Pharmaceutical Aerosols

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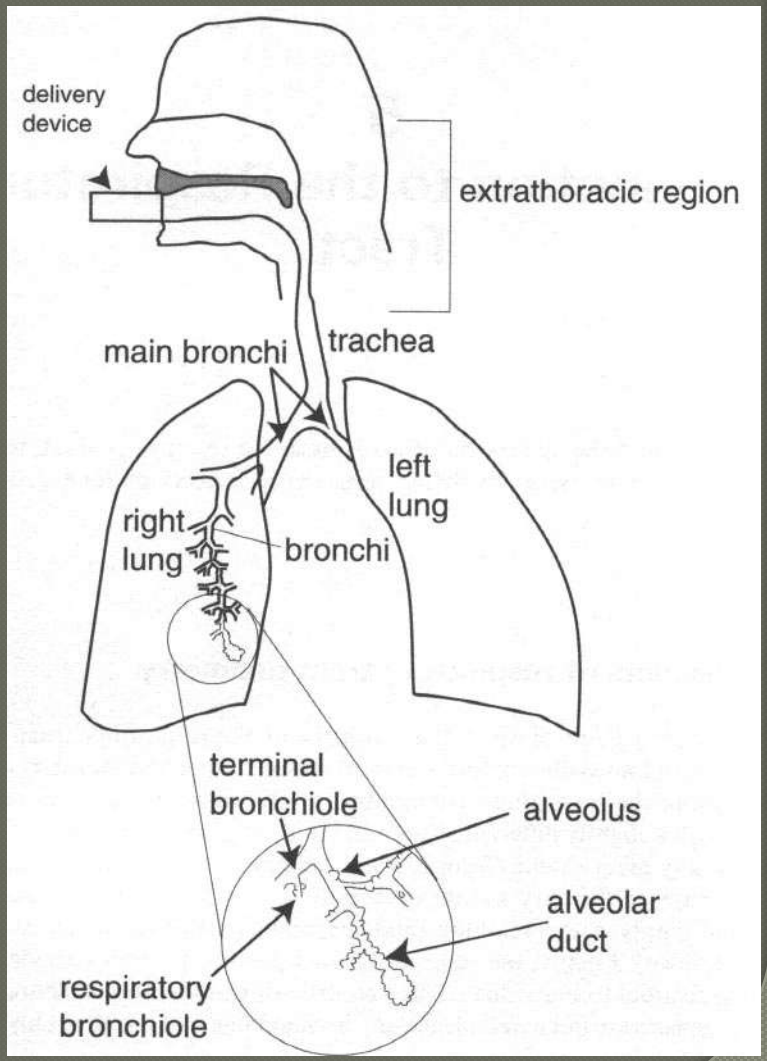
Why Pulmonary Delivery

Route	Advantages	Disadvantages
Oral	Safe	Unpredictable and slow absorption
	Convient	Emzymatic degradation
	Inexpensive	Not localized delivery
Needle	Predictable response	Requires special training
	Rapid absorption	Improver administration can lead to embolism
		Not localized delivery
		Painful
		Infection possible
Inhaled	Safe	Unpredictible deposition
	Convient	
	Rapid absorption	
	Localized delivery	

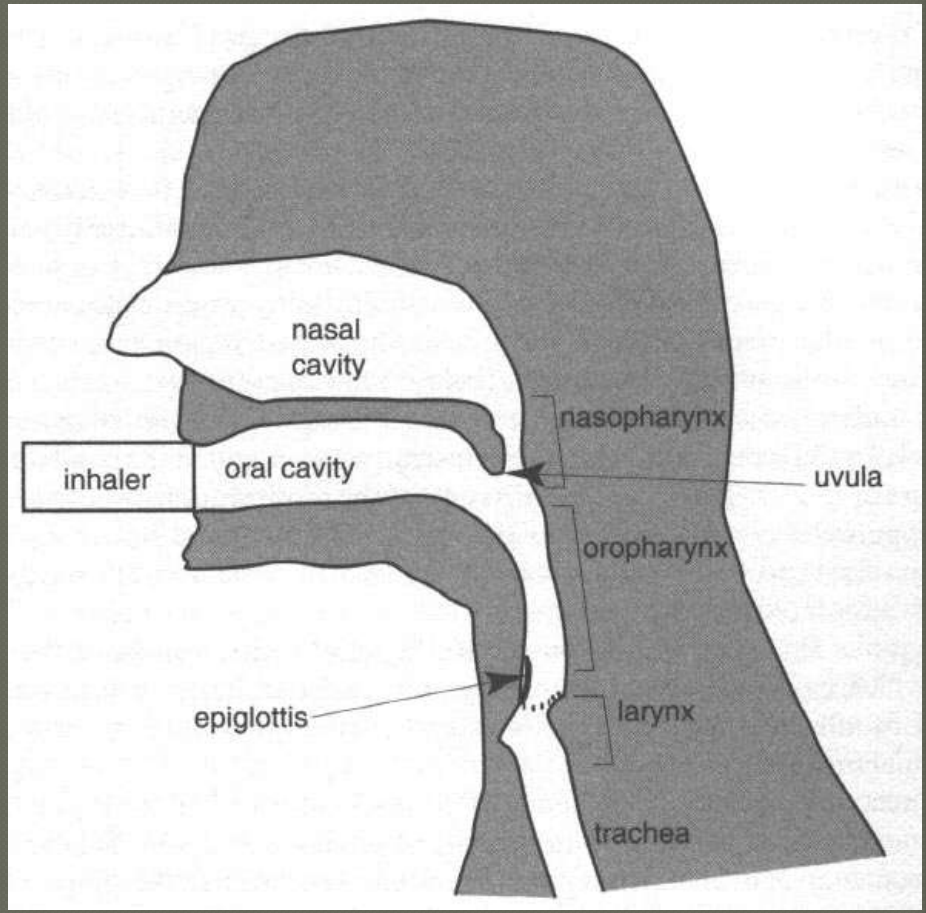
Respiratory Tract

- From an engineering point of view the geometry of the respiratory tract is not well know
  - Geometry contains fine detail
  - Geometry is time dependent
  - Geometry varies between individuals
- Topologically the lungs simply consist of a series of bifurcating pipes
- Three basic regions
  - Extrathoracic region (“upper air ways”)
  - Tracheo-bronchial region
  - Alveolar region



Extrathoracic Region

- Extrathoracic region (“upper air ways”)
  - Oral cavity (“mouth”) – transient with variation in position of tongue and jaw
  - Nasal cavity
  - Larynx (constricted entrance to trachea containing vocal cords and ‘trap door’)
  - Pharynx (throat region of between larynx and mouth – ‘oropharynx’ and between larynx and nose – ‘nasopharynx’)



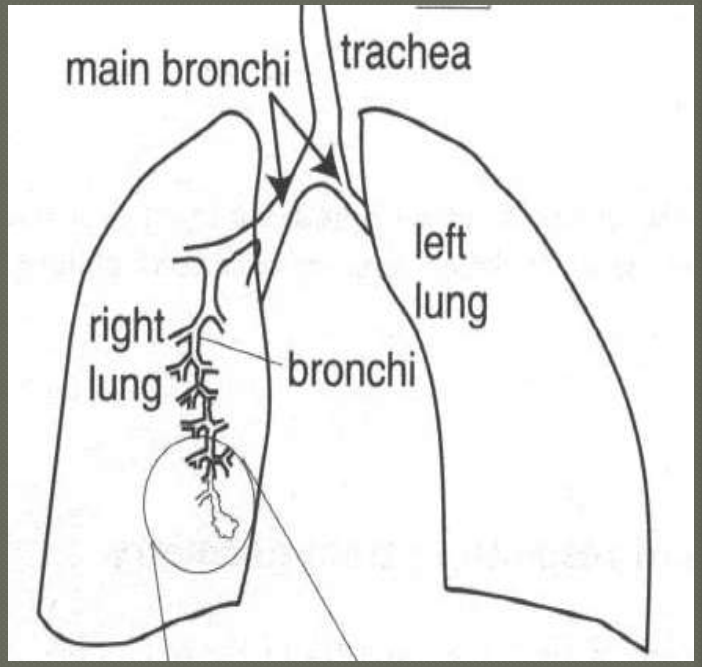
Tracheo-Bronchial Region

Tracheo-bronchial region ("lower airways")

- Airways that conduct air from the larynx to the gas exchange regions

Trachea to bronchi to terminal bronchioles

- Glottis is the opening from the larynx into the trachea which changes shape with flow rate (larger with higher flow rates)
- Main bronchi is the first generation of branching after trachea
- Lobar bronchi branch off the main (second generation)
  - Two in the left lung
  - Three in the right lung
  - Lobar bronchi ventilate lobes
- Segmental bronchi branch off the lobar (third generation)
  - Lobes are subdivided into bronchopulmonary segments each ventilated by segmental bronchi

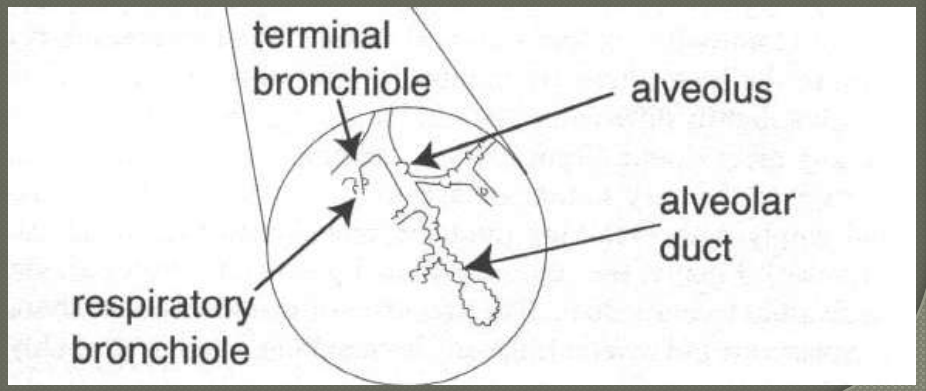


Tracheo-Bronchial Airways

- Covered with a mucus layer that overlays fine hairs (cilia)
  - Cilia act to clear the mucus layer to the throat (swallowed or expectorated)
  - Clearance occurs within 24 hours for particles > 1 micron
  - Particles < 1 micron borrow in mucus layer
- Cartilaginous rings in trachea and main bronchi causing corrugated inner surface (may effect fluid dynamics)
- Extrathoracic and tracheo-bronchial airways are termed the "conducting airways" since the move air to the gas-exchange region

Alveolar Region

- Alveolar region
  - Contains all parts of the lung with alveoli
  - All the daughter generations from a single terminal bronchiole is called acinus
- Respirator Bronchioles
  - first generation daughter branching after the terminal bronchioles
  - Relatively few alveoli
- Subsequent generations will have an increasing number of alveoli
- Alveoli ducts
  - Entirely covered by alveoli
  - Several generations
- Alveoli sacs



Aerosols:

are products that are packaged under pressure and contain therapeutically active ingredients that are released upon activation of an appropriate valve system.

The basic components of an aerosol system are the container, the propellant, the concentrate containing the active ingredient(s), the valve, and the actuator.

Aerosol characteristics:

- Particle size distribution.
- Uniformity of dose for metered valve.
- Delivery rate
- Wetness and temperature of the spray
- Spray pattern
- Velocity of spray
- Foam density.
- Fluid viscosity.

Aerosol components

- Propellants:

Halogenated derivative of hydrocarbons
Low molecular weight hydrocarbons: butane, pentane
Compressed gas

Test for propellants

- Vapor pressure
- Density
- Gas chromatography test for purity
- Moisture, halogen, non-volatile residue

Valves:

- To regulate the flow of the therapeutic agent and propellant from the container.
- Materials used for the manufacturing of valve should be inert to the formulations used.
- Plastic, rubber, aluminum, stainless steel valve components are used.
- Continuous spray valve: used on topical products.
- Metered-dose valve : must deliver an accurate dose within specified tolerance.

Extractable Substances

- Leaching of extractable from plastic components into the formulation is a potential serious problem.
- Extractable include: antioxidants, plasticizers, monomers, nitrosamine, vulcanization accelerators, etc., should be identified and minimized.
- The composition and the quality of materials used in the manufacturing of the *valve* components must be carefully selected and controlled. Their compatibility with formulation components should be well established to minimize change in the medication delivery, leak rate, impurity profile of the drug product over time.

- Actuators: is the fitting attached to an aerosol valve stem, which when depressed or moved, open the valve, and directs the spray containing the drug preparation to the desired area.

- Containers:
- Made of glass, plastic or metal as stainless steel, aluminum, tin.
- Extractable or leachable and particulates on the internal surfaces of containers should be controlled.
- Manufacturing process controls usually include:
- Monitoring of proper formulation and propellant fill weight and pressure testing, leak testing, and valve function testing of the finished aerosol.

QUALITY CONTROL TESTS

It Includes the testing of :

» 1. Propellents
» 2. Valves, Actuator, Dip Tubes
» 3. Containers
» 4. Weight Checking
» 5. Leak Testing
» 6. Spray Testing

1.Propellents:

- All Propellents are accompanied by Specification sheet.

Parameter	Tested By
Identification →	Gas Chromatography
Purity →	Moisture, Halogen, Non-Volatile Residue Determination

2.Valves, Actuator, Dip-tubes

- For metered dose aerosols test methods was developed by
  - → 'Aerosol Specification Committee'
  - → 'Industrial Pharmaceutical Technical Section
  - → 'Academy Of Pharmaceutical Sciences.
- The object of this test is to determine magnitude of valve delivery & degree of uniformity between individual valves.
- Standard test solutions were proposed to rule out variation in valve delivery.

Test Solutions

Ingredients % w/w	Test Solutions 'A'	Test Solutions 'B'	Test Solutions 'C'
Iso Propyl Myristate	0.10%	0.10%	0.10%
Dichloro Difluoro methane	49.95%	25.0%	50.25%
Dichloro tetrafluoro ethane	49.95%	25.0%	24.75%
Trichloro monofluoro methane	-	-	24.9%
Alcohol USP	-	49.9%	-
Specific Gravity @ 25°c	1.384	1.092	1.388

Testing Procedure:

- Take 25 valves & placed on containers,
- Filled with specific test solution
- Actuator with 0.020 inch orifice is attached.
- Valve is actuated to fullest extent for 2 sec.
- Repeat this for total 2 individual delivery from each 25 test units.

$$\text{Valve delivery per actuation in } \mu L = \frac{\text{Individual delivery wt in mg.}}{\text{Specific gravity of test sol}^n}$$

Valve Acceptance:

Deliveries	Limit's
54µL or less	± 15%
55 to 200 µL	± 10%

Of 50 delivery

- If 4 or more are outside limits : valves are rejected
- If 3 delivery are outside limits : another 25 valves are tested
  : lot is rejected if more than 1 delivery outside specification
- If 2 delivery from 1 valve are beyond limits
  : another 25 valves are tested
  : lot is rejected if more than 1 delivery outside specification

3.Containers

- Containers are examined for defects in lining.
- Q.C aspects includes degree of conductivity of electric current as measure of exposed metals.
- Glass containers examined for Flaws.

4.Weight Checking

- Is done by periodically adding tared empty aerosol container to filling lines which after filling with concentrate are removed & weighed.
- Same procedure is used for checking weight of Propellents.

5.Leak Test

- Is done by measuring the Crimp's dimension & comparing.
- Final testing of valve closure is done by passing filled containers through water bath.

6.Spray Testing

- It is done for
  - »To clear dip tube of pure propellant & concentrate,
  - »To check for defects in valves & spray pattern.

Evaluation Tests:

A. Flammability & combustibility:

1. Flash point
2. Flash Projection

B. Physicochemical characteristics:

1. Vapour pressure
2. Density
3. Moisture content
4. Identification of Propellents

C. Performance:

1. Aerosol valve discharge rate
2. Spray pattern
3. Dosage with metered valves
4. Net contents
5. Foam stability
6. Particle size determination

D. Biological testing:

1. Therapeutic activity
2. Toxicity studies

A. Flammability & combustibility:

»

1.Flash point:

Apparatus : Open Cup Tag Apparatus

Test liquids temp. is allowed to increase slowly & temp. at which vapors Ignite is called as Flash Point .

» 2.Flame Projection:

Product is sprayed for 4 sec onto flame & exact length is measured with ruler.

B. Physicochemical characteristics:

Property	Method
1. Vapor Pressure	» Can Puncturing Device.
2. Density	» Hydrometer, » Pycnometer.
3. Moisture	» Karl Fisher Method, » Gas Chromatography.
4. Identification	» Gas Chromatography, » IR Spectroscopy.

C. Performance:

1.Aerosol valve discharge rate :

- Aerosol product of known weight is discharged for specific time.
- By reweighing the container, the change in the wt. per time dispensed is the Discharge rate in gm/sec.

2. Spray pattern :

- The method is based on the impingement of spray on piece of paper that has treated with Dye-Talc mixture.

3. Dosage with metered valves :

- Reproducibility of dosage determined by:

»Assay

»Accurate weighing of filled container followed by dispensing several dosage.
containers again reweighed & diff. in wt. divided by no. of dosage dispensed gives average dose.

4. Net Contents :

- Tared cans placed on filling lines are reweighed & then difference in wt. is equal to net content.
- In Destructive method : opening the container & removing as much of product possible.

5. Foam stability :

Various Methods : » Visual Evaluation,

» Time for given mass to penetrate the foam,

» Time for given rod to fall which is inserted into the foam,

» Rotational Viscometer.

6.Partical Size Determination :

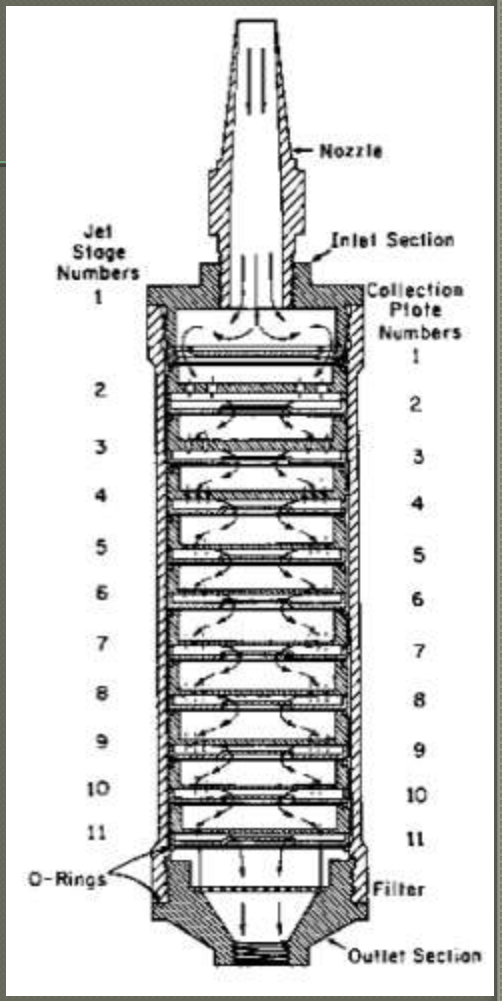
Methods : » Cascade Impactor,

» Light Scattering Decay.

a). Cascade Impactor :

Principle :

Stream of particle projected through a series of nozzle & glass slides at high velocity, larger particle are impacted on low velocity stage , & smaller on higher velocity stage.



b). Light Scattering Decay :

Principal :

As aerosol settles under turbulent condition, the changes in the light of a Tyndall beam is measured.

D. Biological testing:

1.Therapeutic Activity :

» For Inhalation Aerosols : is depends on the particle size.

» For Topical Aerosols : is applied to test areas & adsorption of therapeutic ingredient is determined.

2.Toxicity :

» For Inhalation Aerosols : exposing test animals to vapor sprayed from Aerosol container.

» For Topical Aerosols : Irritation & Chilling effects are determined.

FORMULATION DEVELOPMENT OF AEROSOLS

What exactly is a pharmaceutical aerosol? A pharmaceutical aerosol in a general way can be defined as an aerosol product containing therapeutically active ingredients dissolved, suspended or emulsified in a propellant or a mixture of solvent and propellant and intended for oral or topical administration or for administration into body orifices.

The increasing use of inhalation therapy has been mainly driven by the confluence of three factors:

1. Advances in aerosol generation technology, which provide more efficient and controlled delivery of aerosolized pharmaceutical compounds into the human respiratory airway;
2. Advances in biotechnology, with the development of new therapeutic agents that are often difficult to deliver by other routes of administration;
3. A better understanding of the pathophysiology of disease, which allows physicians and scientists to envision a broader range of therapeutic options.

Table 1—Rationale for using inhalation aerosols

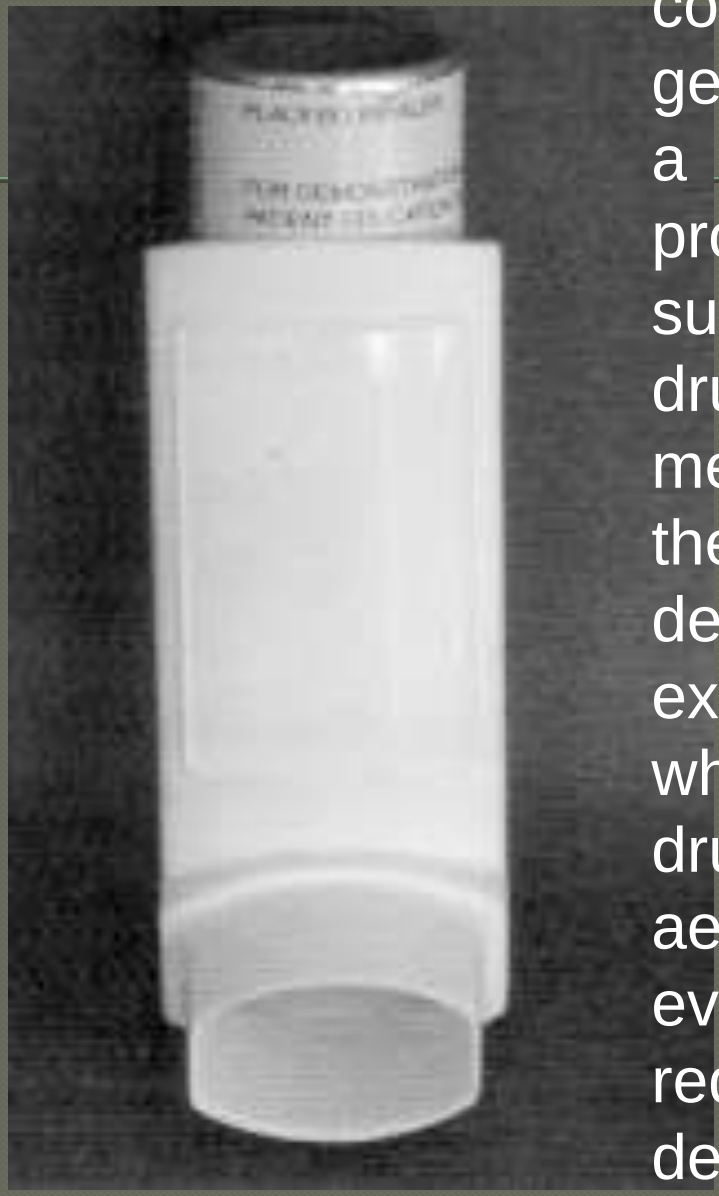
Critical drug delivery issues	Key benefits of lung drug delivery
Dosimetry and dose uniformity	Dose reduction potential compared with injection Often, lung delivery is quantitative based on fractional deposition in the lung.
Ruggedness	Noninvasive, flexible Dosimetry. Most inhalation technologies offer great flexibility and adaptability of dosage form to a wide range of clinical needs
Drug targeting	Site specificity and decreased systemic exposure. Most inhalation products can target only the lung and even when absorbed, systemic drug concentrations are too low to elicit significant risks.
Onset and extent of action	Fast onset of action. The lung has a large, highly permeable, and robust absorptive surface which enables absorption kinetics often comparable to injection.
Patient compliance	Painless, often nonirritating, and useful in ambulatory care.

Table 2—Limitations of conventional aerosols

- Hydrophobic drugs with poor water solubility are hard to deal with
- Micro particular nature of the particles results in limited diffusion and dissolution of the hydrophobic drug at the site of action resulting in low bioavailability.
- Low residence time of drug leading to absence of prolonged duration of action.
- Unwanted deposition of the drug particles in the upper airways (e.g. pharynx).
- Because of the devices inherent inefficiency, patients must inhale relatively large quantities of a drug to ensure that an adequate amount reaches the lungs.
- Not suitable for modulated drug release
- In conventional suspension aerosols many droplets are drug free and others are highly loaded with drug leading to uneven distribution of drug in the lung.

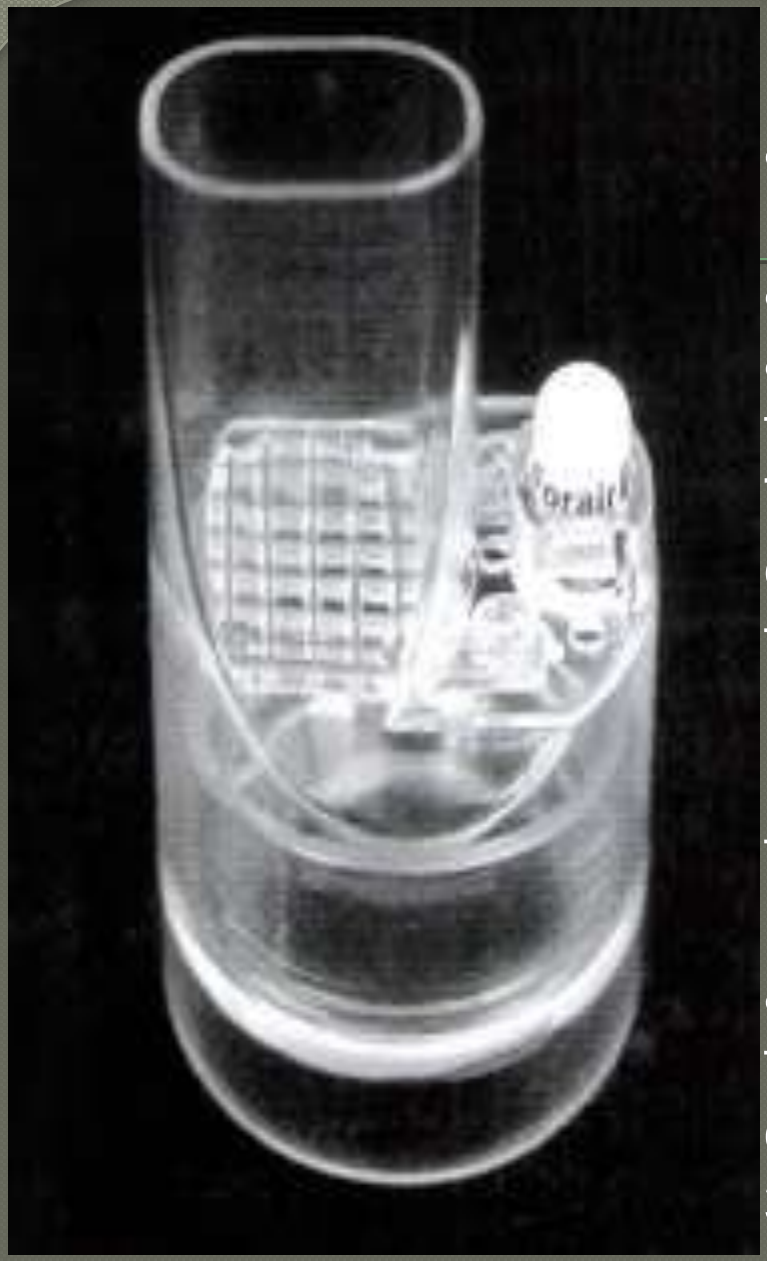
AEROSOL DEVICES

- **Dry Powder Inhalers (DPI)**
- **Metered Dose Inhaler (MDI)**
- **Nebulisers**



Metered dose inhaler.

Metered dose inhalers are the most commonly used devices for generation of aerosol. They consist of a micronised form of the drug in a propellant under pressure with surfactants to prevent clumping of drug crystals. Lubricants for the valve mechanism and other solvents are the other constituents. When the device is actuated, the propellant gets exposed to atmospheric pressure, which leads to aerosolisation of the drug. As it travels through the air, the aerosol warms up leading to evaporation of the propellant that reduces the particle size to the desirable range. The fraction of drug to the airways ranges from 5 percent to 15 percent.



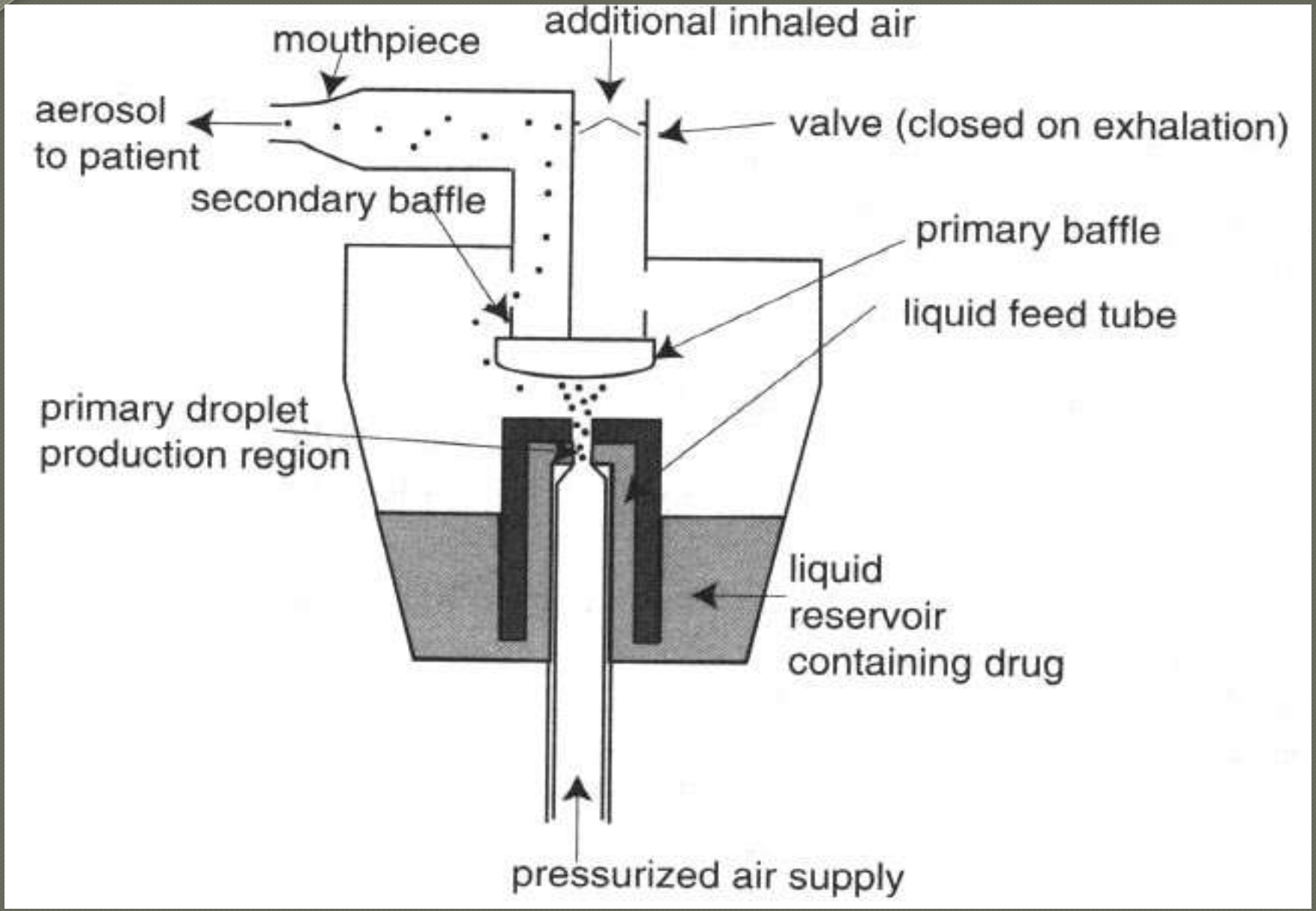
Commonly used dry powder inhaler.

Dry powder inhalers (DPI) consist of pharmacologically active powder as an aggregate of fine micronised particles in an inhalation chamber . These aggregates are converted into an aerosol by inspiratory airflow through the inhaler generated by the patient. This basic fact excludes the problem of coordination between the delivery of the drug and the initiation of inspiration. But the very same fact also makes it unsuitable for patients who are unable to generate high inspiratory flow rates. Lack of requirement of propellant is an advantage of DPIs over MDIs. The fraction of the drug delivered to the site of action by a DPI varies from 9% to 30% and varies among different commercially available products.

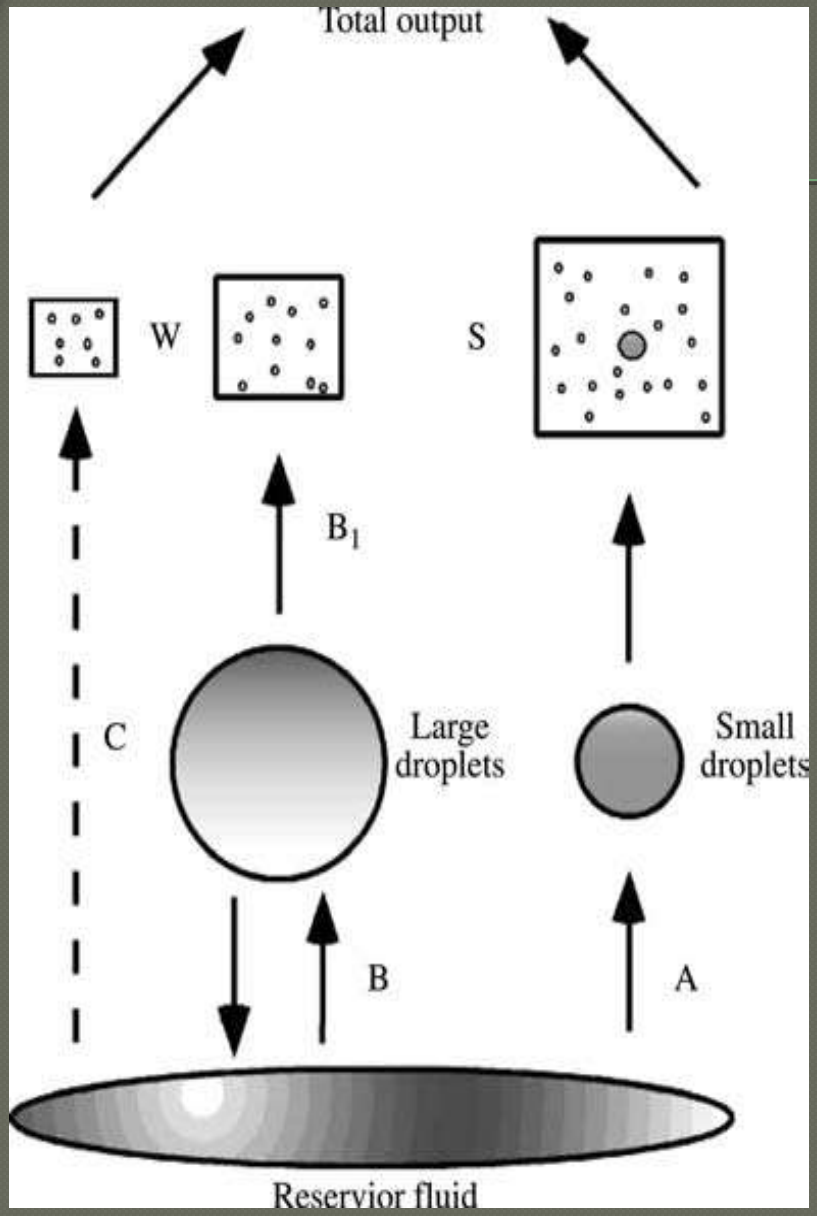
Nebulisers

Two types of nebulisers are available for use as aerosol generators: jet nebuliser and ultrasonic nebuliser. These work on different principles but have many features in common.

These are non-propellant based, do not require patient coordination and can be used to deliver high doses of a particular drug over a short time, such as during acute exacerbations of obstructive airway diseases in emergency settings.



Jet Nebulizer



Schematic diagram of nebulizer output. Droplets small enough will be carried out by air stream (route A), and the large droplets will be either recycled to the nebulizer reservoir (route B) or carried out by the outgoing air stream (route B1). Some of the solvent will be evaporated (route C).

Introduction to the Formulation of Pharmaceutical Areosols

- A wide variety of agents has been administered to the lung via oral inhalation, for the treatment of diverse disease states.
- The most frequent use of inhalation therapy is for the treatment of obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD).
- Drugs such as short- and long-acting beta-sympathomimetics, corticosteroids, and anticholinergic agents.

- Common to all inhalation dosage forms and delivery systems is the need to generate the optimum "respirable dose" (particles ,< 5.0 micron) of a therapeutic agent, and this is a central performance feature in the rational design and selection
- Moreover, this performance, in terms of aerosol quality, should be demonstrated throughout the product's shelf life, in addition to the more usual chemical and physical stability criteria.
- Thus, particularly in the development of metered-dose inhalers (MDIs) and dry powder inhalers(DPIs), device design is integrated with formulation work in the overall product development strategy of a delivery system.

PREFORMULATION ASPECTS ON INHALATION DRUG DELIVERY SYSTEM DESIGN

Particle Engineering:

Micronization-1.0 to 3.0 microns

Supercritical fluid recrystallization

Spray-drying

Controlled precipitation (in which size control could be achieved and other desirable properties, e.g., extended release of the drug may be realized)

Formulations for Nebulization

•Physicochemical parameters such as pKa, log P, isoelectric pH (proteins and peptides), and solubility (vs. pH, ionic strength, buffer, and co-solvent level) are all important.

•Tonicity and solution pH, though typically regarded as formulation issues, must be investigated during preformulation to ensure selection of an appropriate salt form for development.

•For example, acidic (pH <2) hypertonic and hypotonic aerosols have been demonstrated to induce broncho constriction in asthmatic subjects.

- It is important to profile the solution stability of the drug candidate as early as possible to identify the pH of optimum stability.
- The influence of light, oxygen, and trace metals on compound degradation also needs to be considered to assess the requirement for antioxidants (sodium metabisulfite, ascorbic acid, etc.) or chelating agents (EDTA, citric acid, etc.).
- Inclusion of such agents, though required to improve the chemical stability, must be weighed against the potential for adverse effects on the lung.
- Drug stability in solution should be monitored using a stability-indicating assay, following stress storage as a function of elevated temperature.

- As a guide to formulation development, studies should be undertaken to evaluate the contribution of candidate excipients, including preservatives, antioxidants, chelating agents, co-solvents, and buffers on compound stability and solubility. This is particularly important in the development of suspensions for nebulization.

- Compatibility with packaging components also needs to be considered as a matter of priority. Peptides and proteins in particular are notorious in their ability to adsorb onto a variety of surfaces, particularly plastic.

Dry Powder Inhalation Formulations

- Of critical importance in the development of DPI products is the evaluation, optimization, and control of flow and dispersion (de aggregation) characteristics of the formulation. These typically consist of drug blended with a carrier (e.g.,lactose).

- The properties of these blends are a function of the principal adhesive forces that exist between particles, including Vander Waals forces, electrostatic forces, and the surface tension of adsorbed liquid layers .

- These forces are influenced by several fundamental physicochemical properties, including particle density and size distribution, particle morphology (shape, habit, surface texture), and surface composition (including adsorbed moisture)

- It is imperative, during early development, to characterize the moisture sorption and desorption attributes of the drug in relation to available salt forms.
- Assuming solubility is sufficient to ensure adequate absorption, a non hygroscopic form should be explored.
- This would confer a number of advantages, including improved flow properties and dispersion as well as enhanced physical stability in the bulk and final dosage forms due to minimal moisture transfer between the drug, immediate container (e.g., gelatin capsule shell), and the environment.
- Furthermore, improved chemical stability may result in the case of hydrolytically labile drugs

- Environmental factors, including temperature, humidity, and light, are essential considerations during formulation development. Therefore, it is imperative to evaluate the influence of these factors on the physical and chemical stability of the formulation during early preformulation studies.

- The effects of elevated temperature and humidity on product stability can be assessed after stress storage.

- physical changes are evaluated using an array of techniques available to the preformulation scientist, including polarized light microscopy (aggregation, crystal growth), differential scanning calorimetry, infrared spectroscopy, x-ray diffractometry, solution calorimetry, thermo gravimetric analysis, and hot-stage microscopy (moisture uptake, polymorph inter conversion, pseudo polymorph formation).
- Stressed stored samples should also be evaluated for evidence of caking and discoloration.

Metered-Dose Inhaler Formulations

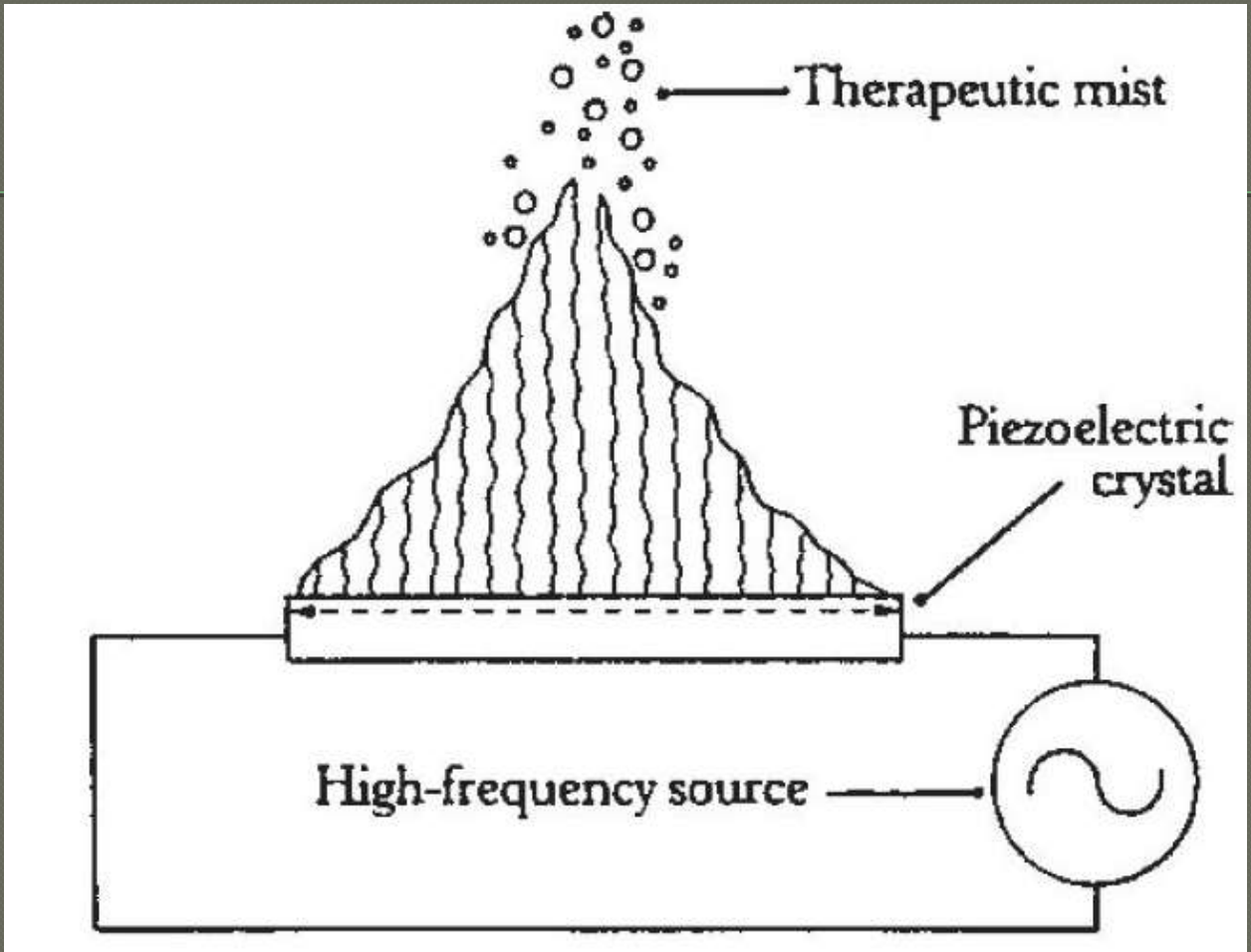
- The development of MDI formulations requires the same core preformulation data as described previously. However, additional parameters must also be evaluated, including solubility in propellant vs. concentration and nature of dispersing agent, crystal growth potential (related to solubility), and, most importantly, suspension properties (sedimentation, re-dispersibility).

- The solubility of a solute is a function of the particle size of the solute.
- Small particles, possessing high surface free energy, are more soluble than larger particles. The increase in solubility is dramatic for particles of less than one micrometer
- Simple formulation- does not use more than two or three excipients, for suspensions ethanol or glycerol can be used to increase the solubility of surface active agents

INHALATION DRUG DELIVERY SYSTEM DESIGN

NEBULIZED DRUG DELIVERY

- In ultrasonic nebulizers, ultrasound waves are formed in an ultrasonic nebulizer chamber by a ceramic piezoelectric crystal that vibrates.
- when electrically excited, these set up high-energy waves in the solution, with in the device chamber, of a precise frequency that generates an aerosol cloud at the solution surface.

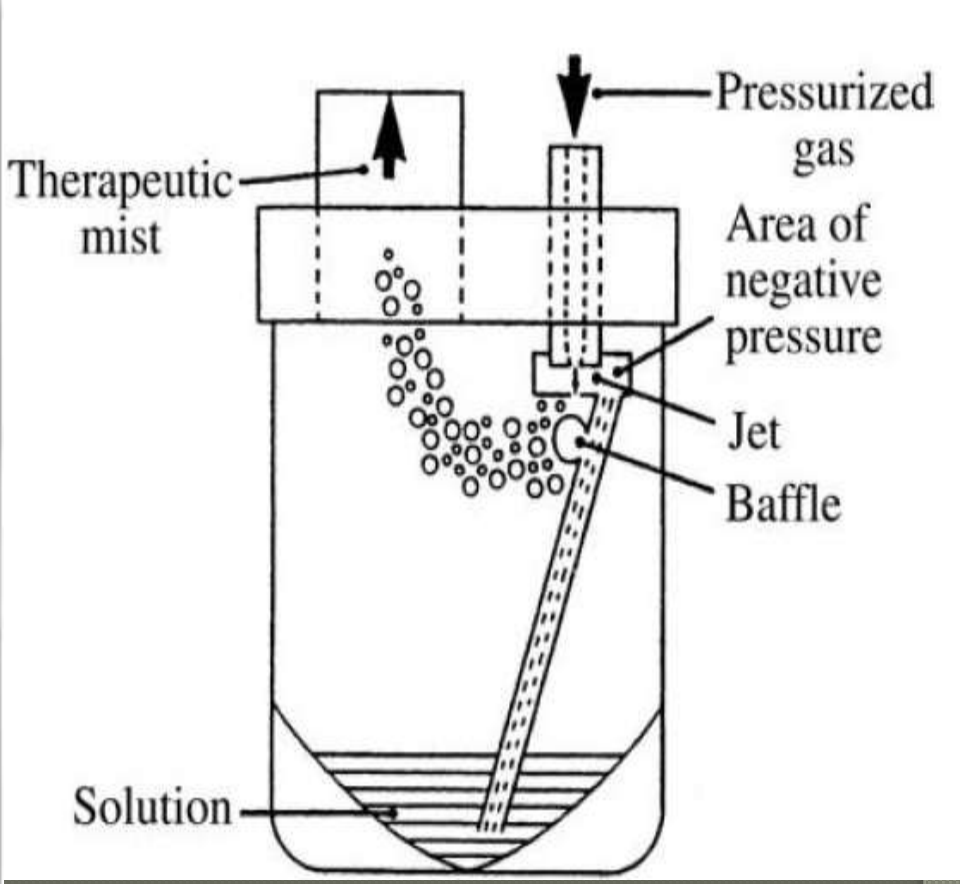


Schematic of an ultrasonic nebulizer

- The aerosol produced by an air-jet nebulizer is generated by a completely different principle. When compressed air is forced through an orifice, an area of low pressure is formed where the air jet exists. A liquid may be withdrawn from a perpendicular nozzle ,(the Bernoulli effect) to mix with the air jet to form droplets.

- A baffle (or baffles) within the nebulizer is often used to facilitate the formation of the aerosol cloud. Carrier air (oxygen) can be used to generate the "air jet."

- Alternatively, compressors may be used to generate the air stream



Schematic of an air-jet nebulizer

- Nebulizers are designed primarily for use with aqueous solutions or suspensions.

- Typically the drug suspensions use primary particles in the range of 2–5 microns.

- Pharmaceutical solution technology, consistent with that used for parenteral products, may be applied to nebulizer solution or suspension formulation and processing.

- Nebulizer solutions are usually formulated in water, although other co-solvents, for example, glycerin, propylene glycol, and ethanol, may be used.
- However, it is important to note that any excipients with possible airway toxicological implications might compromise a drug product
- Thus, such additional excipients should not be introduced unless essential and, if so, formulated at the lowest feasible concentration.
- The range of suspending agents in approved products is limited.

- Nebulizer solution pH may be an important factor in determining compound physical or chemical stability. It has been recommended that solution pH be greater than 5.0, because there is considerable evidence to show that bronco constriction is a function of hydrogen ion concentration.

- Nevertheless, the formulation "buffer capacity" and "titratable acid content," in addition to the nature of the acid present, are perhaps the most important factors for nebulizer solutions of greater than pH 2.0.

- With the advent of the potential of using the inhaled route to deliver macromolecules there has been considerable interest in the development of nebulized formulations of macromolecules .
- Compound stability is a significant issue for these biotechnology products; as such, aqueous nebulizer solutions do not provide an inert vehicle.
- Moreover, the high shear experienced with an air-jet nebulizer may induce secondary or tertiary structural changes in peptide or proteins. In addition, reservoir temperature changes during nebulization may compound problems in physical or chemical stability with biotechnology products.
- Furthermore, macromolecules often produce viscous solutions, with modified interfacial and surface tension.
- A complete investigation of these factors is critical during early product development.

- Nebulizer solutions are typically filled as unit dosages in plastic containers. The latter uses blow-fill-seal technology . Thus drug formulation compatibility with plastics is an important factor.

- Characterization of any sorption processes of plasticizer, monomer, and "extractables" or "leachables" is critical during long-term product-evaluation studies.

- Such sterile unit-dose formulations, in essence, do not require chemical preservation.

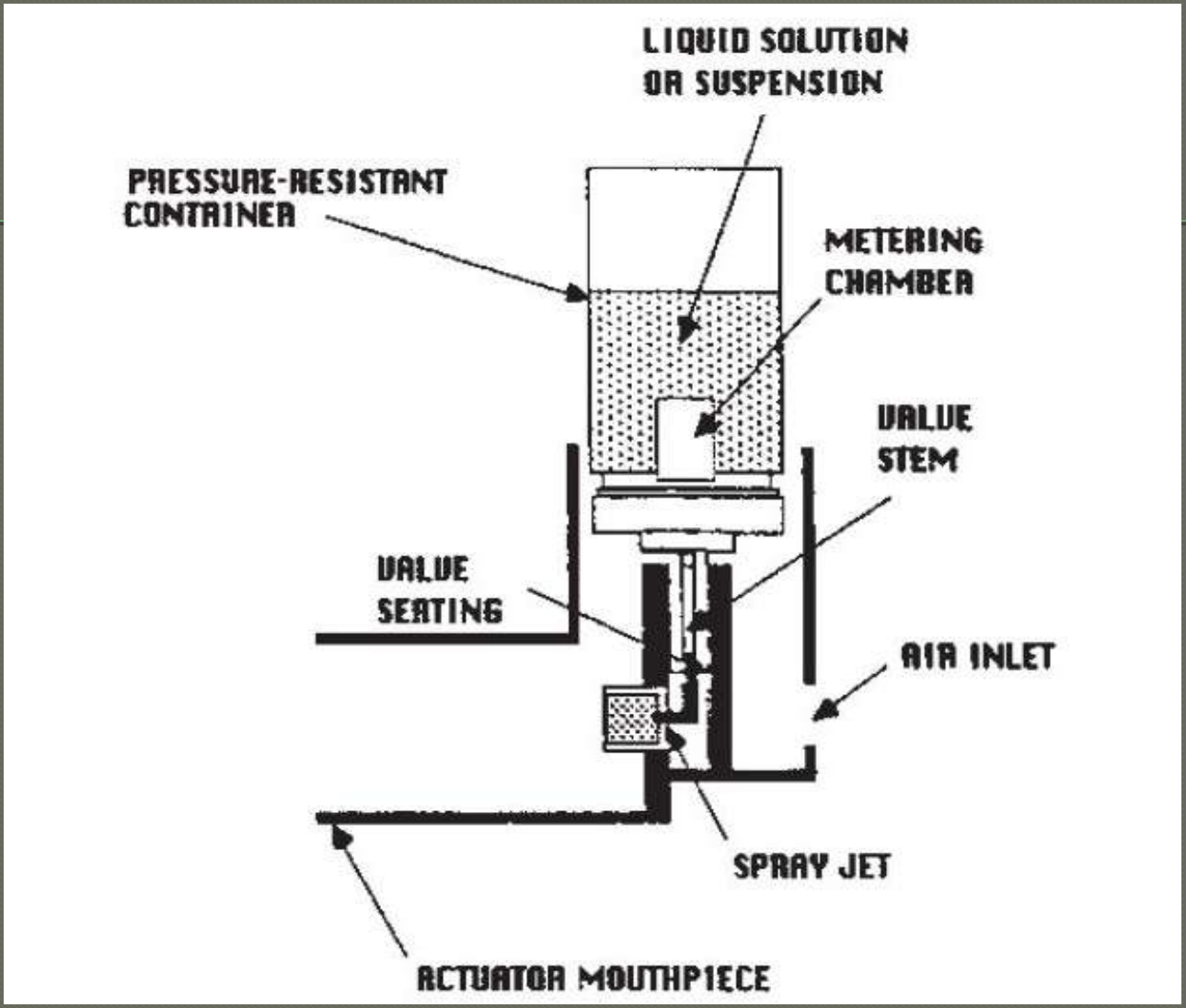
METERED-DOSE INHALERS

- A metered-dose inhaler (MDI) is a complex system designed to provide a fine mist of medicament, generally with an aerodynamic particle size of less than 5 microns, for inhalation directly to the airways for the treatment of respiratory diseases such as asthma and COPD.

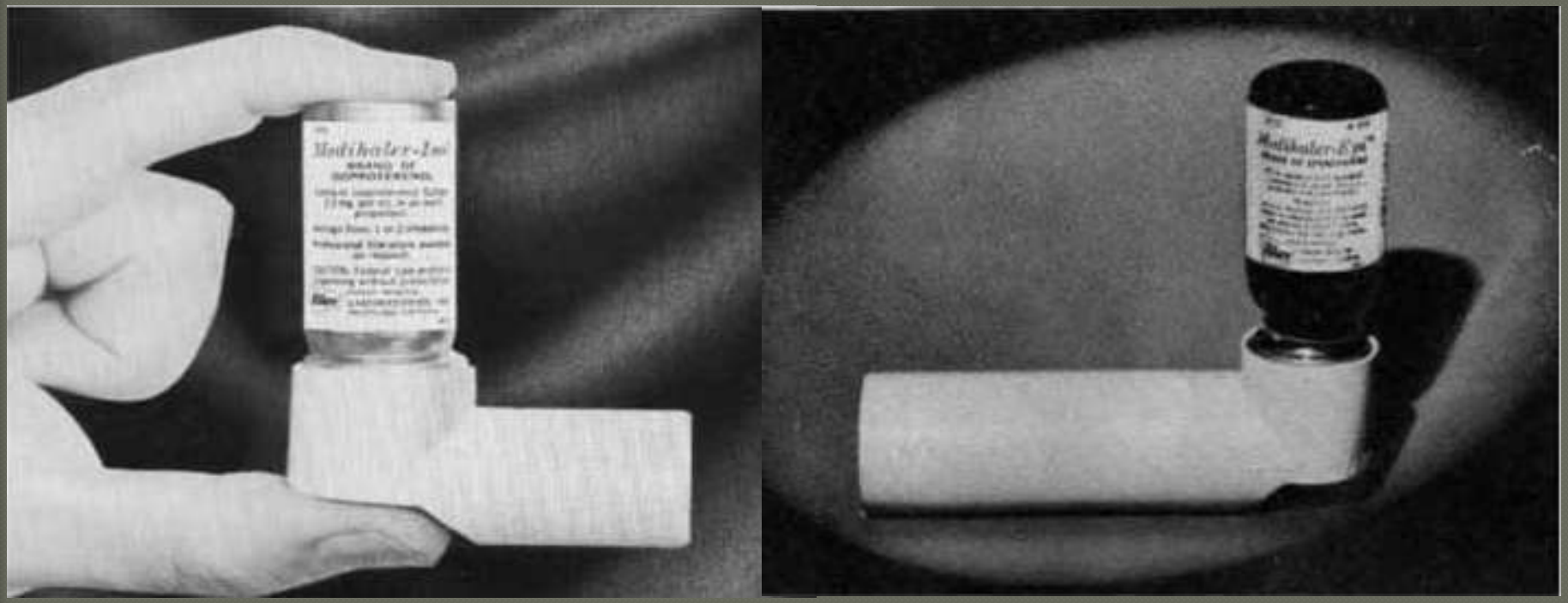
The main components of all MDIs are.

1. The active ingredient.
2. The propellant (a liquefied gas).
3. A metering valve
4. A canister
5. An actuator/mouthpiece

- The active ingredient (the drug) may be either dissolved in the propellant or a co-solvent (e.g., ethanol) or suspended in the propellant.
- A surface-active agent may be included to ensure that the drug is well suspended and to help lubricate the metering valve.
- The metering valve is the key to measuring and presenting a consistent and accurate dose to the patient; it is made up of a number of precision-made plastic or metal components. The valve is crimped onto a canister, which is ordinarily made of aluminum.
- Finally, there is the actuator, which holds the canister and through which the patient inhales the dose.



Essential components of a metered-dose inhaler.



The metered dose inhaler.

There are two types of MDI formulations:

1. Suspension formulations, in which micro particulate drug (typically micronized material) is dispersed in a combination of propellants.
2. Solution formulations, in which the drug freely dissolves in either the propellant or a combination of propellant and an acceptable co-solvent, typically ethanol.

- CFC-containing MDIs contain CFC-12 and CFC-11 and sometimes CFC-114. HFCs 134a and 227.
- Hydrofluroalkane propellants (HFA 134a, HFA227.

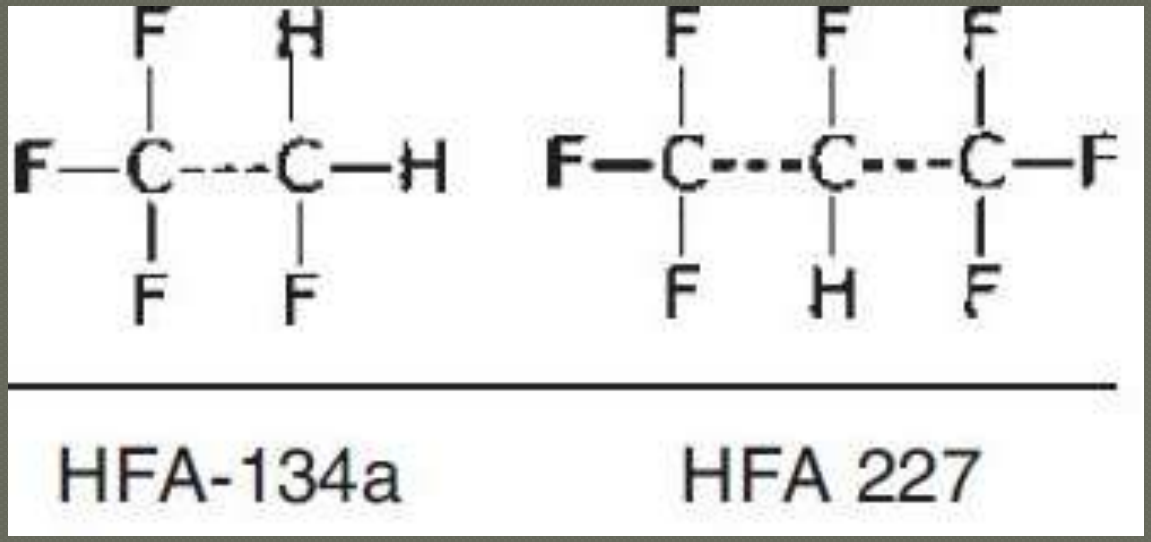


TABLE 2 Typical HFA MDI Formulations

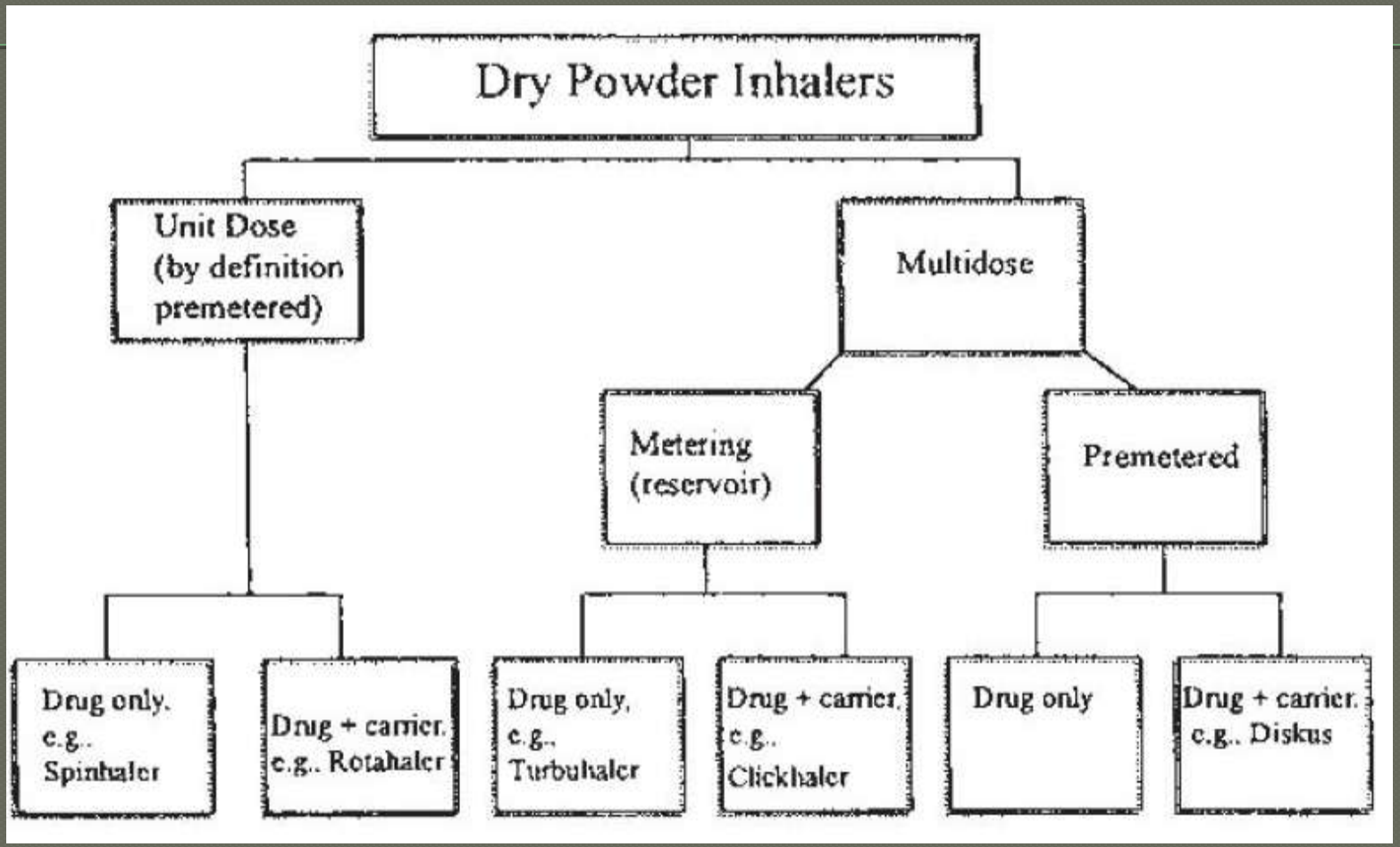
Drug compound	Formulation	Company producing
Salbutamol	Ethanol/surfactant/134a	3M Pharmaceuticals Ivax-Norton Healthcare
	134a alone	GlaxoSmithKline Cipla
Beclomethasone	Ethanol/134a	3M Pharmaceuticals Ivax-Norton Healthcare
	Ethanol/134a/glycerol	Chiesi
Budesonide	Ethanol/134a/glycerol	Chiesi
	134a alone	Cipla

- Commonly used surfactants include sorbitan trioleate (SPAN 85), oleic acid, and lecithins, at levels between 0.1% and 2.0% wt/wt.
- The technique of controlled flocculation is often used as a means of optimizing oral suspensions.
- The principle involves increasing the size of the flocs by manipulation of zeta potential and surfactant concentration, to a point where the sedimentation ratio (sediment volume/total volume) is maximized (ideally F = 1).
- This approach has been widely used in developing HFA formulations.

DRY POWDER INHALERS

Unit-Dose Devices:

- Single-dose powder inhalers are devices in which a powder-containing capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled.
- The capsule residue must be discarded after use and a new capsule inserted for the next dose.
- An asthma attack and requires immediate delivery of drug (Disadvantage)


Dry Powder Inhalers
Unit Dose (by definition premetered)
Multidose
Metering (reservoir)
Premetered
Drug only, e.g., Spinhaler
Drug + carrier, e.g., Rotahaler
Drug only, e.g., Turbuhaler
Drug + carrier, e.g., Clickhaler
Drug only
Drug + carrier, e.g., Diskus

- Multidose Devices: The development of multidose DPIs was pioneered by A. B. Draco (now a division of Astra Zeneca) with their Turbuhaler.
- This device is truly a metered-dose powder delivery system.
- The drug is contained within a storage reservoir and can be dispensed into the dosing chamber by a simple back-and forth twisting action on the base of the unit.
- The device is capable of working at moderate flow rates and also delivers carrier-free particles.
- However, one of the drawbacks of the Turbuhaler has been the fact that it has a highly variable delivery at different flow rates.

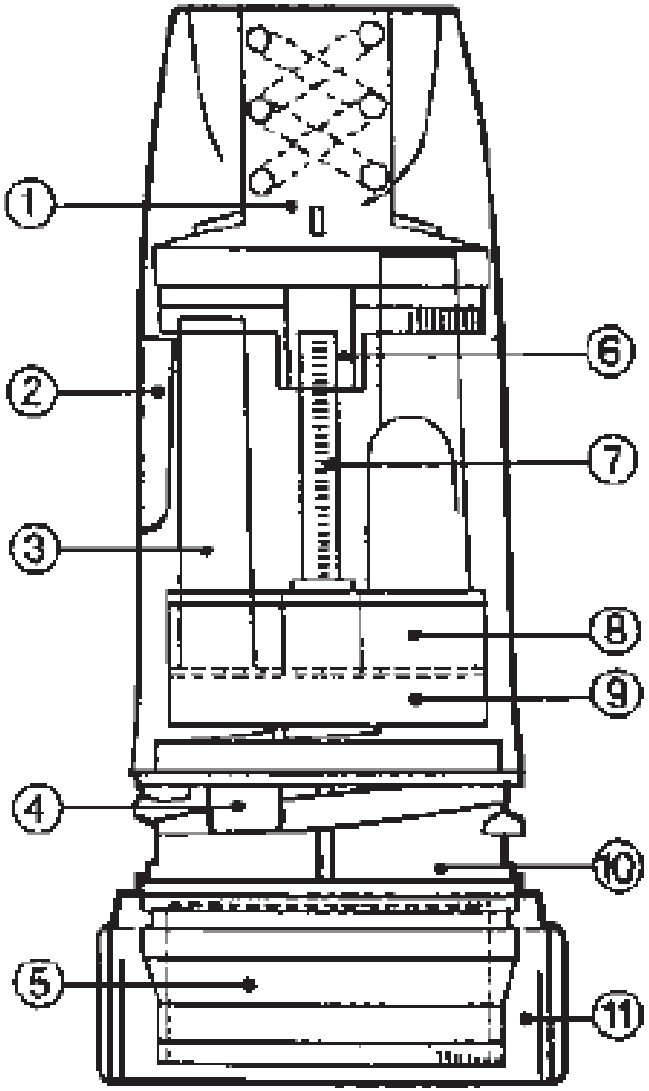
- To address issues associated with a need for multiple dosing and consistent performance, Glaxo developed the Diskhaler , which was used to deliver a range of drugs, including salbutamol and beclomethasone.

- This device uses a circular disk that contains either four or eight powder doses on a single disk.

- This typically would be treatment for one to two days. The doses are maintained in separate aluminum blister reservoirs until just before inspiration.

- On priming the device, the aluminum blister is pierced, and the contents of the pouch are dropped into the dosing chamber.

- This product had limited commercial success and was superseded in the late 90's by the Diskuse. This device is a true multidose device, having 60 doses in a foil–foil aluminum strip that is opened only at the point just prior to patient inspiration .
- Consistent performance and broad patient acceptance has allowed the Diskuse to become the gold standard of multidose powder delivery devices.



Components of the Turbuhaler, a multidose dry powder inhaler.
(1) mouthpiece with insert,
(2) bypass air inlet,
(3) inhalation channel,
(4) air inlet,
(5)desiccant store,
(6) window for dose indicator,
(7) dose indicator,
(8) storage unit for drug compound,
(9) dosing unit,
(10) operating unit,
(11) turning grip.

- Dry powder formulations either contain the active drug alone or have a carrier powder (e.g., lactose) mixed with the drug.
- The drug particles must be of sufficiently small aerodynamic diameter to make it to and deposit on the airways.