NASAL DRUG DELIVERY CONTENTS

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NASAL DRUG DELIVERY

Targeted delivery

“Nose-to-brain” delivery

Tube to middle ear

Lymphoid tissues

Openings to the sinuses

No lung inhalation

Less local irritation
INTRODUCTION:

- In ancient times the Indian Ayurvedic system of medicines used nasal route for administration of drug and the process is called as “Nasya”.
- Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. Undoubtedly, the intranasal administration of medicines for the symptomatic relief and prevention or treatment of topical nasal conditions has been widely used for a long period of time.
- However, recently, the nasal mucosa has seriously emerged as a therapeutically viable route for the systemic drug delivery.
In general, among the primary targets for intranasal administration are pharmacologically active compounds with poor stability in gastrointestinal fluids, poor intestinal absorption and/or extensive hepatic first-pass elimination, such as peptides, proteins and polar drugs. The nasal delivery seems to be a favourable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS)-active compounds. It has also been considered to the administration of vaccines.
**ADVANTAGES**

- Hepatic first pass metabolism avoided.
- Rapid drug absorption and quick onset of action.
- Bioavailability of larger drug molecules can be improved by means of absorption enhancer.
- BA for smaller drug molecules is good.
- Convenient for long term therapy, compared to parenteral medication.
- Drugs possessing poor stability G.I.T fluids given by nasal route.
- Easy and convenient.
- Easily administered to unconscious patients.
DISADVANTAGES

- Pathologic conditions such as cold or allergies may alter significantly the nasal bioavailability.
- The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
- Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
- Nasal cavity provides smaller absorption surface area when compared to GIT.
ANATOMY & PHYSIOLOGY OF NASAL CAVITY

Fig: 1
• The nasal cavity consists three main regions:
  1) Nasal vestibule
  2) Respiratory region
  major drug absorption.
  15-20 % of the respiratory cells covered by layer of long
  cilia size 2-4 μm.
  3) Olfactory region
  small area in the roof of the nasal cavity of about 10 cm²
  drug is exposed to neurons thus facilitate it across the cerebro-
  spinal fluid.
• Normal pH of the nasal secretions in adult → 5.5-6.5.
• Infants and young children → 5.0- 6.7.
• Nasal cavity is covered with a mucous membrane. Mucus secretion is
  composed of 95%- water,2%-mucin,1%-salts,1%-of other proteins
  such as albumin,lysozyme and lactoferrin and 1%-lipids.
MECHANISM OF DRUG ABSORPTION

- **Paracellular (intercellular)**: Slow and passive absorption of peptides and proteins associated with intercellular spaces and tight junctions.

- **Transcellular**: Transport of lipophilic drugs passive diffusion/active transport.

- **Transcytotic**: Particle is taken into a vesicle and transferred to the cell.
Mucoadhesive Carrier

Interaction with Mucus

Hydration and swell of polymer

Drug release

Hydrophilic Macromolecular drug

Ciliary clearance

Enzymatic Metabolism

Internal Absorption

Fig:2 Scheme of Mucoadhesive Nasal Drug Delivery
## THEORIES OF MUCOADHESION

<table>
<thead>
<tr>
<th>Theory</th>
<th>Mechanism of bioadhesion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electronic theory</strong></td>
<td>Attractive electrostatic forces between glycoprotein mucin network and the bioadhesive material</td>
<td>Electron transfer occurs between the two forming a double layer of electric charge at the interface</td>
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<tr>
<td><strong>Adsorption theory</strong></td>
<td>Surface forces resulting in chemical bonding</td>
<td>Strong primary forces: covalent bonds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weak secondary forces: ionic bonds, hydrogen bonds and van der Waal’s forces</td>
</tr>
<tr>
<td><strong>Wetting theory</strong></td>
<td>Ability of bioadhesive polymers to spread and develop intimate contact with the mucus membranes</td>
<td>Spreading coefficients of polymers must be positive Contact angle between polymer and cells must be near to zero</td>
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<tr>
<td><strong>Diffusion theory</strong></td>
<td>Physical entanglement of mucin strands and the flexible polymer chains Interpenetration of mucin strands into the porous structure of the polymer substrate</td>
<td>For maximum diffusion and best bioadhesive strength: solubility parameters (δ) of the bioadhesive polymer and the mucus glycoproteins must be similar</td>
</tr>
<tr>
<td><strong>Fracture theory</strong></td>
<td>Analyses the maximum tensile stress developed during detachment of the BDDS from the mucosal surfaces</td>
<td>Does not require physical entanglement of bioadhesive polymer chains and mucin strands, hence appropriate to study the bioadhesion of hard polymers, which lack flexible chains</td>
</tr>
</tbody>
</table>
FORMULATION APPROACHES

- Nasal gels
- Nasal Drops
- Nasal sprays
- Nasal Powder
- Liposome
- Microspheres
• **Nasal Gels**

  • High-viscosity thickened solutions or suspensions
    
    Advantages:
    
    • reduction of post-nasal drip due to high viscosity
    • reduction of taste impact due to reduced swallowing
    • reduction of anterior leakage of the formulation
    
  • Reduction of irritation by using emollient excipients.

• **Nasal Drops**

  • Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.
Nasal sprays

- Both solution and suspension formulations can be formulated into nasal sprays.
- Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 μm. The particles size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

Nasal Powder

- This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability.
- The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties and nasal irritancy of the active drug and/or excipients. Local application of drug is another advantage of this system.
**Liposomes**

- Liposomal Nasal solutions can be formulated as drug alone or in combination with pharmaceutically acceptable excipients.
- Administered to the respiratory tract as an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose, the particles of the formulation have diameters of less than 50 microns.

**Microspheres**

- Specialized systems becoming popular for designing nasal products, as it provides prolonged contact with the nasal mucosa
- Microspheres (in the powder form) swell in contact with nasal mucosa to form a gel and control the rate of clearance from the nasal cavity. Thus increases the absorption and bioavailability by adhering to the nasal mucosa and increase the nasal residence time of drug.
- The ideal microsphere particle size requirement for nasal delivery should range from 10 to 50 µm as smaller particles.
### Permeation enhancers

<table>
<thead>
<tr>
<th>Type of compound</th>
<th>Examples</th>
<th>Mechanisms of action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bile salts (and derivatives)</strong></td>
<td>Sodium deoxycholate, sodium glycocholate, sodium taurodihydrofusidate</td>
<td>Disrupt membrane, open tight junctions, enzyme inhibition, mucolytic activity</td>
</tr>
<tr>
<td><strong>Surfactants</strong></td>
<td>SLS, saponin, polyoxyethylene-9-lauryl ether</td>
<td>Disrupt membranes</td>
</tr>
<tr>
<td><strong>Chelating agents</strong></td>
<td>Ethylenediaminetetraacetic acid(EDTA), salicylates</td>
<td>Open tight junction</td>
</tr>
<tr>
<td><strong>Fatty acids</strong></td>
<td>Sodium caprylate, sodium laurate, phospholipids</td>
<td>Disrupt membranes</td>
</tr>
<tr>
<td><strong>Bioadhesive materials Powders</strong></td>
<td>Carbopol, starch microspheres, chitosan</td>
<td>Reduce nasal clearance, open tight junctions</td>
</tr>
<tr>
<td><strong>Liquids</strong></td>
<td>Chitosan, carbopol</td>
<td>Reduce nasal clearance, open tight junction</td>
</tr>
</tbody>
</table>
• **Prodrug approach**

  The absorption of peptides like angiotensin II, bradykinin, vasopressin and calcitonin are improved when prepared into enamine derivatives.

• **Structural modification**

  Chemical modification of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) showed better bioavailability.

• **Particulate drug delivery**

  - Microspheres, nanoparticles and liposomes
  - Nasal enzyme inhibitors
    - peptidases and proteases
    - tripsin, aprotinin, borovaline, amastatin, bestatin and boroleucin inhibitors.
Evaluation tests

For Nasal Gels

• **Mucoadhesive testing**
  
  A 1x1 cm piece of goat nasal mucosa was tied to a glass slide using thread. Microparticles spread on the tissue specimen and the prepared glass slide was hung on one of the groves of a USP tablet disintegration test apparatus. The tissue specimen was given regular up and down movements in the beaker of the disintegration apparatus containing phosphate buffer pH 6.4.

• Time required for complete washing of microparticles was noted.

• **In vitro** drug diffusion study

  The drug diffusion from different formulation was determined using treated cellophane membrane and Franz diffusion cell.

  • Drug was placed on cellophane membrane in the donor compartment contained phosphate buffer (pH 6.4).
  
  • Samples were analyzed spectrophotometrically.
• *In vitro* drug release studies of the gels

  1 ml of the gel was taken into a small test tube. The open end of the test tube was closed with the nasal membrane of the pig by tying it with a thread. Then this was placed in a beaker containing the media.

• **Measurement of Gelation Temperature (T1) and Gel Melting Temperature (T2):**

  • A 2ml aliquot of gel was taken in a test tube, immersed in a water bath.
  • The temperature of water bath was increased slowly and left to equilibrate for 5min at each new setting.
  • The sample was then examined for gelation, the meniscus would no longer moves upon tilting through 90°. i.e **GELATION temp T1**.
  • Further heating of gel causes liquefaction of gel and form viscous liquid and it starts flowing, this temperature is noted as **T2 GEL MELTING temp**.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Main Excipients</th>
<th>Supplier</th>
<th>Main Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azelastine</td>
<td>Astelin</td>
<td>Benzalkonium chloride, edetate disodium,</td>
<td>Meda Pharmaceuticals</td>
<td>Management/treatment of symptoms of seasonal and perennial rhinosinusitis</td>
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<tr>
<td>Beclometasone</td>
<td>Beconase</td>
<td>Microcrystalline cellulose, carboxymethyl cellulose sodium, benzalkonium chloride</td>
<td>GlaxoSmithKline</td>
<td></td>
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<tr>
<td>Levocabastine</td>
<td>Livostin</td>
<td>Benzalkonium chloride, edetate disodium, disodium phosphate</td>
<td>Jansen-Cilag</td>
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<tr>
<td>Drug</td>
<td>Brand</td>
<td>Main Excipients</td>
<td>Supplier</td>
<td>Main Indications</td>
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<tr>
<td>Olapatadine</td>
<td>Patanase</td>
<td>Benzalkonium chloride, dibasic sodium phosphate, edetate disodium</td>
<td>Alcon Laboratories</td>
<td>Eradication of nasal staphylococci</td>
</tr>
<tr>
<td>Sodium cromoglicate</td>
<td>Nasalcrom</td>
<td>Benzalkonium chloride, edetate disodium</td>
<td>Sanofi-Aventis</td>
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<tr>
<td>Mupirocin</td>
<td>Bactroban</td>
<td>Paraffin and a mixture of glycerin esters (Softisan 649)</td>
<td>GlaxoSmithKline</td>
<td>Eradication of nasal staphylococci</td>
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<tr>
<td>Triamcinolone acetonide</td>
<td>Nasacort</td>
<td>Microcrystalline cellulose, CMC sodium, polysorbate 80</td>
<td>Sanofi Aventis</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Brand</td>
<td>Main Excipients</td>
<td>Supplier</td>
<td>Main Indications</td>
</tr>
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<tr>
<td>Nicotine</td>
<td>Nicotrol NS</td>
<td>Disodium phosphate, sodium dihydrogen phosphate, citric acid</td>
<td>Pfizer</td>
<td>Smoking cessation</td>
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<tr>
<td>Oxytocin</td>
<td>Syntocinon</td>
<td>Citric acid, chlorobutanol, sodium chloride</td>
<td>Novartis</td>
<td>Labour induction; lactation stimulation</td>
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<tr>
<td>Buserelin</td>
<td>Suprefact</td>
<td>Sodium hydroxide, sodium chloride, sodium dihydrogen</td>
<td>Sanofi-Aventis</td>
<td>Treatment of prostate cancer</td>
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<tr>
<td>Drug</td>
<td>Brand</td>
<td>Main Excipients</td>
<td>Supplier</td>
<td>Main Indications</td>
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<tr>
<td>Salmon calcitonin</td>
<td>Miacalcin</td>
<td>Sodium chloride, benzalkonium chloride, hydrochloric acid</td>
<td>Novartis</td>
<td>Treatment of postmenopausal osteoporosis</td>
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<td>Sumatriptan</td>
<td>Imigran</td>
<td>Potassium dihydrogen cluster headaches phosphate, dibasic sodium phosphate anhydrou</td>
<td>GlaxoSmithKline</td>
<td>Treatment of migraine and Sumatriptan Imigran Potassium dihydrogen cluster headaches</td>
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<td>Estradiol</td>
<td>Aerodiol</td>
<td>Methylbetadex, sodium chloride</td>
<td>Servier laboratories</td>
<td>Hormone replacement therapy</td>
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Marketed products
# PATENTED DRUGS FOR NASAL DELIVERY

<table>
<thead>
<tr>
<th>Cited Patent</th>
<th>Filing date</th>
<th>Issue date</th>
<th>Original Assignee</th>
<th>Title</th>
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<tr>
<td>US3874380</td>
<td>May 28, 1974</td>
<td>1975</td>
<td></td>
<td>Dual nozzle Intranasal drug delivery</td>
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<tr>
<td>Cited Patent</td>
<td>Filing date</td>
<td>Issue date</td>
<td>Original Assignee</td>
<td>Title</td>
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</table>
Currently, the majority of intranasal products on the market are targeted toward local relief or the prevention of nasal symptoms. The trend toward the development of intranasal products for systemic absorption should rise considerably over the next several years. The development of these products will be in a wide variety of therapeutic areas from pain management to treatment for erectile dysfunction.

However, the primary focus of intranasal administration, correlated with increasing molecular scientific knowledge and methods, will be the development of peptides, proteins, recombinant products, and vaccines. The nasal cavity provides an ideal administration site for these agents because of its accessibility, avoidance of hepatic first-pass metabolism, and large vascular supply.

Future technologies in the intranasal arena will be concentrated on improved methods for safe, efficient delivery systems primarily for molecular agents, but also for numerous therapeutic categories.
Delivery of non-peptide Pharmaceuticals

- Adrenal corticosteroids
- Sex hormones: 17β-estradiol, progesterone, norethindrone, and testosterone.
- Vitamins: vitamin B
- Cardiovascular drugs: hydralazine, Angiotensin II antagonist, nitroglycerine, isosobide dinitrate, propanolol.
- CNS stimulants: cocaine, lidocaine
- Narcotics and antagonists: bupemorphine, naloxane
- Histamine and antihistamines: disodium cromoglycate, meclizine
- Antimigrane drugs: dihydrogatamine, ergotamine, tartarate
- Phenicillin, cephalosporins, gentamycin
- Antivirals: Phenyl-p-guanidine benzoate, enviroxime.
Delivery of peptide-based pharmaceuticals

- Peptides and proteins are hydrophilic polar molecules of high molecular weight, poorly absorbed.
- Absorption enhancers like surfactants, glycosides, cyclodextrin and glycols increase the bioavailability.
  Examples are insulin, calcitonin, pituitary hormones etc.

Delivery of diagnostic drugs

- Phenolsulfonphthalein is used to diagnose kidney function.
  Secretin for Pancreatic disorders of the diabetic patients.

Delivery of Vaccines through Nasal Routs

- Anthrax and influenza are treated by using the nasal vaccines
  prepared by using the recombinant Bacillus anthracis protective antigen (rPA) and chitosan respectively.
**Delivery of Drugs to Brain through Nasal Cavity**

Conditions like Parkinson’s disease, Alzheimer’s disease or pain

<table>
<thead>
<tr>
<th>Drug molecule</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve Growth Factor (NGF)</td>
<td>Nerve growth factor plays an important role in the growth, survival, and preservation of cholinergic neurons in the central nervous system</td>
</tr>
<tr>
<td>Insulin like Growth factor (IGF-1)</td>
<td>Treatment of Diabetes Mellitus</td>
</tr>
<tr>
<td>Fibroblast growth factor (FGF)</td>
<td>FGFs are a family of molecules that stimulate cell growth in many areas of the body, and are involved in the growth of multiple tissues. They are also involved in the repair of adult tissues after injury and may mediate the cross-talk between different cell types in the brain; they can be seen as mediators of the property that neuroscientists call “neural plasticity” – the ability of the brain to adapt to stress, experience, disease and the effects of drugs</td>
</tr>
<tr>
<td>Activity-dependent neuro-trophic Factor (ADNF12)</td>
<td>Treatment of Alzheimer disease</td>
</tr>
</tbody>
</table>
CONCLUSION

- Considering the widespread interest in nasal drug delivery and the potential benefits of intranasal administration, it is expected that novel nasal products will continue to reach the market. They will include not only drugs for acute and long term diseases, but also novel nasal vaccines with better local or systemic protection against infections.

- The development of drugs for directly target the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects is feasible. However, it was also stated that intranasal route presents several limitations which must be overcome to develop a successful nasal medicine. Physiological conditions, physicochemical properties of drugs and formulations are the most important factors determining nasal drug absorption.
• The use of prodrugs, enzymatic inhibitors, absorption enhancers, mucoadhesive drug delivery systems and new pharmaceutical formulations are, nowadays, among the mostly applied strategies. Each drug is one particular case and, thus, the relationship between the drug characteristics, the strategies considered and the permeation rate is essential.
PULMONARY DRUG DELIVERY SYSTEM
CONTENTS

- INTRODUCTION
- ADVANTAGES AND LIMITATIONS
- THE RESPIRATORY TRACT
- FORMULATIONS APPROACHES AND DEVICES
- MARKETED PREPARATIONS
- PATENTED PREPARATIONS
- RECENT ADVANCES
- CONCLUSIONS
- REFERENCES
INTRODUCTION

- The respiratory tract is one of the oldest routes used for the administration of drugs. Over the past decades inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases such as asthma or COPD (Chronic Obstructive Pulmonary Disease).
- This type of drug application in the therapy of these diseases is a clear form of targeted drug delivery.
- Currently, over 25 drug substances are marketed as inhalation aerosol products for local pulmonary effects and about the same number of drugs are in different stages of clinical development.
The drug used for asthma and COPD eg.- β2-agonists such as salbutamol (albuterol), Terbutalin formoterol, corticosteroids such as budesonide, Flixotide or beclomethasone and mast-cell stabilizers such as sodium cromoglycate or nedocromi.

The latest and probably one of the most promising applications of pulmonary drug administration is

1) Its use to achieve systemic absorption of the administered drug substances.

2) Particularly for those drug substances that exhibit a poor bioavailability when administered by the oral route, as for example peptides or proteins, the respiratory tract might be a convenient port of entry.
ADVANTAGES OF PULMONARY DRUG DELIVERY.

• It is needle free pulmonary delivery.
• It requires low and fraction of oral dose.
• Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug.
• Onset of action is very quick with pulmonary drug delivery.
• Degradation of drug by liver is avoided in pulmonary drug delivery.

LIMITATIONS

• Stability of drug in vivo.
• Transport.
• Targeting specificity.
• Drug irritation and toxicity.
• Immunogenicity of proteins
• Drug retention and clearance.
THE RESPIRATORY TRACT

Fig: 4

- Lymph node
- Trachea
- Bronchi
- Right lung:
  - Upper lobe
  - Middle lobe
  - Lower lobe
- Left lung:
  - Upper lobe
  - Lower lobe
- Diaphragm
- Artery
- Vein
- Bronchiole
- Alveoli
The human respiratory system is a complicated organ system of very close structure–function relationships. The system consisted of two regions: The conducting airway and The respiratory region.

The airway is further divided into many folds: nasal cavity and the associated sinuses, and the nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles.

The respiratory region consists of respiratory bronchioles, alveolar ducts, and alveolar sacs.

The human respiratory tract is a branching system of air channels with approximately 23 bifurcations from the mouth to the alveoli. The major task of the lungs is gas exchange, by adding oxygen to, and removing carbon dioxide from the blood passing the pulmonary capillary bed.
FORMULATION APPROACHES

- Pulmonary delivered drugs are rapidly absorbed except large macromolecules drugs, which may yield low bioavailability due to enzymatic degradation and/or low mucosal permeability.
- Pulmonary bioavailability of drugs could be improved by including various permeation enhancers such as surfactants, fatty acids, and saccharides, chelating agents and enzyme inhibitors such as protease inhibitors.
- The most important issue is the protein stability in the formulation: the dry powder formulation may need buffers to maintain the pH, and surfactants such as Tween to reduce any chance of protein aggregation. The stabilizers such as sucrose are also added in the formulation to prevent denaturation during prolonged storage.
- Pulmonary bioavailability largely depends on the physical properties of the delivered protein and it is not the same for all peptide and protein drugs.
- Insulin liposomes are one of the recent approaches in the controlled release aerosol preparation. Intratracheal delivery of insulin liposomes (dipalmitoylphosphatidyl choline:cholesterol, 7:2) have significantly enhanced the desired hypoglycemic effect.
- The coating of disodium fluorescein by hydrophobic lauric acid is also an effective way to prolong the pulmonary residence time by increasing the dissolution half time. In another method, pulmonary absorption properties were modified for protein/peptide drug (rhGCSF) in conjugation with polyethylene glycol (PEGylation) to enhance the absorption of the protein drug by using intratracheal instillation delivery in rat.
AEROSOLS

- Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drugs, delivery by aerosols is deposited in the airways by: gravitational sedimentation, inertial impaction, and diffusion. Mostly larger drug particles are deposited by first two mechanisms in the airways, while the smaller particles get their way into the peripheral region of the lungs by following diffusion.

- There are three commonly used clinical aerosols:
  1. Jet or ultrasonic nebulizers,
  2. Metered–dose Inhaler (MDI)
  3. dry-powder inhaler (DPI)

- The basic function of these three completely different devices is to generate a drug-containing aerosol cloud that contains the highest possible fraction of particles in the desired size range.
Nebulizers

- Nebulizers are widely used as aerosolize drug solutions or suspensions for drug delivery to the respiratory tract and are particularly useful for the treatment of hospitalized patients.
- Delivered the drug in the form of mist.
- There are two basic types:
  1) Air jet
  2) Ultrasonic nebulizer
Jet nebulizers

Ultrasonic nebulizers

Fig: 5  
Fig: 6

Signal from piezoelectric crystal
Drug formulation in reservoir

Mesh
To mouthpiece
Dry powder inhalers (DPI)

- DPIs are bolus drug delivery devices that contain solid drug in a dry powder mix (DPI) that is fluidized when the patient inhales.
- DPIs are typically formulated as one-phase, solid particle blends. The drug with particle sizes of less than 5µm is used.
- Dry powder formulations either contain the active drug alone or have a carrier powder (e.g. lactose) mixed with the drug to increase flow properties of drug.
- DPIs are a widely accepted inhaled delivery dosage form, particularly in Europe, where they are currently used by approximately 40% of asthma patients.

Advantages

✓ Propellant-free.
✓ Less need for patient co-ordination.
✓ Less formulation problems.
✓ Dry powders are at a lower energy state, which reduces the rate of chemical degradation.
Disadvantages
✓ Dependency on patient’s inspiratory flow rate and profile.
✓ Device resistance and other design issues.
✓ Greater potential problems in dose uniformity.
✓ More expensive than pressurized metered dose inhalers.
✓ Not available worldwide

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.

Multidose Devices
- 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.
Dry Powder inhalers
Metered Dose Inhalers (MDI)

- Used for treatment of respiratory diseases such as asthma and COPD.
- They can be given in the form of suspension or solution.
- Particle size of less than 5 microns.
- Used to minimize the number of administrations errors.
- It can be deliver measure amount of medicament accurately.
Advantages of MDI

• It delivers specified amount of dose.
• Small size and convenience.
• Usually inexpensive as compare to dry powder inhalers and nebulizers.
• Quick to use.
• Multi dose capability more than 100 doses available.

Disadvantages of MDI

• Difficult to deliver high doses.
• There is no information about the number of doses left in the MDI.
• Accurate co-ordination between actuation of a dose and inhalation is essential.
Canister

Mouthpiece

Push down on the canister and breathe in slowly
## MARKETED DRUGS  Dry Powder Inhaler

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbutaline 0.25mg</td>
<td>Bricanyl</td>
<td>AstraZeneca</td>
<td>UK</td>
</tr>
<tr>
<td>Beclometasone dipropionate 250mcg</td>
<td>Becloforte</td>
<td>Cipla Limited</td>
<td>India</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Flixotide</td>
<td>GlaxoSmithKline</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Salbutamol Dry Powder Capsules</td>
<td>Cipla Limited</td>
<td>India</td>
</tr>
<tr>
<td>Ipratropium Bromide 20 mcg</td>
<td>ATEM</td>
<td>Chiesi Farmaceutici</td>
<td>Italy</td>
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<tr>
<td>Xinafoate</td>
<td>Seretide Evohaler</td>
<td>GlaxoSmithKline</td>
<td>UK</td>
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</table>
# Metered Dose Inhalers (MDI)

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol pressurised inhalation (100µg)</td>
<td>Asthalin</td>
<td>Cipla</td>
<td>India</td>
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<tr>
<td>albuterol</td>
<td>Ventolin</td>
<td>GlaxoSmithKline</td>
<td>India</td>
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<td>levalbuterol HCl</td>
<td>Xopenex</td>
<td>3M Pharmaceuticals</td>
<td>U.S.A.</td>
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<tr>
<td>Fluticasone 50 µg</td>
<td>Flixotide</td>
<td>GlaxoSmithKline</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Formoterol Fumarate 12 mcg</td>
<td>Ultratech</td>
<td></td>
<td>India</td>
</tr>
</tbody>
</table>
Metered-Dose Inhalers

Anti-Inflammatories

Steroidal

Non-Steroidal

Dry Powder Inhalers

Anti-inflammatories and long acting beta agonist

Breath-Actuated Metered Dose Inhaler

Short-Acting Bronchodilator

The Only Breath-Actuated Reliever

Maxair® Autohaler™
(per methyl-x-cyclonexyl inhalation aerosol)
<table>
<thead>
<tr>
<th>Cited Patent</th>
<th>Filing date</th>
<th>Issue date</th>
<th>Original Assignee</th>
<th>Title</th>
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<tbody>
<tr>
<td>US2470296</td>
<td>Apr 30, 1948</td>
<td>May 17, 1949</td>
<td></td>
<td>INHALATOR</td>
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<tr>
<td>US2533065</td>
<td>Mar 8, 1947</td>
<td>Dec 5, 1950</td>
<td></td>
<td>Micropulverized Therapetic agents</td>
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<tr>
<td>Cited Patent</td>
<td>Filing date</td>
<td>Issue date</td>
<td>Original Assignee</td>
<td>Title</td>
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<tr>
<td>US6254854</td>
<td>May 11, 2000</td>
<td>Jul 3, 2001</td>
<td>The Penn Research Foundation</td>
<td>Porous particles for deep lung delivery</td>
</tr>
</tbody>
</table>
RECENT ADVANCES
The Aerogen Pulmonary Delivery Technology

AeroDose inhaler.  AeroNeb portable nebulizer
• AeroGen specializes in the development, manufacture, and commercialization of therapeutic pulmonary products for local and systemic disease.

• The technology being developed at AeroGen consists of a proprietary aerosol generator (AG) that atomizes liquids to a predetermined particle size.

• AeroGentechologies produce a low-velocity, highly respirable aerosol that improves lung deposition of respiratory drugs and biopharmaceuticals.

• These delivery platforms accommodate drugs and biopharmaceuticals formulated as solutions, suspensions, colloids, or liposomes.
The AERx Pulmonary Drug Delivery System

The AERx device (with dosage forms).

The AERx dosage form.

AERx nozzle array.
• The AERx aerosol drug delivery system was developed to efficiently deliver topical and systemically active compounds to the lung in a way that is independent of such factors as user technique or ambient conditions.

• A single-use, disposable dosage form ensures sterility and robust aerosol generation. This dosage form is placed into an electronically controlled mechanical device for delivery.

• After the formulation is dispensed into the blister, a multilayer laminate is heat-sealed to the top of the blister. This laminate, in addition to providing the same storage and stability functions as the blister layer, also contains a single-use disposable nozzle array.
The Spiros Inhaler Technology
• The inhaler has an impeller that is actuated, when the patient inhales, to disperse and deliver the powder aerosol for inhalation. The core technology was initially developed to overcome the patient coordination required for metered-dose inhalers and the inspiratory effort required for first-generation dry powder inhalers in treating asthma.

• All motorized Spiros powder inhaler platforms use the same core technology to achieve powder dispersion that is relatively independent of inspiratory flow rate over a broad range. The high-speed rotating impeller provides mechanical energy to disperse the powder.

• The Spiros DPI blister disk powder storage system is designed for potentially moisture-sensitive substances (e.g., some proteins, peptides, and live vaccines). The blister disk powder storage system contains 16 unit doses.
A) Blisterdisk powder storage system.
B) The interior of a well in a blisterdisk.

Aerosol generator “core” technology
The DirectHaler™ Pulmonary device platform

- **Inhaler Cap** for moisture protection
- **Pharma-blister pack** available, extra protection barrier
- **Mouth piece** for protection of mouth & tongue
- **Transparency** of device for dose visibility: dose ready/taken indicator
- **Air inlet** dimensioned for balanced inspiratory resistance and pre-turbulation of airstream
- **PowderWhirl chamber** for turbulent dispersion of the dose

US Pat. No. 5,797,392
EP Pat. No. 0805696

Novel DirectHaler™ Compliance System for targeting the complete respiratory system
• DirectHaler™ Pulmonary is an innovative and new device for dry powder. Each pre-metered, pre-filled pulmonary dose has its own DirectHaler™ Pulmonary device.

• The device is hygienically disposable and is made of only 0.6 grammes of Polypropylene. DirectHaler™ Pulmonary offers effective, accurate and repeatable dosing in an intuitively easy-to-use device format.

• The powder dose is sealed inside the cap with a laminate foil strip, which is easily torn off for dose-loading into the PowderWhirl chamber, before removing the cap and delivering the dose.

✓ Sensitive powders
✓ Deep lung delivery
✓ High drug payloads
✓ New types of combination dosing
Dr Reddy's Laboratories (DRL) has launched an innovation in the metered dose inhaler (MDI) space with launch of 'Dose Counter Inhalers (DCI) for the first time in India. This the first MDI in India that gives patients an advance indication of when the inhaler is going to be empty. DCI is a new drug delivery device with a single device having 120 metered doses. There is a window in the inhaler that changes color from green to red. Green indicates the inhaler is full and red indicates the inhaler is empty. Half green and half red in the window indicate it's time to change the inhaler.
CONCLUSION

- The lung has served as a route of drug administration for thousands of years. Now a day’s pulmonary drug delivery remains the preferred route for administration of various drugs. Pulmonary drug delivery is an important research area which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various diseases. Inhalation gives the most direct access to drug target. In the treatment of obstructive respiratory diseases, pulmonary delivery can minimize systemic side effects, provide rapid response and minimize the required dose since the drug is delivered directly to the conducting zone of the lungs.

- It is a needle free several techniques have been developed in the recent past, to improve the Quality of pulmonary drug delivery system without affecting their integrity. Because of advancement in applications of pulmonary drug delivery it is useful for multiple diseases. So pulmonary drug delivery is best route of administration.
REFERENCES

- Chien Y.W., Su K.S.E., Chang S.F., Nasal Systemic Drug Delivery, Ch. 1, Marcel-Dekker, New York 1-77.

• http://www.pharmabiz.com
• http://www.lungusa.org
• http://www.ijrps.pharmascope.org
Thank You!