Lesson - 33

Pharmaceutical Aerosols III

(Components and systems of aerosols)

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Learning outcomes

After learning this module you will be able to understand

- Know about the construction of aerosol
- Understand the different systems of aerosol and
- Discuss manufacturing of aerosols.

Lesson Plan

- Valve and actuators
- Aerosol systems
- Different type of systems
- Manufacturing of aerosols

Components of Aerosols

An aerosol system has following major components.
Module 33 Pharmaceutical Aerosols

- Propellant
- Container
- Valve and actuator
- Product concentrate

So far we discussed the definition, advantages, disadvantages, types of aerosols. Propellant (Heart of an aerosol package) and Container (different types Al, SS, plastic, glass). Now let’s move to valve and actuator, and product concentrate.

Valve

It is the vital component of an aerosol package. It helps to deliver the drug in desired form. It determines the performance of a pressurized package. Major functions of valves are as followed: (RPG)

- Regulating the flow of product out of the container
- Providing discharge of desired amount (when needed) and preventing loss when not in use.
- Governing the characteristics of dispensed product.

*Remember the function with acronym RPG.*

Types of Valves

- **Continuous spray valve**

  These valves release the product as long as pressure is maintained on the actuator. These are employed in high speed production technique.

- **Metering valves**

  A finite volume (25 -150 μL for inhalation aerosols, up to 5 ml for topical aerosols) of product is released when the actuator is pressed. No more product is released unless the actuator is returned to its rest position and repressed. Dispersing of potent medication at proper dispersion can be done by these valves.
Fig. 1. Components of Valves.
(Adapted from Semalty et al. Essentials of Pharmaceutical Technology, II edn, 2018, Pharma med Press, Hyderabad)

Components of Valves
Generally pharmaceutical aerosol valve comprises of following components (Fig. 1.).

Valve Cup (Mounting Cup/ferrulae)
It is used to attach the valve properly to the container. It is typically constructed from tinplated steel or aluminum.

Outer Gasket
This is the seal between the valve cup and the aerosol can.

Valve Housing (Valve body)
It is manufactured from nylon or delrin. It contains an opening at the point of the attachment of the dip tube (0.013 inch to 0.08 inch). Sometimes it may contain another opening called vapor tap. Vapor tap prevents clogging, helps in satisfactory dispensing, decreases the chilling effect (of propellant on skin) and flame extension. It contains the valve stem, spring and inner gasket.
Valve Stem
It is the tap through which the product flows. It is made of nylon or delrin.

Inner Gasket
It covers the hole in the valve stem. It is made of BUNA-N and neoprene rubber.

Valve Spring
It holds the gasket in place and closes or opens the gasket. It is usually made of stainless steel.

Dip Tube
It allows the liquid to enter the valve. It prevents propellants from escape without dispensing the contents. Its inner diameter is 0.120 inch to 0.125 inch, while it may be slightly large (upto 0.195 inch) for viscous products.

Actuator
It provides rapid and convenient means for releasing the contents from a pressurized container. An actuator fits onto the valve stem (Fig. 2). It ensures that aerosol product is delivered in the proper and desired form i.e. fine mist, wet spray or semisolid stream etc. Different types of actuators are available for different type of dispensing like Spray actuators, Foam actuators, Solid steam actuators, Special actuators etc. Mechanical breakup actuators are used for systems with low percentage of propellant.

Fig. 2. Standard Actuator
To summarize:

- Valve may me continuous / metering
- Valve cup, gasket, valve body, dip tube and actuator are the component s of valve body.
- Product concentrate is good mix of API with other ingredients

Now we will move to types of aerosol systems.

**Types of Aerosol Systems**

The aerosol systems can be classified on the basis of propellant or container and dosage form.

![Classification of Aerosol Systems]

**Fig. 3. Different classification of aerosol systems**
Liquefied gas system

These systems employ liquefied gas propellants. The liquefied gas propellants generally have boiling point below 21 °C.

They generally exert a vapor pressure of 13.4 to 135 psia at 21 °C. In the system pressure on liquid phase push product concentrate and propellants up in dip tube and dispensed due to large expansion in atmospheric pressure.

Initially there is just a temporary fall in pressure, which is restored when pressure is released and sufficient molecules change from liquid to vapor state.

Further Liquefied gas systems may be classified in two and three phase systems.

Two Phase system

Solution system

Drug may be dissolved in the propellant system. It consists of a solution of active ingredients in pure propellant or a mixture of propellant and solvents.
It is easy to formulate, provided that the ingredients are soluble in the propellant. Smaller spray particle size can be achieved after complete propellant evaporation.

Chemical degradation may occur faster in solution systems. A general formula of solution system is as followed.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>wt%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/active ingredient</td>
<td>10-15</td>
</tr>
<tr>
<td>Propellants 12/11 (50:50) to 100</td>
<td></td>
</tr>
</tbody>
</table>

**Suspension/dispersion system**

These systems can be used to deliver insoluble drugs. Higher doses can be delivered by suspension systems. Constant agitation during manufacturing and use is required for these systems. But these systems may be associated with physical instability (due to agglomeration, caking, particle-size growth and valve clogging or closing).

A general formula of suspension system is as followed.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>wt%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/active ingredient</td>
<td>0.5 to 1</td>
</tr>
<tr>
<td>Sorbiton trioleate (STO)</td>
<td>0.5</td>
</tr>
<tr>
<td>Propellants 12/114 (49.5:49.5) to 100</td>
<td></td>
</tr>
</tbody>
</table>

**Improving the stability of aerosol dispersions**

- Lower the Moisture content (< 300 ppm)
- Use API’s derivative
- Reduce particle size < 5 μ (50-100 μ for topical aerosols)
- Adjust density of propellants and/or suspensoid
• Use dispersing agent like surfactant with HLB < 10 e.g. Sorbiton trioleate (STO), Sorbiton mono-oleate (SMO), Isopropyl myristate (IPM), Minerol oil

Summarizing so far

• The aerosols may be classified in different systems on the propellant/container based or dosage form based.
• Propellant/ container based are 3 systems: LG, CG and barrier type systems
• Dosage form based they may be solution suspension or emulsion type
• Liquefied gas systems may be 2 or 3 phase systems
• System stability must be focused in aerosol specially with suspension type systems

Now let’s move to 3 phase systems……..

Three Phase/water based system

It allows greater use of liquid components not miscible with the propellants. These include formation of three phases consisting of liquid propellant, vaporized propellant and aqueous solution of active ingredient. As low percentage of propellants is used in these systems, special types of actuators (Mechanical breakup actuators) are needed.

A general formula of water based systems or aquasol is as followed.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>wt %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/active ingredient</td>
<td>40-85</td>
</tr>
<tr>
<td>Surfactant</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Propellants</td>
<td>to 5-10</td>
</tr>
</tbody>
</table>
Working of Aquasol

Vapor phase of propellants + Product $\rightarrow$ Mixing chamber in actuator through special ducts. Vaporized propellant enters moving at tremendous speed and product is forced to actuator by the pressure of propellants. So the product and vaporized propellants get mixed and dispensed in spray form.

Foam or Emulsion Systems

In these systems, propellants are emulsified. These are suitable for topical aerosols.

Propellants are used at 40-50 psig at 21 $^\circ$C with 4-7 % concentration.

Two types of emulsions can be formulated-o/w or w/o.

- If the propellant is in the internal phase $\rightarrow$ O/W emulsion $\rightarrow$ foam is emitted.
- If the product concentrate is dispersed throughout the propellant $\rightarrow$ W/O emulsion $\rightarrow$ the product is dispensed as wet stream

Compressed gas system

These are used to dispense semisolid, foam or spray discharge.

An initial high pressure of 90-100 psig at 21 $^\circ$C is required for these systems.
**Barrier type systems**

In these systems propellants are separated from the product with some physical barrier. The pressure outside the barrier pushes the contents from the container. On the basis of type of barrier these aerosol systems are classified as followed.

(i) **Piston type:** For semisolid dispensing, e.g. Ointment, cake decorating creams

(ii) **Plastic Bag type:** Provides stream, fine mist dispensing, e.g. Creams, ointment, gels.

(iii) **Can in Can type:** Nasal aerosols with aqueous solution of Insulin

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**Fig. 5. Barrier type aerosols**

**Manufacturing of Aerosols**

Aerosols are generally manufactured by following methods:

- Pressure filling
- Cold filling
Pressure filling

- Step 1: Chilled product concentrate is added to an open container
- Step 2: Valve is crimped in place
- Step 3: Propellant is added under pressure through the valve
- Step 4: The filled pack is passed through the water path (for leak test)

![Steps of Pressure Filling](image)

Cold filling

- Step 1: Product concentrate is cooled/freezed to -30 to -40 °C
- Step 2: Cold concentrate is added to chilled container.
- Step 3: Propellant is added
- Step 4: Valve is crimped in place
- Step 5: The filled pack is passed through the water bath at 55 °C (for leak test)

Selection of Drug Particle Size with Reference to Pulmonary Delivery


- Administration of drugs by the pulmonary route is technically challenging because oral deposition can be high, and variations in inhalation technique can affect the quantity of drug delivered to the lungs.
- Therefore, there have been considerable efforts to provide more efficient and reproducible aerosol systems through improved drug delivery devices and through better formulations that disperse more readily during inhalation.
The size of the suspended drug particles depends on the intended use of the product. Particle size plays an important role in lung deposition, along with particle velocity and settling time.

As particle size increases above 3 μm, there is a shift in aerosol deposition from the periphery to the conducting airways. Oropharyngeal deposition also increases as particle sizes increase above 6 μm. Exhaled loss is high with very small particles of 1 μm or less. These data support the view that particle sizes of 1-5 μm are best for reaching the lung periphery, while 5-10 μm particles deposit preferentially in the conducting airways (Fig. 7).

Aerosol devices in clinical use produce heterodisperse (also termed polydisperse) particle sizes, meaning that there is a mix of sizes in the aerosol.

This is contrasted with monodisperse aerosols, which consist of a single particle size. A measure that can be useful in describing a polydisperse aerosol is the mass median diameter (MMD), which is defined as the particle size (in μm) above and below which 50% of the mass of the particles is contained. This is the particle size that evenly divides the mass, or amount of the drug in the particle size distribution. This is usually given as the mass median aerodynamic diameter, or MMAD, due to the way sizes are measured. The higher the MMAD, the more particle sizes are of larger diameters and lesser is their respirable fraction.

So for pulmonary delivery, the dry particles of drug in product concentrate of aerosol device must be prepared in respirable sizes. The production of respirable aerosol particles has traditionally been achieved by micronization.
of the drug. This involves the introduction of bulk particles on a gas stream under high pressure.

Particles impact on each other and are thereby ground into small particles, which ultimately pass through a cyclone separator and are collected in a vessel or a bag filter. These particles can be produced in size ranges less than 5 μm, which is suitable for lung deposition.

Nowadays spray drying is more popular for the production of more spherical particles. Spray drying is also more suitable method than jet milling for the production of thermolabile substances. The recently developed and more successful method for the production is the supercritical fluid technology. This technology involves controlled crystallization of drugs from dispersion in supercritical fluid, notably carbon dioxide.

Take Away Message

- Valve function: RPG
- The components of valve.
- The classification of aerosol systems: LG, CG and Barrier type
- LG: sub classified into 2 and 3 phase systems
- All aerosol systems need stability but suspensions type systems need utmost attention.
- Cold and pressure filling are two major methods of aerosol manufacturing

Further Readings

- Banker & Rhodes, Modern Pharmaceutics, CRC Press.
- Semalty et al., Essentials of Pharmaceutical Technology, II Edn. Pharma Med press, Hyderabad, India
Credits/References

- Lachman L, Lieberman HA. Theory and Practice of Industrial Pharmacy, Varghese Publishing House, Bombay, India