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Pharmaceutical Aerosols

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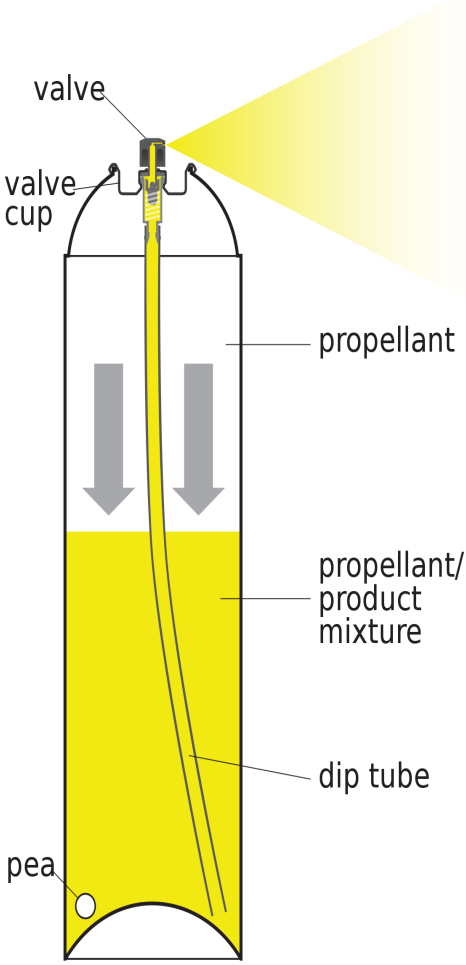
Pharmaceutical Aerosols

- A system that depends on the power of compressed **pre-liquefied gas** to expel the contents from the container.

Advantages:

1. The dose can be **delivered directly** to the site of action such as an inhaler.
2. Relatively **easy to use.**
3. **Rapid** onset of action.
4. **Avoid first-pass** metabolism and degradation in the GI tract.
5. **A lower dose** is used, especially in the case of **steroids**, in which most of the steroid reaches the respiratory tract and less is swallowed.
6. **An alternative route is** when a therapeutic agent may interact chemically or physically with other medicinal needs **concurrently**.
7. Container and valve closure are **tamperproof**.
8. The dose can be adjusted accurately using the **metered valve**.

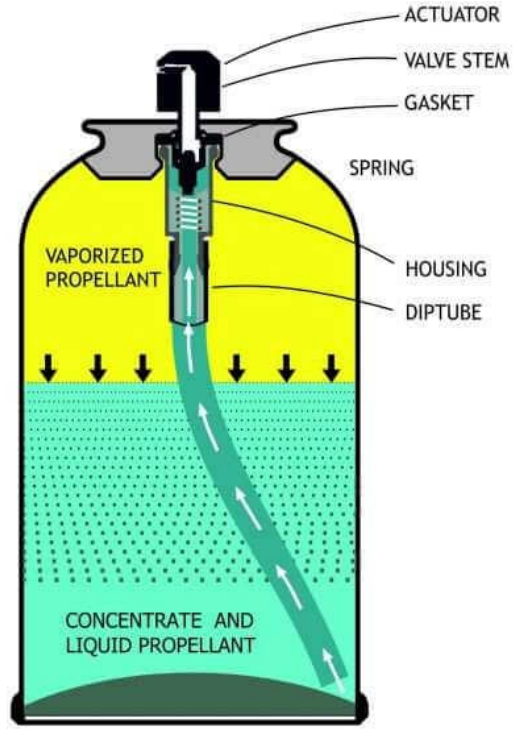


Component of Aerosol Package

- **Actuator** and **valve**, **propellant**, **drug concentrate,** and **container**.

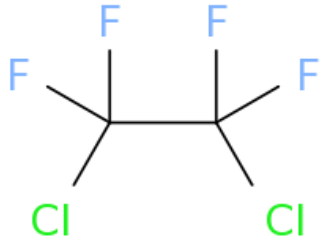
1. Propellant:

- Responsible for developing the proper **pressure** within the container, and it **expels** the product when the valve is opened.
  - It aids in the atomization or foam production of the product.
  - Usually, a **blend** of propellants is used in pharmaceutical aerosols. This will allow us to get the desired **vapor pressure.**
  - Act as a solvent or diluent
- **Liquified gas:**
  - Chlorofluorocarbons (CFCs)
  - Hydrochlorofluorocarbons (HCFCs).
  - Hydrofluorocarbons (HFCs).
  - Hydrocarbons.
- **Compressed gas** (used for products such as hair preparations).
  - Nitrogen (N_2)



Liquified Gases

- Used for **orally** administered aerosols.
- These gases are **turned into liquid** by **decreasing** the temperature below boiling point and/or increasing the pressure.
- When in a sealed container, the liquified gas will be in **two phases** which are liquid and vapor.
- Has the advantage of maintaining a constant pressure inside the container and effectively dispersing the active ingredients.
- **Chlorofluorocarbons CFC.**
- Defined by the global numerical number which depends on the number of C, F, and H. For example diclorotetrafluoroethane ($C_2Cl_2F_4$) =C 2-1, H 0+1, F 4, so it's called **propellant 114.**
- **Nontoxic**, and **non-flammable**.
- **Limited use nowadays** due to the effect on the ozone layer. And replaced with other types.



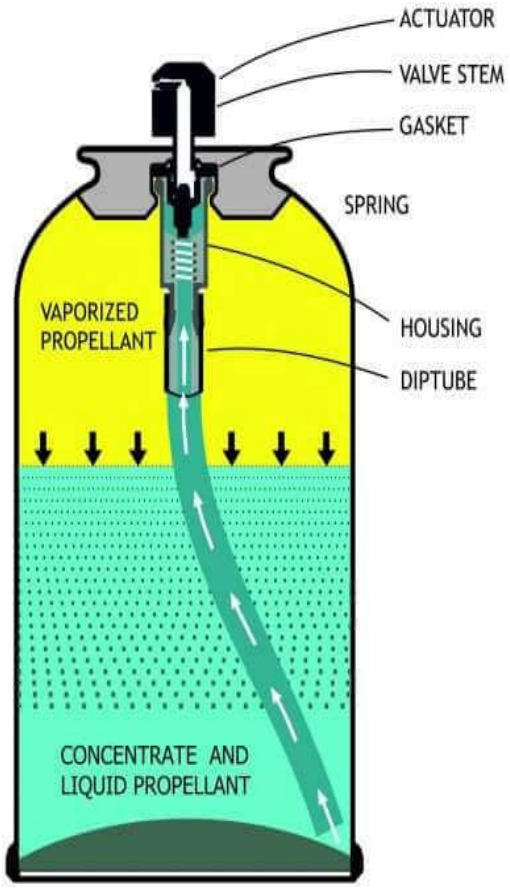
Hydrocarbons

- Used mainly for topical application
- As compared to fluorinated hydrocarbons:
  - They are **flammable**, but less toxic and more economical, more soluble, and more chemically stable.
  - It has **little** expansion pressure and will produce a **wet spray**.
- Examples:
- Butane, propane

Formulation of Pharmaceutical Aerosols

- Aerosols consist of **two** main components: **product concentrate and propellant**.

1. **Product concentrate** consists of an active ingredient, or a mixture of active ingredients and other necessary agents such as solvents, antioxidants, and surfactants.
2. **Propellants** may be a single type or a blend of various propellants. The propellant is selected to give the desired vapor pressure, solubility, and particle size.



- Vapor pressure can be controlled to the desired pressure by **mixing** another propellant with different properties (different vapor pressure)
- The total vapor pressure of the mixture is the sum of vapor pressures of the mixture component (**Dalton Law**):
- $P_{total} = P_a + P_b$

Vapor pressure of Blend of Propellant

- The partial pressure of each component is calculated according to **Raoult's** law.
- In ideal behavior, this can be represented by the following equations for propellant A and Propellant B:
- $P_a = \left(\frac{n_a}{n_a + n_b}\right) * P_A o = N_A * P_A o$ **Partial pressure for propellant A**,
- n= moles of propellant; $P_A o$ = vapor pressure of pure propellant A; N_A= mole fraction of component A
- For **propellant B** the equation will be:
- $P_b = \left(\frac{n_b}{n_a + n_b}\right) * P_B o = N_B * P_B o$ **Partial pressure for propellant B**

Component of Aerosol Package

2. Valves

- It is a multifunctional part of aerosol dosage forms that is capable of being easily opened and closed and able to deliver the content in the desired **form** and **amount**.
- The primary purpose is to regulate flow from the container.
- **Types**:
- **Metered valves**: contain a chamber whose size determines the amount of the medication dispensed.
- **Continuous spray** valve: no metered chamber.

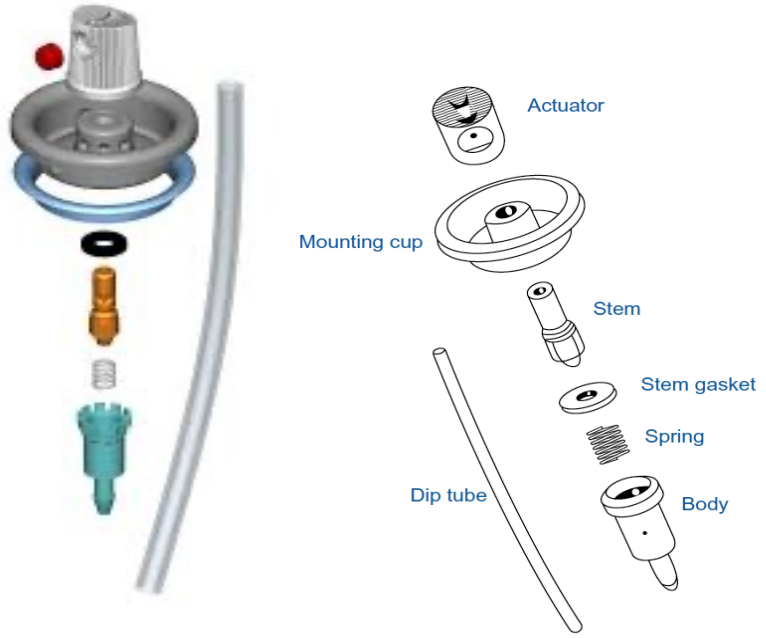
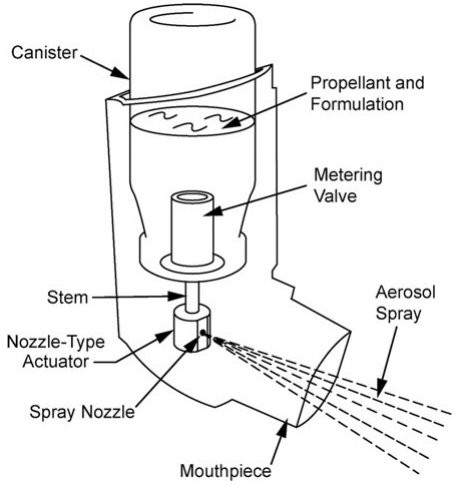


Figure 33-7. Continuous-spray aerosol valve, showing subcomponents used for sprays, foams, and semisolids.



Component of Aerosol Package

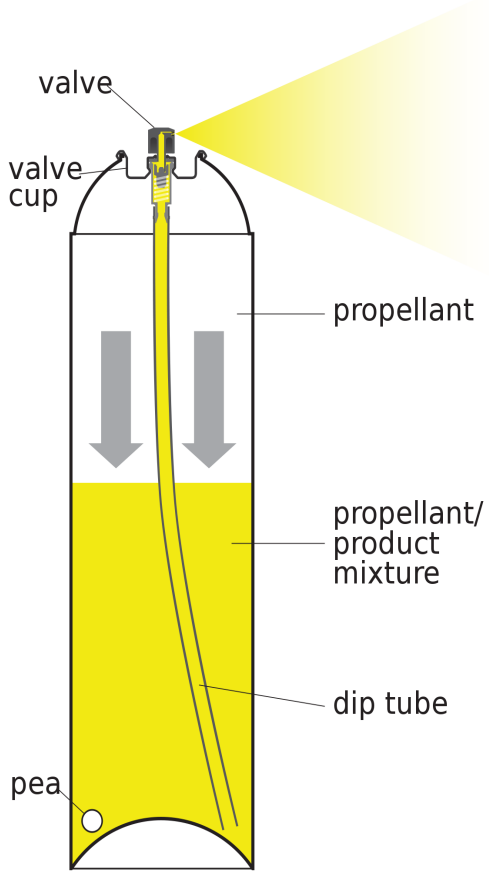
3. Actuators

- To ensure that aerosol product is delivered in the **proper and desired form**.
- Different types of actuators:

1. **Spray**: mostly used for pharmaceutical applications. If the product contains a **low** amount of propellant, these sprays will deliver the product as a stream rather than a spray because the amount of propellant is not sufficient to fully **disperse** the product.
2. **Foam**: consists of relatively **large** **orifices** and a large **chamber** that allows the product to **expand**.
3. **Solid** stream: essentially similar to foam type and used for dispensing semisolid products such as ointment.
4. **Special applications**: special design to deliver medication to the site of action such as throat, nose, or vaginal tract.

Types of Aerosols Systems

- **Solution system/two-phase system.**
- **The simplest** and most widely used system that composed of **vapor** and **liquid phases**.
- In this system, the active ingredient is soluble in the propellant
- The liquid phase consists of a **solution** of active ingredients in liquid propellant or a mixture of liquid propellant and a solvent.
  - The solvent is **miscible** with the propellant.
- The amount of propellant may vary from 5% for foam to to 95% for inhalation products.
  - This amount will affect the vapor pressure of the system which is the main factor that will **determine** the size of the particle produced and the type of spray (fine spray, wet mist, or foam).



Types of Aerosols Systems

- **Water-based system** (**three-phase** system): propellant, water, vapor
- A relatively large amount of water can be used to replace all or part of the non-aqueous solvent used in aerosols.
- The active ingredient is dissolved in water and then formulated as an emulsion of water droplets in the propellent
  - Water+ drug droplet is the **internal** phase and propellent is the external phase.
- **Water is not miscible with liquefied gas propellants.**
- Vaporized propellent will disperse the active ingredients into minute particles.
- This system is **useful** for **topical** pharmaceutical aerosols in that it allows a greater use of liquid components not miscible with the propellants.
- Depending on the formulation, the product will be emitted as a spray or foam.

Types of Aerosols Systems

- **Suspension or dispersion system**
- This system helps to overcome problems resulting from the use of **cosolvent**.
- This involves the **dispersion of the active ingredient in the propellant**.
  - **Surfactant** may be added to decrease the settling of the particle.
- These systems are developed primarily for use for oral inhalations.
- The **physical** stability of an aerosol dispersion can be **increased** by
  1. Control of **moisture** content (moisture will increase drug solubility ➔ and cause particle growth).
  2. Use of derivatives of active ingredients that have **minimum solubility** in the propellant (but must have the same pharmacological activity).
  3. Reduction of the initial **particle size**.
  4. Adjustment of the **density** of propellant and/or suspension so they are equalized.
  5. Use of **dispersing** agents.

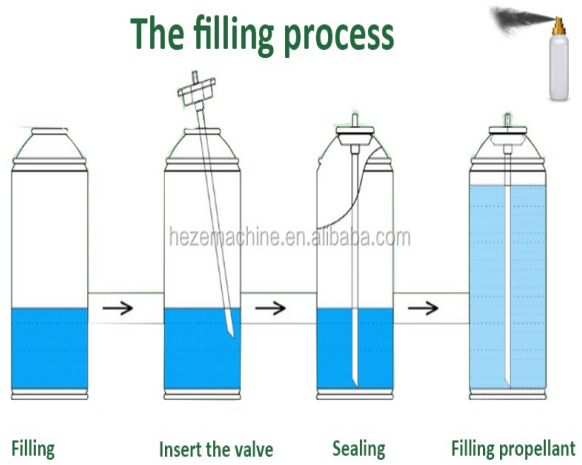
Types of Aerosols Systems: Foam System

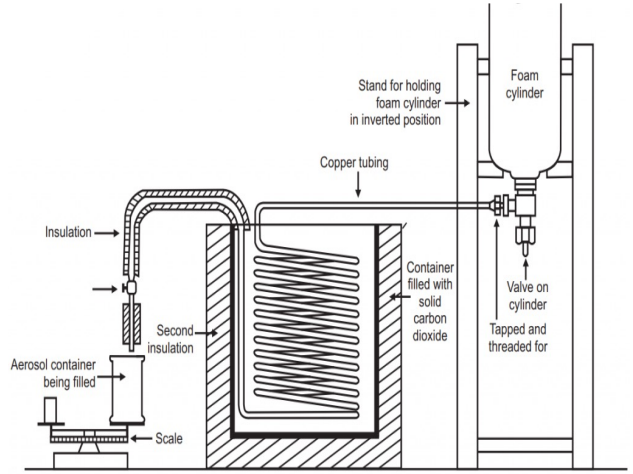
- **Foam** aerosols consist of a **three-phase** system in which the liquid propellant, which normally does not exceed 10 to 15% by weight, is emulsified (internal phase) with the drug-containing liquid.
- So we have propellant (**internal phase**), and drug dissolved in a solvent (**external phase**)
- When the valve is depressed, the emulsion is forced through the nozzle, and in the presence of warm air and at atmospheric pressure, the entrapped propellant reverts to a vapor and whips the emulsion into a foam. ➔ the product is emitted as a liquid and then converted to foam

- **Note**: there is another foam type called **quick-breaking foam** in which the propellant is the external phase.
  - The product is emitted as a foam.

Manufacturing of Pharmaceutical Aerosols: Filling

- **Pressure filling apparatus**: propellant (**liquified gas**) is pressurized into the aerosol container. The container already **contains** the **product** concentrate and the valve attached **prior** to the filling process. This is carried out at **room temp**.
- **Cold filling apparatus: simple** and fast filling method which includes **cooling** the content to about -30˚F. The cooled contents (drug and propellant) are added to a cooled container and **then** a valve is **placed**. However, this is **suitable only** for **non-aqueous** content because aqueous contents will **freeze** at that temperature.
- **Compressed gas filling apparatus: similar** to pressure filling in which concentrate is filled in the container then the valve is placed and then filled with compressed gas. This is mostly **used in labs or for small-size production**.





Cold filling

Quality Control of Pharmaceutical Aerosols

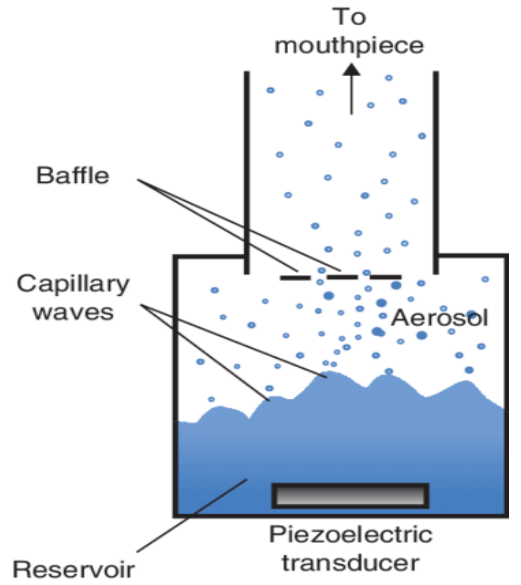
- It includes the testing of :

1. **Propellant**: need to check specifications like vapor pressure and purity.
2. **Valves, Actuator, and Dip tube:** test solutions of known components are prepared and filled in the aerosol package to be tested. Then product is actuated and the **delivered dose** is weighed and compared with others.
3. **Containers:** sample containers are collected and examined for defects.
4. **Weight checking: The** weight of filled containers is periodically checked.
5. **Leak testing**: passing full container into a water bath heated to 130˚F.
6. **Spray testing**: is done for **all aerosols** to ensure the **dip tube** is empty of pure concentrate or pure propellant. This will ensure that the patient will get the required dose the first time.

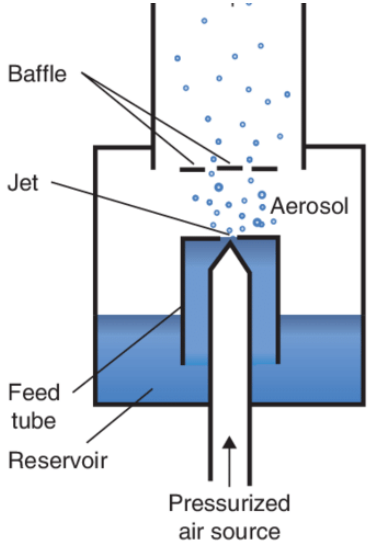
Aerosols for Pulmonary Drug Delivery

- **Nebulizers**: dosage form for dispensing a **non-pressurized** liquid formulation.
- They are either electric or pneumatic

1. **The electric (ultrasonic)** type produce **high-frequency sound waves** in the liquid which will form small droplet at the surface and these droplets are moved by **inhalation.**



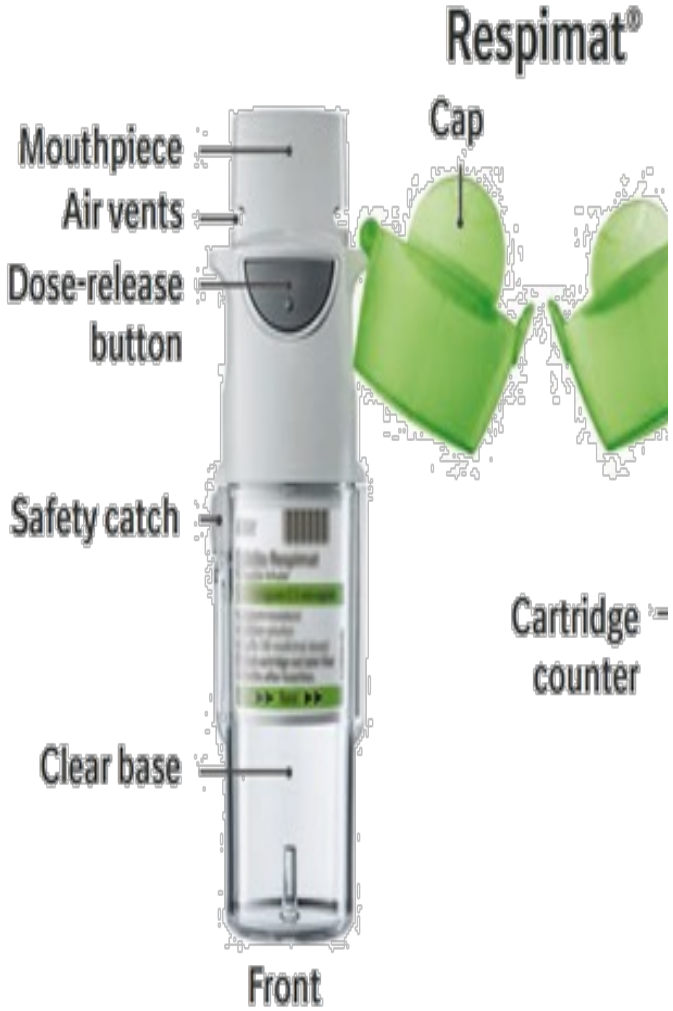
2. **Hydrodynamic nebulizers (jet Neb.)**: compressed air will generate a droplet that is delivered to patients.



3. **Mesh type:** in which liquid passes through a very fine mesh to produce a fine droplet

Advantages and Disadvantages

- **Advantages**:
  - They can deliver **larger volumes** that cannot be delivered using the metered dose inhaler.
  - Also, **no** high oropharyngeal impaction which will lower the side effects.
- **Disadvantage**:
  - Nebulizers are **bulky** and require a fixed **power source**.



- However, the newer design allows for the manufacturing of a portable nebulizer such as Respimat®

Aerosols for Pulmonary Drug Delivery

- **Metered dose inhaler**: a **pressurized** formulation in which the **valve contains a metered chamber** to deliver the right dose each time. The preparation is usually a suspension.
- **Advantage**;
  1. Delivers a relatively accurate amount of drug each time.
  2. Easy to handle multidose and can be operated by patients.
- **Disadvantage**:
  1. Only a **fraction** of the dose reaches the lung because the **velocity** of the impact makes the particle stick to the mouthpiece and oropharynx.
  2. Requires some **patient education** for proper use that the patient should inhale while pressing the actuator which may make it a little difficult to use.
- Note: newer modifications such as a **spacer** reduced this problem.

Spacer

Aerosols for Pulmonary Drug Delivery

- **Dry Powder Inhaler:**
- They **depend** on **inhalation** to draw the drug from the inhaler to the lung.
- The micronized drug is mixed with a carrier.

Aerosols for Intranasal Drug Delivery

- Intranasal route offer several **advantages** include the relatively **rapid onset**, **easy** to use, and avoid **first pass** metabolism.
- Product are available for local effects such as Beconase® or for systemic effect such as desmopressin.