

# NOVEL INNOVATIONS IN METERED DOSAGE INHALERS

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## INTRODUCTION

- With advancing technology day by day, the dream of utilizing the huge surface area of lungs to deliver drugs into the blood circulation has been slowly transforming into reality.
- Lungs are considered the best alternative for drugs needing to bypass the gastrointestinal tract, such as proteins, peptides and other molecules.
- For targeted delivery, this can improve efficacy and reduce unwanted systemic side effects, a large surface area for absorption, thin alveolar epithelium permitting rapid absorption, absence of first-pass metabolism, rapid onset of action and high bio-availability.

### It can be used for systemic administration of drug because

- Large surface area of alveoli.
- High permeability of alveolar epithelium:
- Rich perfusion permits extremely rapid absorption
- Avoidance of first pass metabolism
- Generally well accepted route of administration

### Where do inhaled particle deposit?

- ✓ **Inhaled particle**
  - Size ,shape ,hygroscopicity, density
- ✓ **Patient**
  - Lung anatomy, disease state, breathing pattern.
- ✓ **Principle and design of the generation device**
- ✓ **Aerodynamic diameter:** it is determined by the actual size of the particle, its shape and its density. Particle between 0.5 and 3.5 micro meter will largely by pass the bronchial airway during inhalation and penetrate almost entirely to the deep lung .larger particle are dominated by the inertial mass and will impact in upper air way due to their inertia.
- ✓ **Hygroscopic growth:** initially dry 1-3.5 micro meter particle may take up water vapor over a wide range of ambient condition and grow to the diameter outside the optimum size range during inhalation.

### The available delivery systems include

1. METERED DOSE INHALERS (MDIS),
2. DRY POWDER INHALERS (DPIS),
3. NEBULIZERS.

### **Metered Dose Inhalers**

- MDIs were among the first to be introduced in the United States in the mid 1950s.

Metered dose inhalers are pressurized canisters containing a mixture of propellants, surfactants, preservatives, and flavor agents. When the actuator is depressed, the mixture is

released from the canister through a metering valve and stem. The nominal dose of medication with the metered dose inhaler is much smaller than with the nebulizers.

### **Nebulizers**

Nebulizers are used to convert liquids into aerosols at a size small enough to be easily inhaled into the lower respiratory tract.

Although the metered dose inhaler is the first choice of aerosol generator for the delivery of bronchodilators and steroids, nebulizers are more useful because there are some inhalation drugs that are available only in solution form, and correct use of the metered dose inhaler is more difficult to master.

The physiologic benefits of metered dose inhalers and nebulizers are virtually equivalent. Choosing between the two devices is really a matter of preference rather than a selection of which is best.

### **HISTORY OF METERED DOSE INHALERS**

1956	First MDI Medihaler
1974	This year saw the publication of the 'ozone depletion theory', put forward by two American scientists, Rowland and Molina.
1987	"Montreal protocol" This agreement set target dates for significant reductions in the use of CFCs. The protocol was revised in 1990, in order to phase out the use of CFCs by the year 2000. CFC propellants are now only used in certain 'exempt' products.
1995	First HFA MDI. "Airomir "

### **TYPES OF METERED DOSE INHALERS**

- There are mainly two types of metered dose inhalers are available based on the type of systems used.
  - a) NON – PRESSURIZED SYSTEMS
  - b) PRESSURIZED SYSTEMS

#### **1. NON – PRESSURIZED SYSTEMS**

Generally the most common used inhalation drug delivery systems are Pressurized metered dose inhalers but due to some environmental concern regarding the CFCs propellants alternative non pressurized systems are used as MDIs.

That includes

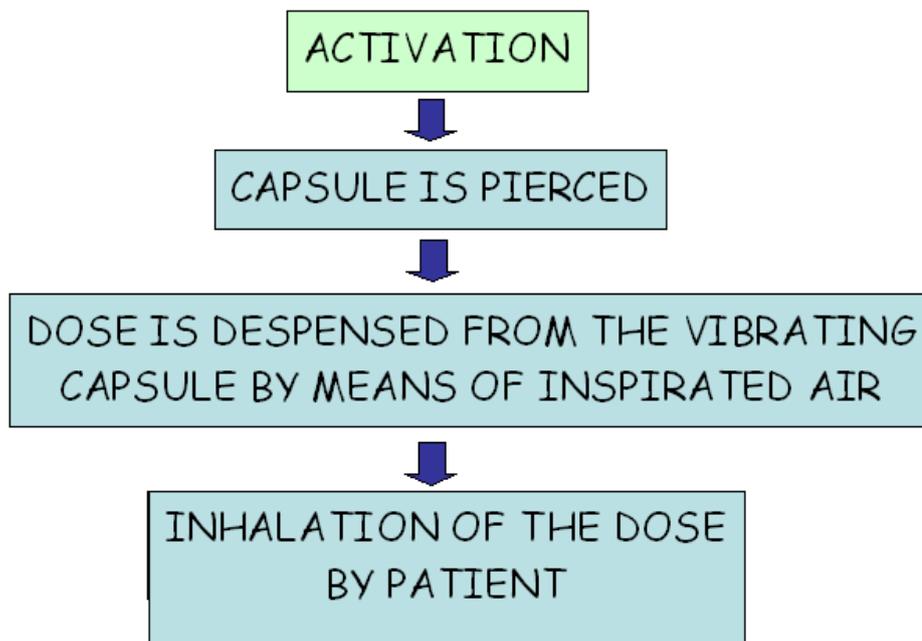
- 1. POWDER INHALERS:**
- 2. NOVEL NEBULIZATION DEVICE:**

#### **POWDER INHALERS**

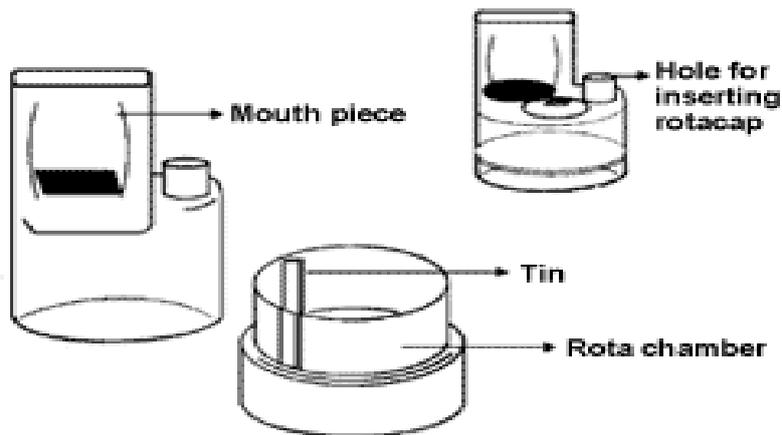
- They dispense powder in a stream of metered air.
  - PARTICLE SIZE SHOULD BE  $< 5 \mu$
  - The classical DPIs are breath actuated .thus the problem is synchronization. However energy needed to mobilize the powder bed and entrain it in to the air stream and break up the powder formulation into smaller particles is derived from the patient's breath (passive DPIs) hence the performance of these depend on the patient's technique and ability to inhale sufficient volume of air at an adequate inspiratory flow rate. More recently active DPIs entered into development .such devices utilize some form of stored energy with a view to eliminate the dependency of eliminated dose and particle size distribution on the patient effort. However it need to remembered that the regional distribution of the drug in the respiratory tract depends on the inspiratory flow rate and inspired volume even if the generated dose and its particle size distribution remain constant.
- 
- Generally of two types:

**UNIT DOSE DEVICES:**

The drug mixture is prefilled in to hard gelatin capsule and loaded into Device.



## ROTAHALER



### QUALI-V®-I: A New Key for Dry Powder Inhalers

Quali-V-I capsules, the hard two-piece hypromellose capsules for use in DPIs,

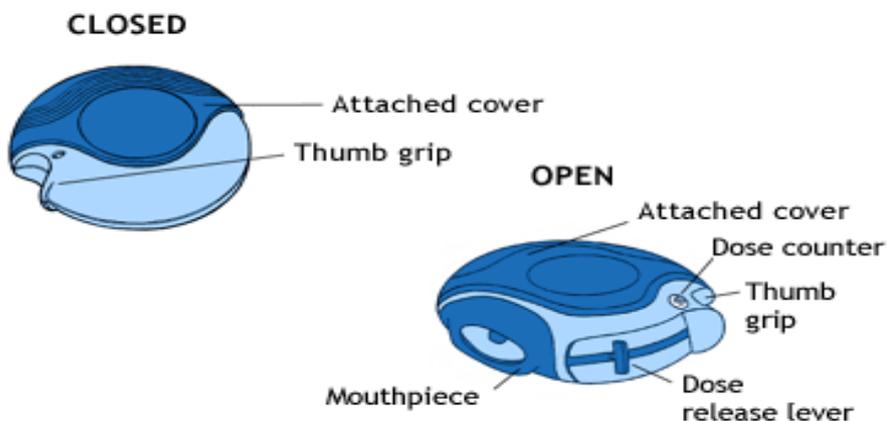
- ✓ Superior physical performance at lower moisture contents,
- ✓ Better cutting and puncturing performance in standard DPIs.
- ✓ Elimination of the generation of shell particles in use.
- ✓ Tighter weight specification available if required.

### **MULTIPLE DOSE DEVICES:**

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 base of the Unit.

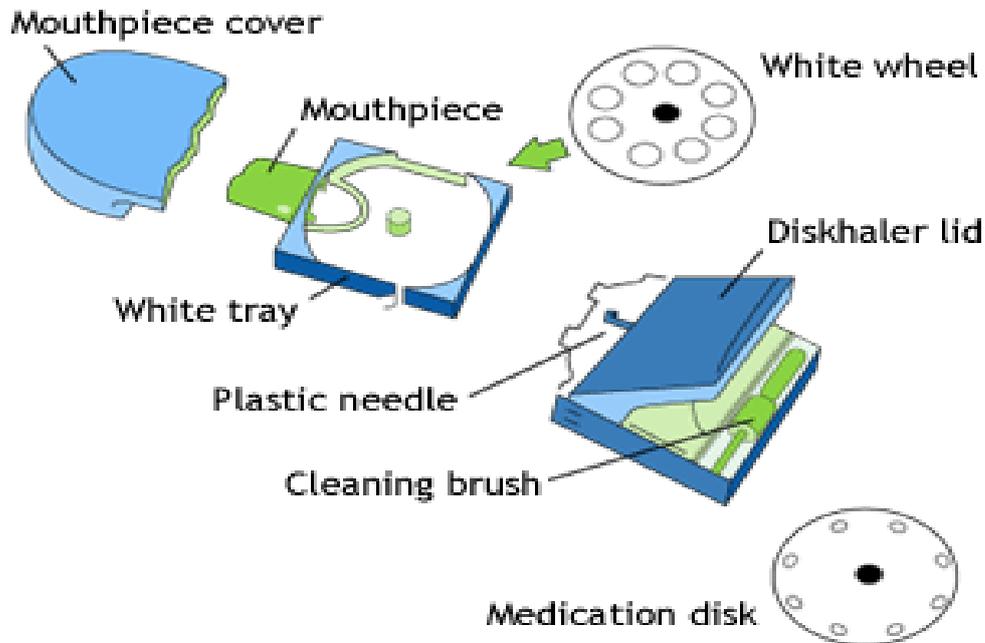
### DISKUS

- Dry-powder inhaler that holds 60 doses.
- It features a built-in counter, so that you always know how many doses you have left in it.

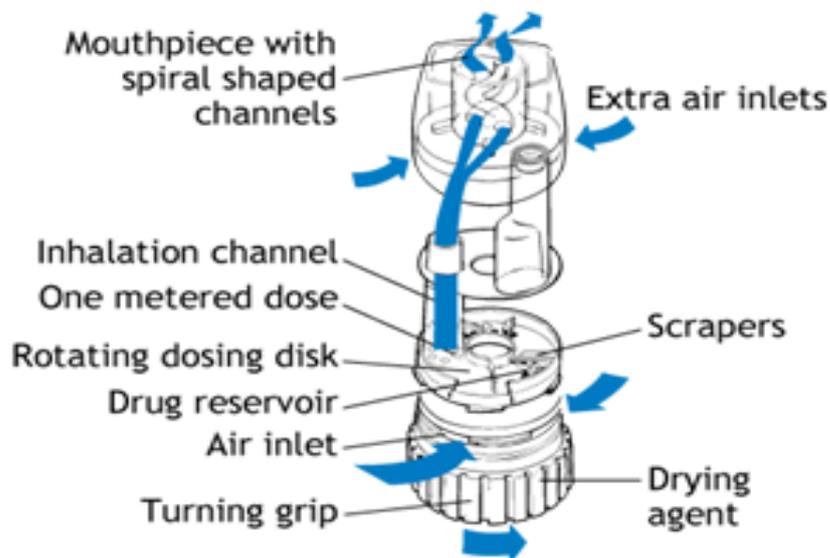


## DISK HALER

- A Disk haler® is a dry-powder inhaler that holds small pouches (or blisters), each containing a dose of medication, on a disk.(60 doses)
- The powder passes through single crucifix grid to generate the necessary turbulence for efficient dispersion of powder.
- The Diskhaler® punctures each blister so that its medication can be inhaled.



## TURBUHALER



- Some Turbuhaler® feature a dose counter that shows the exact amount of medication left. And is pre-loaded to 200 doses
- Have a long path so that drug agglomerates are broken in to smaller particles.
- If your Turbuhaler® doesn't have a dose counter, then check for a red indicator in the windows on the side of the device. When you see red in the window, there are approximately 20 doses left and it's time to order a refill.

### **ADVANTAGES OF POWDER INHALERS**

#### **Active research area because**

- Requires less precise coordination than all MDIs.
- Breath – actuated.
- They are environment friendly as they don't use CFCs.(no propellant)
- Potential drug stability advantage.
- High dose carrying capacity.
- Using energy from only patient inhalation
- Less potential from extractable from device component.

### **DISADVANTAGES OF POWDER INHALERS**

- ✓ It requires high inspiratory flow rates for good dispersion of powder charge.
- ✓ Product performance is very much dependent on inspiration efforts, which is Product of inhalation flow rate and device resistance.
- ✓ So large variability in product performance.
- ✓ More expensive than pMDIs.

### **NEBULIZERS**

- Solutions and occasionally suspensions can be nebulized. Nebulizer is a device used to administer medication to people in forms of a liquid mist to the airways
- Nebulizer solutions are commonly formulated in water, glycerin, propylene glycol, or ethanol
- Nebulizers are used mainly in hospital for severe attacks of asthma when large doses of inhaled drugs are needed. They are used less commonly than in the past as modern spacer devices are usually just as good as nebulizers for giving large doses of inhaled drugs

#### **Two types:**

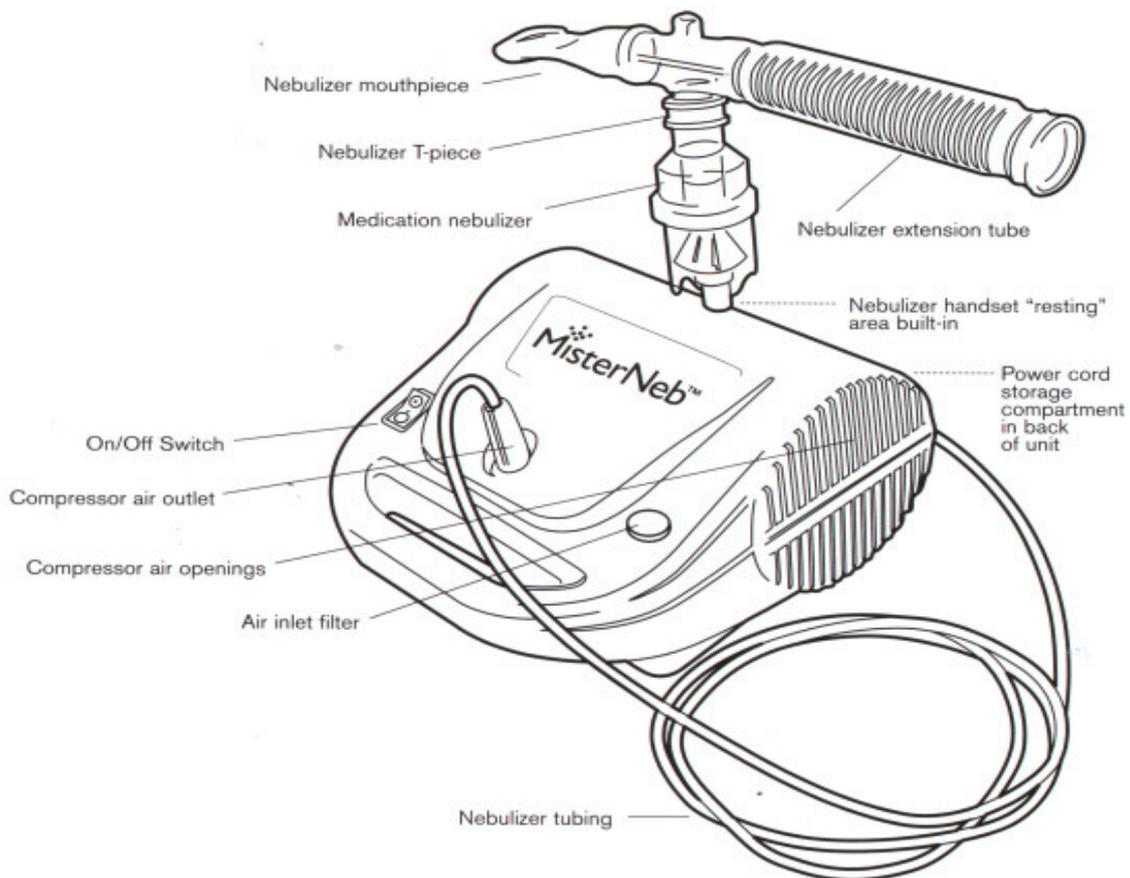
1. *Air jet nebulizers*
2. *Ultrasonic nebulizers*

## Air jet nebulizers



## Ultrasonic nebulizers

- ✓ Traditionally use of flow of compressed air flow lateralization
- ✓ But ultrasonic Nebulizer uses a high frequency vibrating plate to provide the energy needed to aerolize the liquid.



**Note:** the new regulation in the united state which come into force in 2002 requires that all inhalation solution for nebulization be sterile, thus eliminate the need for preservatives in these product

## PRESSURIZED METERED DOSE INHALERS:

The MDI contains a pressurized inactive gas that propels a dose of drug in each 'puff'. Each dose is released by pressing the top of the inhaler. This type of inhaler is quick to use, small, and convenient to carry. It needs good co-ordination to press the canister, and breathe in fully at the same time

### Contemporary Issue:

- 1) Less than 20% drug deposition in the lung
- 2) Unproven platform for delicate molecules
- 3) CFC to HFA poses formulation and bioequivalence challenge.

**Breath-activated MDIs** are an alternative (for example, the autohaler). You don't have to push the canister to release a dose. Instead, you trigger a dose by breathing in at the mouthpiece. So, these type of MDI inhalers require less co-ordination than the standard MDI. They tend to be slightly bigger than the standard MDI.

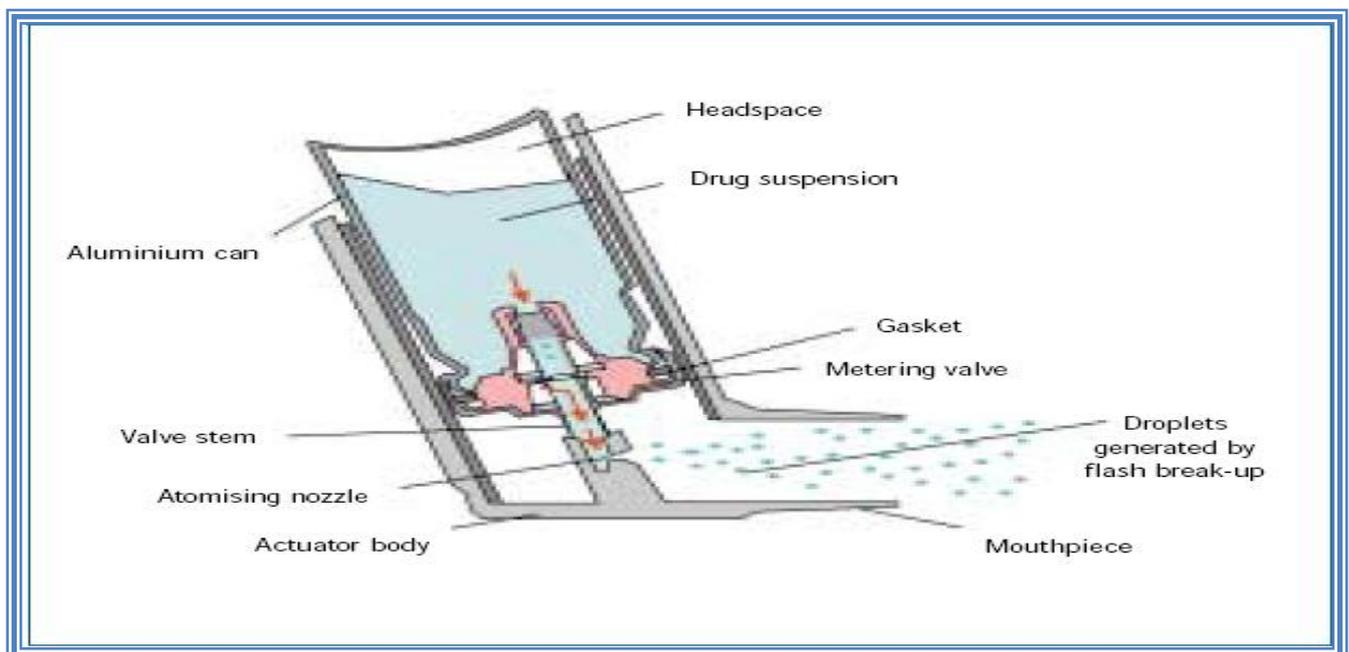
### ADD ON DEVICE FOR pMDIs

**Spacer devices** are used with pressurized MDIs (Metered Dose Inhalers). The spacer between the inhaler and the mouth holds the drug like a reservoir when the inhaler is Pressed. A valve at the mouth end ensures that the drug is kept within the spacer until you breathe in. When you breathe out, the valve closes. So you don't need to have good co-ordination to use a spacer device. They are commonly used by children.

- i) Slow down droplets
- ii) Control inhalation rate
- iii) Trap large droplets
- iv) Allow droplet evaporation yielding smaller particles
- v) Exhalation diversion

Aid coordinated actuation and inhalation.

- pMDIs offer a unique combination of reliability, accurate dosing, convenience and



low cost for delivering drugs to the lungs.

➤ However,

The phase-out of CFC propellants prompted by the ***Montreal Protocol Agreement in 1987*** has challenged manufacturers to reformulate their pMDIs using the alternate environment-friendly HFA propellants (134a and 227).

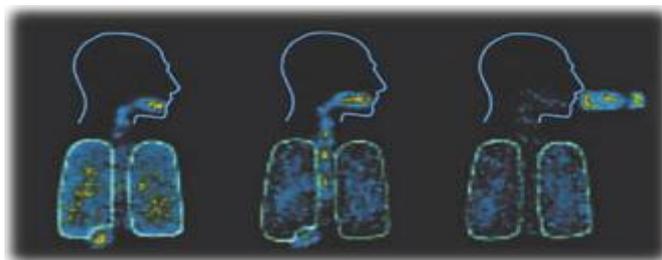
➤ Today, most pMDIs products have been reformulated as an HFA formulation,

➤ Such as Ventolin® HFA, Flovent® HFA, and Seretide.

## **RESPIMAT**

Respimat, a possible alternative to the conventional metered dose inhaler (MDI), is a novel, reusable, propellant-free, multidose soft mist inhaler. Respimat slowly releases a metered dose of active substance as a soft mist with a high proportion of the dose in the fine particle fraction, leading to improved lung deposition following inhalation when compared with the conventional MDI.

- ✓ High lung deposition
- ✓ Low mouth deposition : Long lasting, slow moving Soft Mist™ is much slower than aerosol clouds from MDIs ; therefore it leads to lower deposition in the mouth and throat compared with CFC- and HFA-MDIs and simplifies inhalation to the lungs, where the medication is of most benefit to the patient



- ✓ Efficient and effective
- ✓ Simplifies coordination between inhalation and actuation.
- ✓ The advantages of Respimat® Soft Mist™ Inhaler which result from the features of the Soft Mist™ make it suitable for all patients with asthma or Chronic Obstructive Pulmonary Disease (COPD) who require inhaled respiratory therapy.
- ✓ Easy and convenient to use: The Respimat® Soft Mist™ Inhaler is actuated using the dose-release button in combination with a deep inspiration
- ✓ Independent of inspiratory flow: The Soft Mist™ produced by the inhaler which is slow moving and long lasting, and is easily inhaled, is generated independent of the patient's inspiratory flow
- ✓ Without propellant : Different from CFC- and HFA- inhalation products Respimat® Soft Mist™ Inhaler is propellant free and therefore environmentally friendly. No propellant or energy source is needed. A spring provides the power to force the solution through the uniblock to provide the unique Soft Mist
- ✓ Dose indicator

## **WHICH IS THE BEST INHALER DEVICE TO USE?**

This depends on various factors such as:

- ✓ Convenience. Some inhalers are small, can go easily in a pocket, and are quick to use. For example, the standard MDI inhaler.
- ✓ Your age. Children under six generally cannot use dry powder inhalers. Children under 12 generally cannot use standard MDI inhalers without a spacer. Some elderly people find the MDI inhalers difficult to use.
- ✓ Your co-ordination. Some devices need more co-ordination than others. In particular, the standard MDI.
- ✓ Side effects. Some of the inhaler drug hits the back of the throat. Sometimes this can cause problems such as thrush in the mouth. This tends to be more a problem with higher doses of steroid inhalers. Less drug hits the throat when using a spacer device. Therefore, a spacer device may be advised if you get throat problems, or need a high dose of inhaled steroid.

## **DESIGN SPECIFICATON**

- 1) Patient consideration
  - a) Good patient acceptance
  - b) Usable by children, adult, and elderly.
  - c) Dose counter
  - d) Simple operation
  - e) Competitive pricing with MDI for generic products
- 2) Inhalation consideration
  - a) Breath actuated
  - b) No extraordinary breathing maneuvers
  - c) Not detrimentally influence by exhalation through device .
- 3) Engineering issues
  - a) Minimal numbers of small parts
  - b) Disposable unit or refillable durable unit
  - c) Can deliver a range of doses or drugs without major reengineering
  - d) Provide high level of drug protection
  - e) Minimal opportunity of accidental double dosing
- 4) Pharmaceutical issue
  - a) High level of drug stability
  - b) Multidose
  - c) Reproducible emitted dose
  - d) High lung deposition
  - e) Low oropharyngeal deposition-low exit velocity
  - f) No priming requirement
  - g) Rapid tail-off or lock out

### FILLING METHODS:

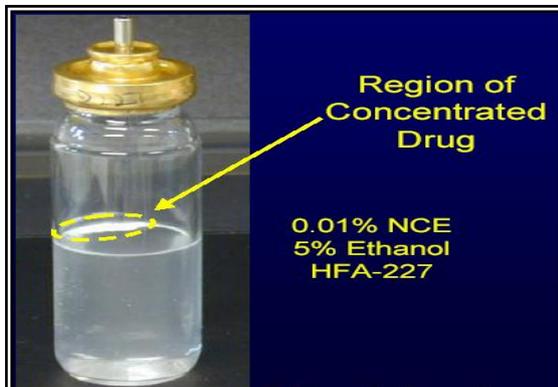
- a) Cold Filling
- b) Pressure Filling
- c) Under Cup Filling

### FACTORS AFFECTING MDI DOSING RANGE;

- Challenges delivering low dose
  1. Dosing consistency
  2. manufacturing consistency
  3. loss of drug
  4. degradation of drug
  
- challenges delivering high dose
  1. physics of aerosol
  2. blockage
  3. dosing consistency

*(Dosing consistency for low dose suspensions*

- 1. drug creams or settles into small volume*
- 2. migration of drug into or out of metering volume resulting into poor dosing after storage*
- 3. formulation with small creams / sediment are problematic )*



### EVALUATION OF MDI AS PER FDA:

- a. Appearance and Color
- b. Identification
- c. Microbial Limits
- d. Water or Moisture Content
- e. Dehydrated Alcohol Content
- f. Net Content (Fill) Weight
- g. Drug Content (Assay)
- h. Impurities and Degradation Products
- i. Dose Content Uniformity
- j. Dose Content Uniformity Through Container Life

- k. Particle Size Distribution
- l. Spray Pattern and Plume Geometry
- m. Leak Rate
- n. Pressure Testing
- o. Valve Delivery (Shot Weight)
- p. Leachables

### **Particle Size Distribution**

- This parameter is dependent on the
    - ✓ Formulation,
    - ✓ The valve, and
    - ✓ The mouthpiece
  - The optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized as being in the range of 1–5 microns.
- I. A multistage cascade impactor is used.
  - II. Single Particle Optical Sizers (SPOS)
  - III. Light scatter decay method

### **Spray Pattern**

- Cross sectional uniformity of the spray to be determined at specified distances away from the pump orifice tip.
- Laser sheet and digital camera using electronic images and automated analysis.

### **Plume Geometry**

- Side view parallel to the axis of the plume of the spray or aerosol cloud to be determined.
- Plume angle, plume width, and plume height using high-speed flash photography.
- Laser sheet and high-speed digital camera with electronic images.

## **INNOVATIONS:**

### **MODIFIED RELEASE FORMULATION FOR PULMONARY DELIVERY**

#### ✓ **Why challenge?**

The problem is quite complex because different part of the respiratory tract are cleared by different mechanism .the resident time of the drug in various part of the respiratory tract as it is released from particles and droplets is therefore affected not only by the nature of the formulation but also by the ability of the muco-ciliary escalator and macrophage to remove such foreign matter from the conducting airways and alveoli.

Further since the therapeutic effect of the drug in the respiratory tract are presumably related to the drug released from the controlled release carrier, the right balance between the rate of release and the rate of clearance from the lung has to be found

## **Innovation in the DPIs**

### **POWDER PRODUCTION METHODS**

The DPI formulation aims at pulmonary drug delivery having uniform distribution, small dose variation, good flow ability, adequate physical stability in the device before use and good performance in terms of emitted dose and fine particle fraction. In the last decade many patents have been filed claiming improvement in aerosol performance of dry powder inhalers through the use of

- ✓ Incorporation of fines of carrier particles to occupy active sites on the surface and use of hydrophobic carriers to facilitate deaggregation through reduced surface energy and particle interaction.
- ✓ Reducing aerodynamic diameters through particle engineering and incorporating drug into porous or low particle density.
- ✓ Preparing less cohesive and adhesive particles through corrugated surfaces, low bulk density, reduced surface energy and particle interaction and hydrophobic additives.

### **TECHNIQUES FOR FORMULATION OF STABLE MICRON SIZED DPI PRODUCTS**

It includes co-precipitation of drug and carrier by lyophilization and milling, spray freeze drying, ultrasound assisted crystallization, flash crystallization, controlled precipitation, and supercritical fluid technologies. These methods have the advantages of higher product yield, lower operating temperature, and higher powder crystallinity. However, all the techniques suffer from the disadvantage of high operating cost and impurity.

- ✓ Spray freeze drying was explored for pharmaceutical application in early 90s. It involves spraying the drug solution into a freezing medium (usually liquid nitrogen) followed by lyophilization. Compared to spray drying, this process produces light and porous particles with enhanced aerosol performance, and the production yield is almost 100%. The method has been applied to prepare rhDNase and anti-IgE antibody particles for inhalation and can also be used for anti-asthmatic compounds. However, this is an expensive process and would only be justifiable for expensive drugs as it requires the additional use of liquid nitrogen and the freeze drying step is more time consuming.
- ✓ The solvent precipitation technique involves Sonocrystallization and micro precipitation by opposing liquid jets. Inhalable particles can potentially be obtained by rapid precipitation from aqueous solutions using anti-solvents. Recently, ultrasonic radiation has been applied to control the precipitation process. The setup simply comprises an ultrasound probe in a mechanically stirred reaction tank where the anti-solvent is mixed with the drug solution to precipitate the fine drug particles. Various anti-asthmatic drugs were prepared using the Sonocrystallization technique. In Micro precipitation technique, precipitation occurs in a region of extreme turbulence and intense mixing created by a jet of drug solution opposing a jet of anti-solvent coming through two opposing nozzles mounted in a small chamber. As two liquid jets mix, the anti-solvent causes the drug to precipitate as fine particles. The crucial process parameters include the speed of the liquid jets and concentration of the drug solution. A high jet stream speed or a high drug

concentration was found to give finer particles but higher residual solvent level and vice versa.

- ✓ Spray drying was explored in the 1980s as an alternative means of making fine particles with desirable flow and dispersion characteristics without need of using coarse carriers. Spray drying is the most promising alternative method for producing particles above 2  $\mu\text{m}$ . Spray drying has been employed as a method for preparing micron-sized powders for pulmonary administration and has better control on particle formation and hence can be easily translated to large scale production. Although the drying air temperature can be relatively high ( $>100^\circ\text{C}$ ), the actual temperature of the evaporating droplets is significantly lower due to cooling by the latent heat of vaporization. Thus, thermal degradation of the active ingredient is not so much a concern as it first appears. Spray drying is not limited to aqueous solutions. Spray drying of ethanolic solutions containing anti-asthmatic drugs has been reported. Non-aqueous systems have also been used to prepare porous particles suitable for aerosol delivery. The properties of the spray dried powders are controlled by both the process (atomizing nozzle type, powder collection technique and droplet drying time and rate) and formulation parameters (effects of the active ingredient).
- ✓ Supercritical fluid technology (SCF): The advantages of SCF technology include use of mild conditions for pharmaceutical processing (which is advantageous for labile proteins and peptides) and production of particles with controllable morphology and narrow size distribution.

On the basis of claims of improving aerosol performance, **the patents may be classified into the four broad categories** such as blends and ternary systems, reducing aerodynamic diameters through porous / low density particle, preparing less cohesive and adhesive particles and novel DPIs.

### **1. BLENDS AND TERNARY SYSTEMS**

Early formulation of DPIs consists of coarse carrier lactose for enhancing the powder flow of the formulations and increasing the powder bulk for capsule filling. It was found that there are high energy active sites on the surface of the coarse carrier particles thereby leading to a strong adherence of the drug particles to the coarse carriers (Particle size  $> 20 \mu\text{m}$ ). Addition of fine carrier particles or particles of ternary additives (Fines  $< 10 \mu\text{m}$ ) saturates the active sites of coarse carrier particles partially to which, then, micronized drug is attached. Hence, drug adheres to passive sites i.e. less energy sites and facilitates the deaggregation of the micronized drug during inhalation leading to enhanced respirable fraction. The sequence and amount of addition of fines and drug to coarse carrier were found to be critical.

### **2. REDUCING AERODYNAMIC DIAMETERS THROUGH POROUS / LOW DENSITY PARTICLES**

Recently, research has been focused towards development of porous/low density particles having particle size in the range of 5  $\mu\text{m}$  to 30  $\mu\text{m}$ , density below 0.4  $\text{g}/\text{cm}^3$ , and mean mass aerodynamic diameter (MMAD) between 1-3  $\mu\text{m}$  to achieve higher respirable fraction and avoid the natural clearance mechanism in lungs (alveolar macrophage uptake)

due to higher geometric diameter of the particles. Such aerodynamically light particles also provide a solution to particle aggregation and preserve the flow ability of the powder by reducing particle interactions. The aerodynamically light particles are prepared from variety of materials such as biodegradable polymers as PLA, PGA and their copolymers PLGA, polyester graft copolymer, phospholipids, surfactants as phosphoglycerides for ex. dipalmitoyl phosphatidylcholine (DPPC) and amino acids as leucine.

### **3. PREPARING LESS COHESIVE AND ADHESIVE PARTICLES**

Less cohesive and adhesive particles were developed by particle engineering for enhanced delivery of therapeutics to lungs to overcome the constraints associated with conventional DPIs.

Stable agglomeration of the active particles with the known powders may lead to decreased deposition of the active material in the lower lung, together with poor dose uniformity because, when the small active particles agglomerates, their particle size may increase up to 100  $\mu\text{m}$  or more. If those agglomerates do not break up when the powder is inhaled, they are unlikely to reach the lower lung due to their size.

The addition of the anti-adherent material decreases the cohesion between the particles of the powder containing the active material. It is thought that the additive material interferes with the weak bonding forces, such as Van der Waal's and Coulomb forces, between the small particles which helps to keep the particles separated and may be thought of as weak links or "chain breakers" between the particles and also reducing adhesion of the particles to the walls of the device. When agglomerates of particles are formed, the addition of the additive material decreases the stability of those agglomerates so that they are more likely to break up in the turbulent air stream created on inhalation to form small individual particles which are likely to reach the lower lung.

The various materials which may be useful as antiadherent includes antistatic agents, lubricants as magnesium stearate, amino acids, peptides and polypeptides as leucine, isoleucine, lysine, valine, methionine, cysteine, and phenylalanine and their derivatives.

### **4. NOVEL DELIVERY SYSTEMS**

#### ***4.1. Liposome and Lipid Based DPI:***

- ✓ Liposomal drug encapsulation has been shown to be promising in sustaining the drug residence time within lung, improving therapeutic index, and delaying systemic dilution and thereby, reducing side effects.
- ✓ Further by perturbing the structure of the liposomal vesicle one is able to tailor a particular mode of release as well as extend of drug release in the airways.
- ✓ Delivery of corticosteroid for asthma, ribonucleotides for respiratory influenza aminoglycosides (Tobramycin Sulphate, Amikacin Sulphate) and other antibiotics (Ciprofloxacin) for local pulmonary infections and cystic fibrosis has been reported using liposome technology.
- ✓ In liposomal DPI formulations, drug encapsulated liposomes are homogenized, dispersed into carrier and converted into DPI by spray and / or freeze drying. On inhalation, drug encapsulated liposome's get rehydrated in lung and release drug over a period of time.
- ✓ New steroidal derivatives obtained by modification of corticosteroids, with fatty acid

esters were incorporated in the lipid portion of liposome's for delivery via inhalation resulting into prolonged steroid retention in the respiratory tract of experimental animals

#### **4.2 Nanocochleates**

Cochleates are derived from liposomes, which are suspended in an aqueous containing two-phase polymer solution, enabling the differential partitioning of polar molecule based-structure by phase separation. The liposome containing two-phase polymer solution, treated with positively charged molecules such as  $\text{Ca}^{2+}$  or  $\text{Zn}^{2+}$ , forms a cochleate precipitate of a particle size less than 1  $\mu\text{m}$ . Novel lipid-based cochleate delivery system were used to achieve efficient systemic and mucosal delivery of pharmaceutical agents.

#### **4.3 Proliposomes**

A process of manufacture of proliposomes powder comprising a single phase discrete particles of a biologically active component together with a lipid or mixture of lipids having a phase transition temperature of below  $37^\circ\text{C}$  for inhalation has been described . A DPI formulation comprising a lipid component and an active agent having a liquid phase transition temperature of less than or equal to  $37^\circ\text{C}$  on hydration and a liquid phase transition temperature of greater than  $57^\circ\text{C}$  in dry form. On inhalation the drug spontaneously encapsulates into lipid inside lungs. The disclosed formulation is useful in treatment of anthrax infection on inhalation.

#### **4.4. Micro and Nanoparticulates DPI Compositions**

Respirable particles carrying active principles or diagnostics in nanoparticle form were produced by mixing the nanoparticles with liquid carrier, then forming the resultant mixture into respirable particles. The respirable particles were produced by spray-drying or freeze spray drying followed by comminution, for delivery to the lungs via DPIs. Active principles were covalently attached, adsorbed or incorporated to nanoparticles.

#### **4.5. Delivery of Proteins, Peptides and Macromolecules for Local and Systemic Delivery Using DPIs**

A number of companies are in advanced clinical trials with inhaled insulin, surprisingly, it has been found that inhaled dry insulin powders are deposited in the alveolar regions of the lungs and rapidly absorbed through the epithelial cells of the alveolar region into blood circulation. Thus, pulmonary delivery of insulin powders can be an effective alternative to administration by subcutaneous injection. The insulin powder preferably comprises particles having a diameter range from 0.1  $\mu\text{m}$  to 5  $\mu\text{m}$ .

**Nektar therapeutics** in 2005 came with the patent disclosing pulmonary administration of chemically modified insulin providing active, hydrophilic polymer modified derivatives of insulin and exhibiting pharmacokinetic and/or pharmacodynamic properties that are significantly improved over native insulin. The formulations of covalently coupled insulin to one or more molecules of a non-naturally occurring hydrophilic polymer, such as poly-alkylene glycol (polyethylene glycol).

A patent on pulmonary malarial vaccine relates to particulate compositions comprising nanoparticulates for pulmonary delivery, which provide sustained release of antigens, preferably DNA and/or peptide and/or protein antigens has been developed.

Aggregate nanoparticles are in the aerodynamic range of 1-5 microns diameter and fly deep into the lungs. As the aggregate particles degrade in the body, MSP-1 and AMA-1 proteins are released into the blood stimulating a humoral immune response. The individual particles in the range of 0.1 micron are referentially phagocytosed by APCs which express the proteins encoded by AMA-1 and MSP-1 plasmid DNA thereby initiating the cellular immune response that is necessary for a complete immunity.

#### **4.6 Matrix formation:**

Matrix particles consists of drug and excipient in a matrix and are involved in improving the therapeutic index of a drug by, improving transport and the proportion of drug that reaches its site of action (intracellular and extracellular); improving stability of the drug *in vivo*; increasing the specific delivery of drug to target tissues; decreasing irritation caused by the drug; decreasing toxicity due to high doses of drug; altering immunogenicity of proteins; and avoidance of alveolar macrophage uptake, muco-ciliary clearance and rapid absorption.

#### **4.7 Pro-drugs and pegylation:**

Pegylation are noncovalently linked complex with PEG. Both of this molecular species transform into their parent form once in the lung the chemical transformation process being absorption rate limiting.

### **5. NOVEL EXCEPIENTS.**

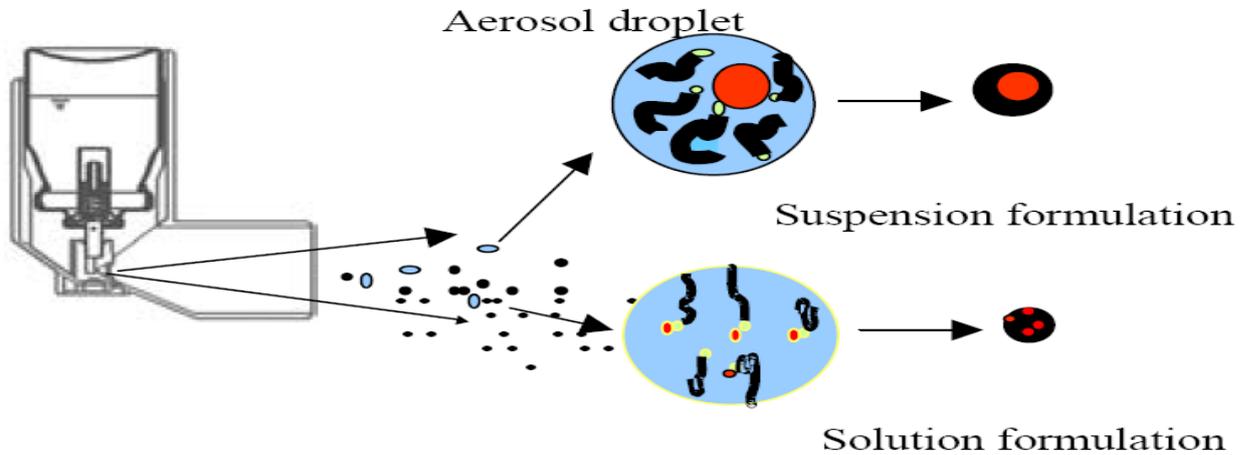
#### **Aim:-**

- ✓ Suspension aids: - for preparation high- quality suspension.
- ✓ Solubilizer: - to enable solution formulations at high dose.
- ✓ Sustained release agent: - Increase bio-availability by increasing lung residence time.

#### **I. SUSTAINED RELEASE SUSPENSION AEROSOL FORMULATIONS WITH OLIGOLACTIC ACID (OLA)**

- Oligo-lactic acids (OLA) are a family of designed excipients which can be used in either solution or suspension aerosol formulations
- When a suspension formulation containing OLA is actuated, propellant evaporates from the sprayed aerosol droplets leaving OLA-coated drug particles.
- When solution formulations are actuated, a homogeneous microsphere composed of drug and OLA is generated as evidenced by the absence of the original drug or OLA transitions in modulated DSC scans.
- In either case, in-situ generated microspheres are formed and either approach may modulate the drugs release profile.
- Compared to MDI formulations that utilize preformed microspheres, these in situ generated microspheres are likely to be simple and economic to produce.

## *In-Situ* generated microspheres



## II. POLYMERIC MATERIALS

- Encapsulation or entrapment of proteins in biocompatible polymeric devices represents the most widely reported systems for the controlled release of peptides and proteins.
- Polymers such as PLGA, PLA, PEG and chitosan have been applied as delivery vehicles in pulmonary delivery of proteins, producing sustained systemic therapeutic activities.
- Proteins such as Insulin and deslorelin have either been conjugated to PEG or encapsulated in PLGA,

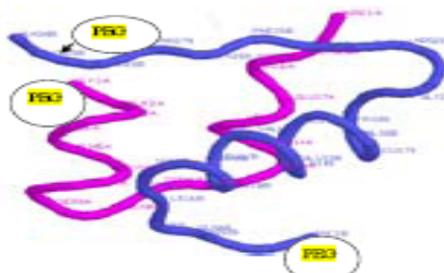


Fig 1. Diagram of Insulin showing potential sites for PEG conjugation. (from Leach et al. with permission).

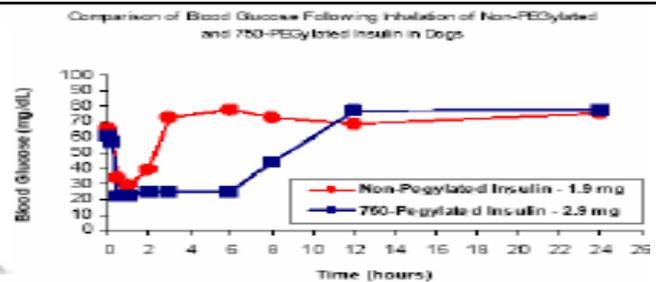


Fig. 2. Graph showing the effect of PEGylation of Insulin on blood glucose suppression in dogs (from Leach et al. with permission).

### Insulin-PEG.

- PEG has successfully been conjugated to insulin with a resultant controlled release profile following endotracheal tube delivery into the lungs of beagle dogs
- PEG-Insulin inhalation maintained glucose suppression for 6 to 12 hours as compared to 3 to 4 hours of glucose suppression for unmodified insulin.

## PROTEIN MICRO CRYSTALS

- The use of protein microcrystal has been discussed as a potential means for controlled release delivery of therapeutic proteins..
- The process used in this example was seed zone crystallization which gave yields in the region of 96%.
- The microcrystal obtained was rhombohedral with some rhombus forms.

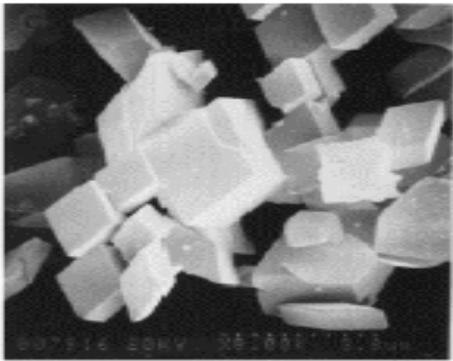


Fig. 5. Shape of insulin microcrystals obtained by seed zone method. (from Kwon et al. with permission from Elsevier).

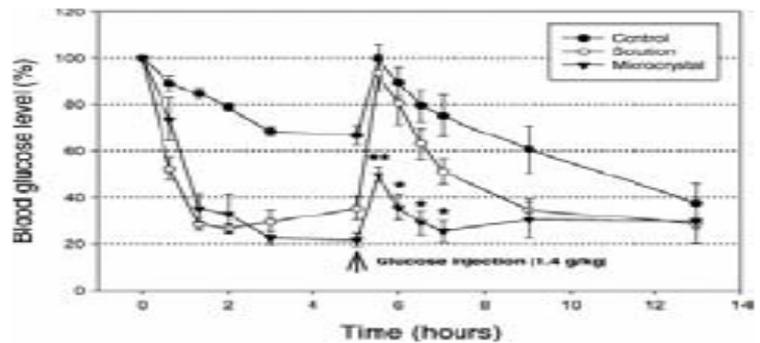
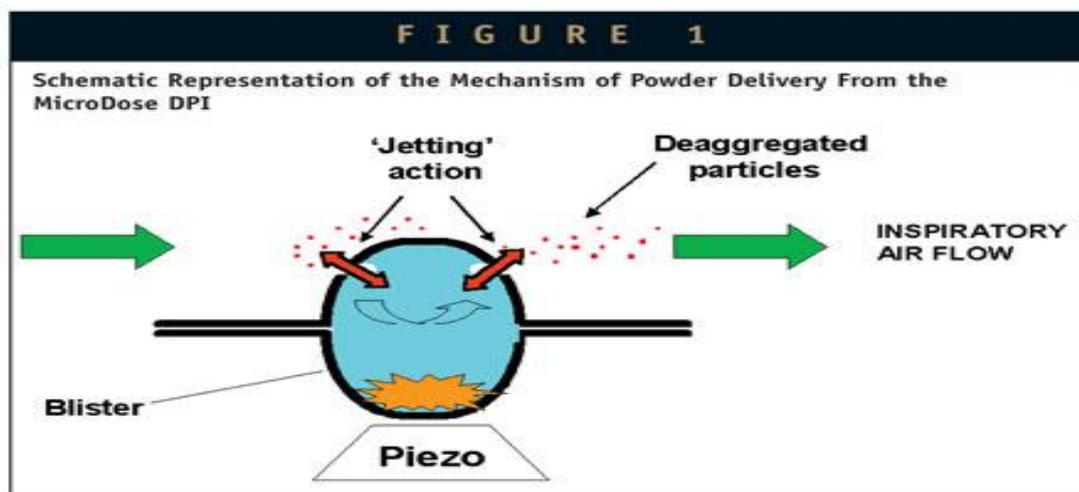


Fig. 6. Conc.-time profile of glucose levels in blood after intratracheal inhalation. (from Kwon et al. with permission from Elsevier).

## 6. NOVEL DEVICES:

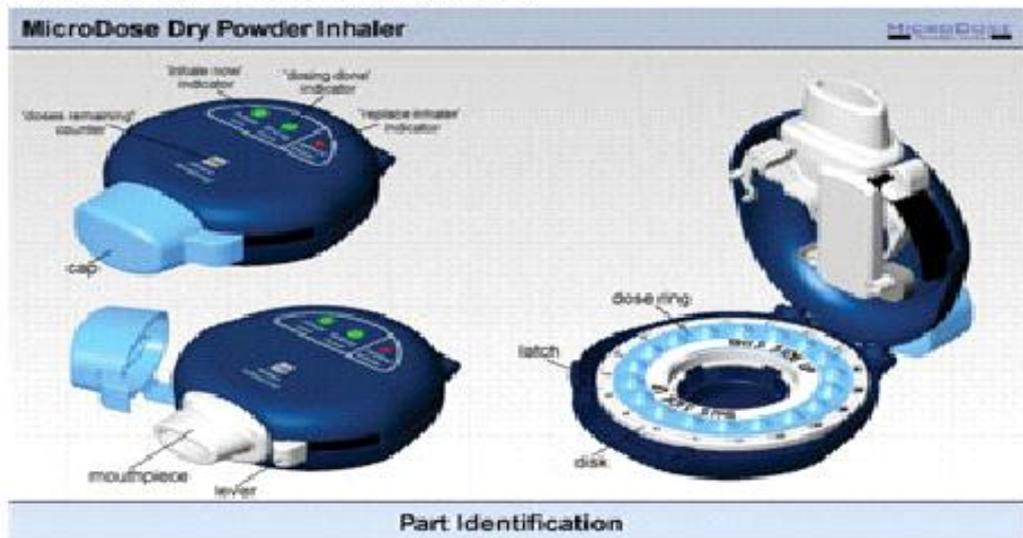
### A) A PIEZO-ELECTRONIC INHALER FOR LOCAL & SYSTEMIC APPLICATIONS

- The DPI uses a piezo vibrator to disaggregate the drug powder packaged in aluminum blisters. Actuation of the driver signal is affected upon detection of a threshold level of inspiratory airflow by the patient (sensed by a directional inhalation sensor).
- Thus, the piezo is automatically activated by a built-in flow sensor, which senses when the patient is inhaling through the device.



- The piezo vibrator converts electrical energy to mechanical motion, which is transferred through the blister into the powder. This process is shown schematically in Figure.
- The vibrations and pressure resulting from this coupling levitate and disperse the powder and create air pressure at small holes in the top of the blister.
- These pressure pulses create jets that provide the mechanism by which the powder is evacuated from the blister. In-flowing jets also help to disaggregate large clumps of particles within the blister. Deaggregation of smaller powder clumps is believed to occur at the holes of the blisters, where the aerodynamic shear forces are highest. Powder emitted from the blister is entrained in the patient's inspiratory airflow and subsequently inhaled into the lungs.

### Multiple Dose Version of the MicroDose DPI



### B] THE TEMPO™ INHALER

- MAP has developed the Tempo™ Inhaler, which may overcome limitations with a breath activated system.



It consists of two lead differentiating features

- Flow Control Chamber  
The *flow control chamber* manipulates the flow of the discharged plume to reduce droplet momentum and size and to match the plume velocity with the patient's inspiratory breath.
- Synchronous Trigger

The *synchronous trigger* automatically discharges drug at a specific set point in the patient's inspiration to consistently target desired bio space.

### C] AERx dosage form.

- ✓ it is the multi layered laminated designed to both ensure the stability of pharmaceutical compound and facilitate the robust generation of the aerosol and also provide a barrier to the loss of water during storage .
- ✓ To eliminate the variability due to uncontrolled inhalation rate the device prompts and trains the subjects to inhale at the optimal rate by presenting multicolored flashing and steady light emitting diode. In addition to monitoring inhalation rate the device calculate inhaled volume and will trigger the generation of aerosol only if the inhalation rate is in the best range.
- ✓ When the patient achieve this optimum flow or volume an electronically control motor actuated a piston which pressurize the formulation blister in the dosage form . when the formulation is pressurized the heat seal opens in the controlled region and the formulation flow from the blister through the nozzle array forming an aerosol .
- ✓ Unique feature of this system is the ability to titrate fractional doses from the single dosage form. This is accomplished by controlling the stroke of the piston. This feature is valuable when the dose delivered needs to be tightly controlled and varies in time and the patients.

### D] CAMBRIDGE SPEEDS INHALER TESTING

#### VariDose:-

- ✓ Is an optimal instrument to speed up the measurement of drug inhaler performance by testing drug device combination at the development.
- ✓ It employs opto – electronics to perform tests **in less than 60 seconds**.
- ✓ It measures the cloud of drug released from an inhaler as it passed through a tube intersected by co planar because of red , blue and infra red light.
- ✓ Sensor monitor the structure of the evolving drug cloud as the light passes through and this analysis can be used to investigate essential cloud characterize related to variability in PSD fine particle fraction and dose to pin point how design modification could improve effectiveness.

#### Andersen' Cascade Impactor

- ✓ The 'Andersen 'Cascade Impactor (ACI) is an eight stage cascade impactor that has been designed for measuring the fine particle dose and size of the aerosol cloud generated by Metered Dose Inhalers and Dry Powder Inhalers



## 7. NOVEL EVALUATION TECHNIQUES:

### RACES –

A Rigorous Accelerated Candidate Evaluation Service for Pressurized Metered Dose Inhalers  
New molecules intended for inhalation delivery can be effectively assessed for technical suitability with a pMDIs system within 80 working days.

- Preparation Activities
- Pre-Formulation Activities
- Stability Study
- Compatibility Study
- Additional Studies

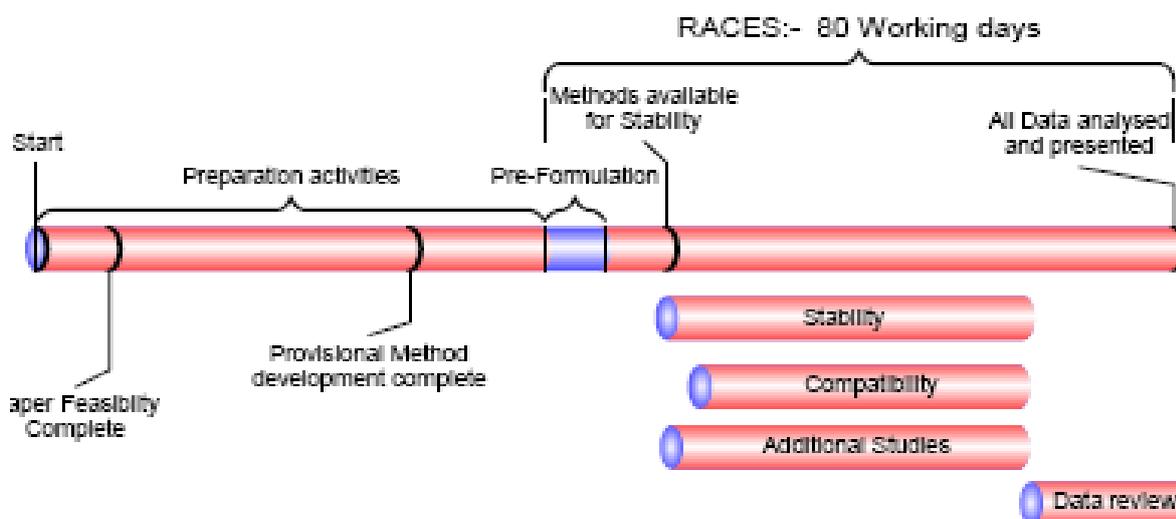


Figure 1. RACES process timeline

### RESEARCH WORK GOING ON NOW A DAY.

#### 1. To improve bio-availability:

Suspension of EPI hNE 4 10 mg per liter was prepared in sodium acetate and sodium chloride solution of pH. 4 improve bio-availability over conventional dosage form.

#### 2. In vitro investigation of drug particulate interaction and aerosol performance of pressurized MDI.

Study suggests that micronised drug particle has significantly different aerosolisation profile when manufactured as single and combination formulation.

For example salbutamol sulphate formulation are cohesive hence forming tight flocks, not deaggregated on excretion from aerosols. Salbutamol sulphate and budesonide interparticle interaction improve performance.

#### 3. Inhalation insulin:

The preparation with preprandial inhaled insulin in the patient with type I and type II compared to conventional and intensive insulin resulted in similar glycemic control. Inhaled insulin combined with oral agent was effective in patient with type 2 diabetes.

#### 4. Perflourocarbon compound as vehicle for pulmonary delivery:

Drug delivery to diseased lung is hindered by the built up of the fluid and shunting of blood flow away from the site of injury. The use of PFC overcome this, its homogeneity fill the lung and recruit the airway by replacing edematous fluid. Also higher drug concentration in lung than conventional. But poor solvent so dispersion, prodrug, solubilising agent etc.

#### 5. Comparison of invitro performance CFC propellant salbutamol pressurized MDI with HFA propellant.

The mass median aerodynamic diameter of CFC was 3.9 micrometer while with that of HFA propellant 3.4 micrometer. The cooling effect of HFA propellant was more than that of CFC. Both revealed similar invitro performance. The content per actuation and delivered dose uniformity were 80-120% of labeled amt and leak rate of both were less than the 1.8%.

#### 6. Face masking and aerosol delivery by MDI valved holding chamber in young children. A tight seal makes the difference.

Even a small leak can reduce the dose delivery to lung. But the tight seal is difficult to obtain when child is not co-operative. Performance also depends on the design of face mask (like dead space).

#### MARKET FORMULATIONS

PRODUCT NAME	COMPANY NAME	INDICATION	DEV.STATUS	TECHNOLOGY	DESCRIPT'N
Exubera	nektar	Type I and ii diabetes	Filled for approval in us and uk	Inhance	DPI
morphine	aradign	Pain	Phase ii	Arex	Electronic aqueous droplets
VR 004	Vectura	Erectile dysfunction	Phase II	aspirair	DPI
Leuprolide	Nectar/enzon	Endometriosis	Phase I	Inhance	DPI
Human growth factor	Alkermes/lilly	Growth hormone deficiency	Phase I	AIR	DPI
Alveair	Coremed USA	Type I and II Diabetes	Phase I	Alveair	Bioadhesive polymer technology
Bio air (insulin)	Biosante		Preclinical	CAP particles	Formulation technology.

Small molecule analgesic	Direct haler A/S	Pain	Early research	Direct haler pulmonary	DPI
Testosterone	Aradigm	Undisclosed	NA	Arex	Electronic aqueous droplets
Undisclosed	Chrysalis technology	Undisclosed	Early research	Aria	Soft mist
Undisclosed	Microdose	Undisclosed	Early research	Microdose	Piexo-electric aqueous droplets

## LOOKING TO THE FUTURE

### (What's in development)?

- Proteins and peptides( insulin , desmopressin, calcitonin)
- Pain management( morphine, fentanyl )
- Vaccines
- Hormones
- Immunoglobulin's
- Gene therapy vectors and oligonucleotides.

### STUDY QUESTIONS?????????

1. Draw a schematic diagram of MDI.
2. Write a note on non pressurized MDI systems.
3. Enlist evaluation tests of MDI as per FDA.
4. Discuss application of MDI in systemic medication giving market product formulations.
5. Write a short note on MDI.
6. Define role of the excipients in the formulation of the inhalers ? how peptides and proteins are delivered via inhalation?
7. Dr. Zinzuvadia wants to formulate insulin inhalation as a powder form , suggest the manufacturing requirements , stability criteria which must be controlled . describe the tests anticipated by FDA.(first internal exam -2005)
8. Suggest a chronological development of MDI and what is its role in pulmonary drug delivery system?  
Write a note on the turbo-haler.

### Extra questions:

1. Write a note on powder inhalers.
2. Write a note on innovations in metered dose inhalers.

3. Write in detail about pressurized metered dose inhalers.
4. Use of novel excipients - oligolactic acid in aerosol formulation.
5. Describe the role of polymeric material, protein microcrystal and liposomes in MDI.
6. Write a note on innovation in DPI.
7. Write a note on novel delivery system in aerosols.