity : 1000-2000 Cans/Hour

Manufacturing of aerosols

Industrial manufacturing

Quality control of aerosols

Quality controls

Flammability and combustibility

1. Flash point

2. Flame extension, including flashback

Quality controls

Physiochemical characteristics

- Density
- Moisture content
- Vapor pressure
- Identification of propellant(s)
- Concentrate-propellant ratio

Quality controls

Performance

- Aerosol valve discharge rate
- Spray pattern
- Dosage with metered valves
- Net contents
- Foam stability
- Particle size determination
- Leakage

Quality controls

Biopharmaceutical

- Biologic characteristics
- Therapeutic activity

Packaging of aerosols

Packaging

Labelling

The label states:

- the method of use,
- any precautions to be taken,
- for a container with a metering dose valve,
- the amount of active substance in a unit-spray.

Bag on Valve

- Bag-on-Valve (BOV) aerosol is a superior spray dispensing system, with modern packaging that improves cosmetic, medical or food products.
- Compared to traditional aerosol spray technology (and other alternative packaging), BOV has several benefits, for manufacturers, consumers and the environment.

Bag on Valve

- Good to the last ‚drop' with up to 100% product emptying
- Longer shelf life with less preservatives
- Even and controlled spraying pattern delivers optimal results at any change
- Less-chilling product discharge making it ideal for wounds or sensitive skin
- No pumping motion needed
- Reduced spray noise

Bag on Valve

- No need for flammable propellants
- Hygienic and sterilisable
- Used with eco-friendly air or nitrogen
- Less need for preservatives
- 100% recyclable

Bag on Valve

- The propellant of BOV product is compressed air or nitrogen which is contained between the bag and the can, never coming in contact with the product.
- The product is sealed inside the bag throughout the entire shelf life, offering complete protection against oxygen exposure.

Bag on Valve

- Longer shelf life for oxygen-sensitive products
- Suitable for liquids and viscous products
- Use with standard actuators and aerosol cans

Thank you
for your attention!

Important dates:
17. March
14. April
05. May