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A PRACTICE SCHOOL REPORT ON CURRENT TRENDS IN PULMONARY DRUG DELIVERYSYSTEM

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Abstract:

The pulmonary drug delivery system offers several merits over other drug delivery systems and therefore, this delivery route has been in prime focus for various applications like local and systemic therapeutics delivery. The overall development of drug delivery system depends on its efficacy, quality and safety and to achieve such attributes there is a need of reliable evaluation methods to test them. This review provides an in-depth analysis of the development in the evaluation of pulmonary drug delivery systems. In vitro methods of testing pulmonary products such as particle morphological studies, powder flow characteristics, moisture content test, aerosol turboelectric characterization, particles interparticulate forces measurement and solid state characterizations were discussed. Particle size and zeta potential measurement and evaluation of aerosol performance such as dose uniformity and aerodynamic particle size distribution were reviewed in detail. The development of dissolution methods for pulmonary products is also elaborated. Various cell culture methods for testing pulmonary products were overviewed. The in vivo testing methods including drug administration systems, drug deposition studies and pharmacokinetic studies and ex vivo testing models were also highlighted. Together an overview of current advancement in evaluation and characterization of pulmonary drug delivery system can be analyzed and studied through this review.The pulmonary drug delivery system offers several merits over other drug delivery systems and therefore, this delivery route has been in prime focus for various applications like local and systemic therapeutics delivery. The overall development of drug delivery system depends on its efficacy, quality and safety and to achieve such attributes there is a need of reliable evaluation methods to test them. This review provides an in-depth analysis of the development in the evaluation of pulmonary drug delivery systems. In vitro methods of testing pulmonary products such as particle morphological studies, powder flow characteristics, moisture content test, aerosol turboelectric characterization, particles interparticulate forces measurement and solid state characterizations were discussed. Particle size and zeta potential measurement and evaluation of aerosol performance such as dose uniformity and aerodynamic particle size distribution were reviewed in detail. The development of dissolution methods for pulmonary products is also elaborated. Various cell culture methods for testing pulmonary products were overviewed. The in vivo testing methods including drug administration systems, drug deposition studies and pharmacokinetic studies and ex vivo testing models were also highlighted. Together an overview of current advancement in evaluation and characterization of pulmonary drug delivery system can be analyzed and studied through this review.

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INTRODUCTION:

Pulmonary drug delivery (PDD) systems were recently introduced into the pharmaceutical field to treat both the local and the systemic type of lung diseases. PDD systems are known to be able to simply deliver the drug to the required site in the body directly or to other distant sites through the bloodstream. The lungs provide a huge surface area of alveoli with rich capillary network, which acts as an excellent absorbing surface foradministration of drugs.[1]

Throughout the past several years, rapid onset of action and higher efficiency has been responsible for the success of pulmonary delivery system for symptomatic relief in treatment of asthma and chronic obstructive pulmonary disease (COPD). The efficacy of a treatment mostly depends on the techniques by which the drug is delivered and optimum concentration of the drug, above or below this range can be toxic or produce no therapeutic benefit at all. The slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutic agents to targets in tissues.[2] The efficacy of the drug and its treatment can be achieved from the new ideas on controlling the pharmacokinetics, pharmaco-dynamics, immuneginecity, and bio-recognition.[3] These new strategies based on interdisciplinary approaches such as polymer science, pharmaceutical technology, bio-conjugate chemistry, and molecular biology, are often called novel/advanced drug delivery systems. Different drug delivery/drug targeting systems already exist and currently under development can be efficiently used to minimize the drug degradation and loss, to prevent harmful side effects and to increase drug bioavailability. For over 20 years, the potential benefit of nanotechnology is appreciated by most of the researchers and it is providing vast improvements in drug delivery and drug targeting. New advancements in the drug delivery strategies are minimizing the unwanted toxicities and improving the efficacy of the treatments.

Pulmonary delivery of drug has become an attractive target and of tremendous scientific and biomedical interest in the health care research area as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery. The respiratory epithelial cells have a prominent role in the regulation of airway tone and the production of airway lining fluid. In this respect, growing attention has been given to the potential of a pulmonary route as a non-invasive administration for systemic and local delivery of therapeutic agents, because the high permeability and large absorptive surface area of lungs, (approximately 70-140 m2 in adult humans having extremely thin absorptive mucosal membrane) and good blood supply.[4]

Pulmonary delivery of drug has become an attractive target and of tremendous scientific and biomedical interest in the health care research area as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery. The respiratory epithelial cells have a prominent role in the regulation of airway tone and the production of airway lining fluid. In this respect, growing attention has been given to the potential of a pulmonary route as a non-invasive administration for systemic and local delivery of therapeutic agents, because the high permeability and large absorptive surface area of lungs, (approximately 70-140 m2 in adult humans having extremely thin absorptive mucosal membrane) and good blood supply.[5] The alveolar epithelium of the distal lung has been shown to be an absorption site for most of the therapeutics and various macromolecules.[6,7] Further advantages over peroral applications are the comparatively low enzymatic activity, rapid absorption of drug and the capacity for overcoming first-pass metabolism. It has been already reported that, the local respiratory disorders and some systemic diseases can be well treated by delivering the drugs through pulmonary route. This includes the topical treatment of asthma, local infectious diseases, pulmonary hypertension, the systemic use of insulin, human growth hormones, and oxytocin. Presently this is true for many biotherapeutics currently injected intravenously, such as growth hormones, glucagons, or insulin, each of which could possibly be delivered to humans by inhation were the efficiency of inhalation therapy is greater.[8]

Understanding the transport and deposition of inhaled aerosols is of fundamental importance to inhalation therapy. Herein we address issues that related to the technical, physiological, and efficacy aspects of pulmonary drug delivery system.**[9]** This review also focused on transepithelial transport and mechanisms of pulmonary administration. In addition, polymer selections in dosage and types of delivery devices have also been compiled.

Advantages of Pulmonary Routes of Drug Delivery:

1. Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug. [10]
2. Onset of action is very quick with pulmonary drug delivery.
3. Degradation of drug by liver is avoided in pulmonary drug delivery.
4. The ability to nebulize viscous drug formulations for pulmonary delivery, therebyovercoming drug solubility issues with the ability to use lipid, water or lipid/water emulsions as drug carriers.[11]
5. Increased drug delivery efficacy due to size-stable aerosol droplets with reducedhygroscopic growth and evaporative shrinkage.
6. Liposomal drug formulations remain stable, when nebulized.
7. Ability to nebulizer protein-containing solutions.
8. Inhaled drug delivery puts drug where it is needed.

Limitations of Pulmonary Routes of Drug Delivery :

1. The oropharyngeal settlement may give local adverse effects.
2. Patients may have trouble using the delivery devices correctly.
3. Various aspects affect the reproducibility of drug delivery to the lungs, including physiological (respiratory scheme) and pharmaceutical (tool, formulation) variables. Forthe systemic delivery of drugs with a small therapeutic index, such deviations may be undesirable.[12]
4. Drug absorption may be limited due to the barrier action of the mucus and the drug–mucus interactions.
5. Mucociliary clearance diminishes the retention time of drugs within the lungs that may affect the pharmacological efficacy of the slowly absorbed drugs.
6. The lungs are not an easily reachable surface for drug delivery, and complex deliverydevices are required for targeted drug delivery.

Mechanisms of Respiratory Deposition :

The respiratory tract deposition of inhaled aerosol particles is due to three principal mechanisms: inertia impaction, Brownian diffusion and gravitational settling. A theory is developed to predict the particle deposition and its distribution in human respiratory tract for anybreathing condition. [13]

Once the particle enters the respiratory tract via either the nose or mouth, it may be deposited in different regions of the respiratory tract. During breathing, the airflow undergoes several direction changes in the nasal/mouth, pharynx, larynx regions, and airway bifurcations. [14]

Larger particles (>0.5 μm) may deposit by impaction in these regions because they could notfollow the air streamline. In fact, deposition by impaction in the oro-pharyngeal region remains a major portion of the emitted dose for pMDI and DPI devices.

In the small airways and alveolar region, deposition by sedimentation is the major deposition mechanism of inhaled particles. [15]

Small particles (<0.2 μm) may be deposited by diffusion in all regions of the respiratory tract. Diffusion deposition is important for nano-particles <100 nm.

Interception deposition is important for elongated particles such as fibrous aerosols when the long particle dimension is comparable with the pulmonary airway dimension.

Physiochemical properties of drug:

Molecular size:

The molecular size of the drug influence absorption of the drug through the nasal route. The oleophilic medication have direct relationship between the MW associated drug permeation whereas water- soluble compounds depict an inverse relationship. The speed of permeation is high-ly sensitive to molecular size for compounds with MW ≥ three hundred Daltons.

Lipophilic-hydrophilic balance. [16]:

The deliquescent and oleophilic nature of the drug additionally affects the method of absorption. By increasing lipophilicity, the permeation of the compound usually in-creases through nasal mucous membrane. though the nasal mu-cosa was found to possess some deliquescent character, it seems that these mucosae are primarily oleophilic in nature and also the lipid domain plays a very important role within the barrier operate of those membranes.

Oleophilic medication like Narcan, buprenorphine, androgen and 17a-ethinyl- estrogen are nearly utterly absorbed once administered intranasal route.[17]

Enzymatic degradation in cavum:
In case of peptides and proteins are having low bio-availability across the cavum, thus these medication might have chance to bear catalyst degradation of the drug molecule within the lumen of the cavum or throughout passage through the animal tissue barrier. [18] These each sites are having exo-peptidases and endopeptidases, exo-peptidases are mono-amino peptidases and di-amino peptidases. These are having capability to cleave peptides at their N and C termini and endopeptidases like aminoalkanoic acid and aminoalkanoic acid, which may attack internal amide bonds. [19]

Nasal effect factors:
Membrane permeability:
Nasal membrane porousness is that the most significant issue, that have an effect on the absorption of the drug through the nasal route. The water soluble medication and particularly massive mass medication like peptides and proteins area unit having the low membrane porousness. That the compounds like peptides and proteins area unit main-ly absorbed through the endocytotic transport method in low amounts. Soluble high mass medication cross the nasal membrane principally by passive diffusion through the liquid pores (i.e. tight junction)[20]

Environmental pH:
Hydrogen ion concentration:
The environmental hydrogen ion concentration plays a crucial role within the potency of nasal drug absorption. little soluble compounds like carboxylic acid, 2-hydroxybenzoic acid, and organic compound acid show that their nasal absorption in rat occurred to the best extent at those hydrogen ion concentration values wherever these compounds area unit within the unionized kind. However, at hydrogen ion concentration values wherever these compounds area unit partly ionized, substantial absorption was found. This implies that the unionized oleophilic kind crosses the nasal animal tissue barrier via transcellular route, whereas the additional oleophilic ionized kind passes through the liquid paracellular route.**[21]** Mucociliary clearance

Mucociliary clearance may be a one among the functions of the higher tract is to forestall baneful sub-stances (allergens, bacteria, viruses, toxins etc.) from reaching the lungs. Once such materials adhere to, or dissolve in, the secretion lining of the cavum, they're transported towards the cavity for ultimate discharge into the epithelial duct. Clearance of this secretion and therefore the adsorbed/dissolved substances into the bum is named the MCC.**[**22] This clearance mechanism influence the absorption method thanks to the dissolved medicine within the cavum square measure discharge by the each the secretion and therefore the cilia, that is that the motor of the MCC and therefore the secretion transport rate is half dozen mm/min. it's of utmost importance that the MCC isn't impaired so as to forestall lower tract infections. [23]

Cold, rhinitis Rhinitis may be a most often associated common malady, it influence the bioavailability of the drug. It's chiefly classified into coryza and customary, the symptoms square measure hyper secretion, skin sensation and physiological reaction chiefly caused by the viruses, microorganism or irritants. coryza is that the allergic airway malady, that affects 100 percent of population. It's caused by chronic or acute inflammation of the mucosa of the nose. These conditions have an effect on the absorption of drug through the secretion membrane due the inflammation. [24]

Formulation (Concentration, pH, Osmolarity)
The pH of the formulation and nasal surface, will have an effect on a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation ought to be adjusted to four.5–6.5 as a result of muramidase is found in nasal secretions that is answerable for destroying sure microorganism at acidic pH. Below basic conditions, muramidase is inactivated and therefore the tissue is liable to microorganism infection. In addition to avoiding irritation, it ends up in getting efficient drug permeation and prevents the expansion of bacteria.[25]

Concentration gradient plays important role within the absorption / permeation method of drug through the nasal membrane thanks to nasal tissue layer injury. Examples for this are nasal absorption of L-Tyrosine was shown to extend with drug concentration in nasal introduction experiments. Another is absorption of hydroxy acid was found to say no with concentration. This decline is probably going thanks to nasal tissue layer injury by the permanent.

The osmolarity of the indefinite quantity type affects the nasal absorption of the drug; it absolutely was studied within the rats by victimization model drug. The binary compound concentration of the formulation affects the nasal absorption. The maximum absorption was achieved by zero.462 M binary compound concentration; the upper

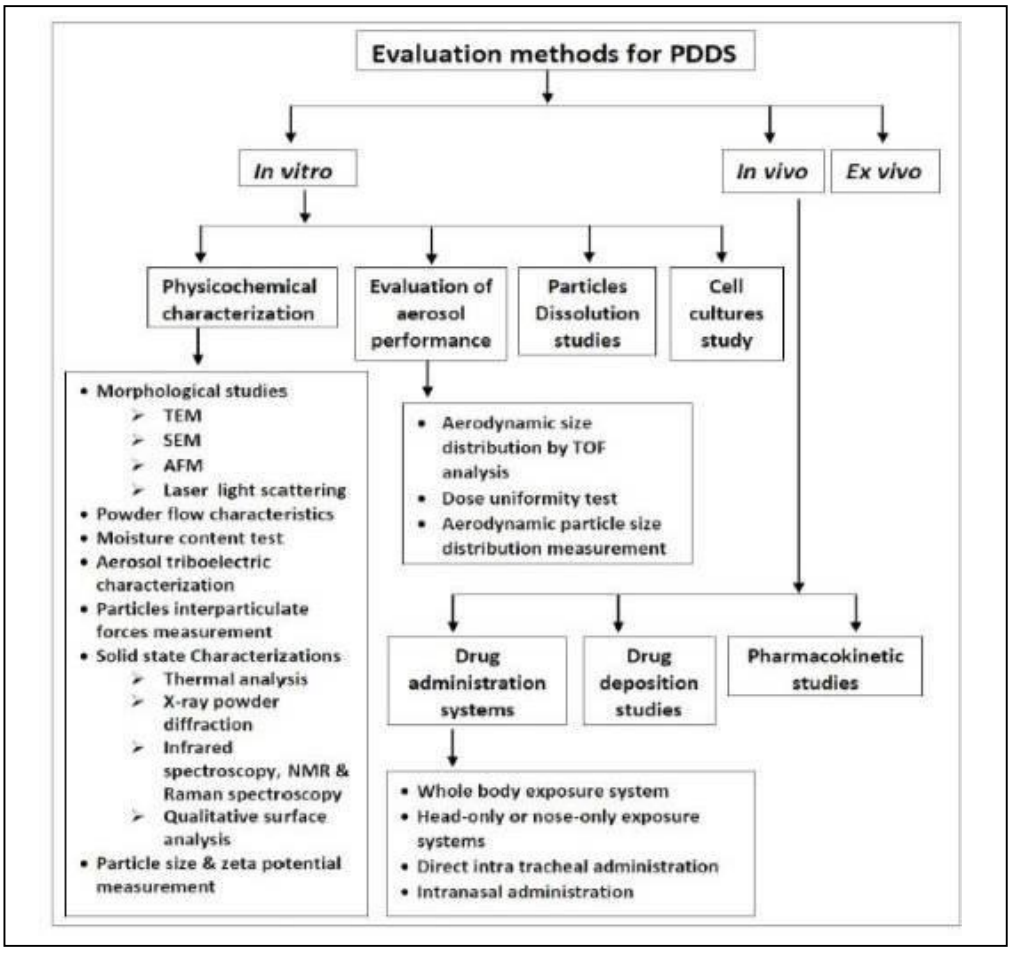
concentration not solely causes augmented bioavailability however conjointly ends up in the toxicity to the nasal epithelial tissue.[26]

Drugs distribution and deposition :

The drug distribution within the cavity is one among the important factors, which affect the efficiency of nasal absorption. The mode of drug administration could effect the distribution of drug in cavity, which successively will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms mainly depends on the location of disposition. The anterior portion of the nose provides a protracted nasal residential time for disposition of formulation, it enhances the absorption of the drug. And the posterior chamber of cavity will use for the deposition of dosage form; it's eliminated by the mucociliary clearance process and hence shows low bioavailability. The site of disposition and distribution of the dosage forms are mainly depends on delivery device, mode of physiochemical property of drugs molecule. [27]

Development in the Evaluation of Pulmonary Drug Delivery System :

In recent years, there has been a considerable advancement in the field of evaluation and characterization of pulmonary drug delivery system.**[28]** These methods can be classified as in vitro, in vivo and ex vivo methods. Various in vitro methods like physicochemical characterization of particles, evaluation of aerosol performance, particle dissolution studies and cell cultures study have been evolved. Drug administration system, drug deposition and pharmacokinetic studies are the in vivo methods which are currently in research studies. Ex vivo methods are also developed to check the efficacy and safety parameters of drugs and their delivery mechanisms. Various evaluation methods for pulmonary drug delivery systems are given in fig. [29]



Formulation of Inhalers :
Dry power inhalers: The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs. Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus.[30]

The dry powder platform comprises devices that generate an aerosol directly from 1 to 5 µm size drug powder, or mixtures with excipients. Excipients used in DPI are used as carrier for Active Pharmaceutical Ingredient (API). Most commonly used carrier is Lactose Monohydrate.

Formulation of DPI mainly includes following three steps;

API Production:
The important requirement of API in case of DPI is particle size. Particle size of drug should be less than 5 µm. It should be in the range of 2-5 µm. There are various sort of mills used for size reduction of drugs but few of them are appropriate for DPI to reduce the size in the range of 2-5 µm such as fluid-energy mills, such as the jet mill; high-peripheral-speed mills, such as the pin- mill; and the ball mill.[31]

Formulation of API with or without carriers:
The part of carrier in DPI is enhancing the flow property of powder and also aerosol performance of the cohesive drugs and fine lactose. After drug and carrier (s) have separately been brought to their desired forms, they are combined in the blending process.

Integration of the formulation into device:
After the formulation has been blended, it is filled into capsules, multi-dose blisters, or reservoirs for use with the inhaler device. The filling process is automated and depends on the nature of the metering system.[32]

The primary inhaler parts are same for all type of devices on the market and many in system, powder de-agglomeration principle and mouthpiece. development. Dry Powder Inhaler device consists of; powder formulation, dose measuring system, powder de-agglomeration principle and mouthpiece.[33]

Fig. 1: Dry Powder Inhaler

Currently there are two types:

- Unit dose devices : In a single-unit dose device, the drug is formulated as a micronized drug powder and carrier system and supplied in individual gelatin capsules, which are then embedded into the device for a single dose.
- Multi dose Devices : The multi-unit dose device utilizes factory metered and sealed doses packaged in a way that the device can hold multiple doses without having to reload. Commonly, the packaging comprises of replaceable disks or cartridges, or strips of foil

polymer blister packaging that may or may not be reloadable. [34]

New developments in dry powder inhalation technology:

Changes in the performance of the DPI can be achieved either through changes in the designe the device through changes in the powder formulation, or . described extensively, the forces gov ernng the particle–
particle interactions in the agglomerates and the forces playing a role in the deagglomeration pro cess .Recent developments regarding the powder formulation aim at a reduction of the adhesive a nd cohesive forces between the particles to increase the FPF.[35]

Supercritical fluid technology is applied to improve the surface properties of the drug substance Large porous particles have reduced inter-particulate forces because of their low density, the irregular surface structure and/or reduced
surface free energy . Moreover, these particles are claimed to have improved aerodynamic behavior in the airways, whereas phagocytosis of the deposited particles in the alveoli is reduced . In another approach, smaller porous particles (3– 5 mm) have been used to improve deagglomeration and lung deposition.

Changes in device technologies are few new developments really aim at an increase of the deagglomeration forces generated during the inhalation. It is well known that if the more efficient the force is,
higher the FPF will be. A main classification parameters in the new device developments is whether or not the powder deagglomeration is power assisted (active devices) or depends on the kinetic energy of the inhalation flow generated by the patient (passive devices). Regarding the passive devices, recently two DPI devices were introduced that apply impaction forces for the generation of the aerosol. [36]

Powder flow characteristics :

Powder flow characteristics of inhalable powders are done to evaluate the flow characteristics and its relationship with the aerodynamic properties. The angle of repose, bulk density, tapped density, apparent density and porosity are some of the powder flow characteristics need to be measured for quality control. The angle that the side of the conical heap of powders makes with the horizontal plane is termed as angle of repose. Apparent density and porosity values of inhalable powders were determined by mercury porosimeter (Micromeritics AutoPore IV 9500; Micromeritics Instrument Corporation, Norcross, USA). A tap density tester (Stampfvolumeter, STAV 2003) are used to measure tap density. Carr's compressibility index and Hausner ratio were determined by the values of bulk and tapped density. The powders are tested for their moisture content by using a dynamic vapour sorption instrument (Surface Management Systems, UK) [37]

Dry Powder Inhaler Formulation:

Formulation of powders for inhalation Drugs delivered by DPIs are formulated as either pure drug or mixed with aninactive excipient.The budesonide preparation for use in the Turbuhalers DPI (AstraZeneca) is an example of a pure drug powder formulation. Powder blends contain micronized particles of the drug with an excipient, usually lactose, which may be micronized, but which more often comprises larger ''carrier'' particles. While the optimal therapeutic particle size distribution for aninhaled dry powder asthma medication is generally considered to be o5mm, or possibly 1 ^ 5 mm , particles this small are typically not free £owing. Cohesion and staticcharge interfere with drug handling during manufacture and with inhaler ¢lling, can reduce uniformity in metering individual doses, and can cause drug retention within the device.The useof excipients can help to improve dose uniformity, partly because a larger mass of powder is generally easier to meter accurately.Under speci¢c manufacturing conditions, the micronized particles can be combined to form stabilized agglomerates with controlled uniformity and hardness. For example, a novel DPI (Twisthalers, Schering-Plough) uses agglomerates of the corticosteroid mometasone furoate and lactose, stabilized to the appropriate hardness and size for handling and metering. Agglomerates of drug particles, or of drug and lactose, must be deagglomerated by shear forces during inhalation, producing ¢ne particles which are carried by the air£ow into the lungs. Particles o5 mm in size can be distributed deep into the smaller airways and this penetration correlates with good clinical response. DPI design issues The design of a DPI must be coordinated with the formulation of the drug.Inhaler design, particularly the geometry of the mouthpiece, is critical for patients to produce an air£ow su⁄cient to lift the drug from the dose chamber or capsule, break up the agglomerates in a turbulent airstream, and deliver a dose to the lungs as therapeutically e¡ective ¢ne particles. The air£ow generated by inhalation directly determines particle velocity and hence the easewith which particles are

deagglomerated.[38]

The materials used in the construction of DPIs and characteristics of the formulation a¡ect electrostatic charge accumulation. Some formulations, as well as inhaler materials, accumulate and retain electrostatic charge more strongly than others, and this will a¡ect both drug retention within these inhalers as well delivered aerosol behaviour.

Dry Powder Inhalers :

Pulmonary drug delivery (PDD) systems were recently introduced into the pharmaceutical field to treat both the local and the systemic type of lung diseases. PDD systems are known to beable to simply deliver the drug to the required site in the body directly or to other distant sites through the bloodstream. Different forms of PDD systems including the nebulizers and inhalers were introduced as alternative treatments for many diseases related to the lung. PDD systems have great advantages that include their high permeability, the large surface area which accounts for approximately 100 m2, and the rapid onset that might be comparable to the onset of intravenous dosage forms.[39]

DPIs performance depends on the behavior of their composite particles. Particle flow behavior was shown to be the driving factor that affects the performance of DPIs. Several operations, including fluidization, metering, and the dispersion of solid particles are greatly dependent on the flowability of solid particles (Hickey et al., 2007). There are different aspects regarding particle characteristics which should be taken into consideration when developing DPIformulations. One of these aspects is particle interactions including cohesive forces between drugs and the carrier. The performance of DPI formulations depends on the impact of adhesive forces formed between the drug and its carrier because if the amount of adhesive forces increased excessively, the drug will not be able to be detached from the carrier so that poor drug dispersion will result. A parameter was developed to evaluate fine particles' deposition ability within the lung. This parameter is known as the aerodynamic diameter, which has been shown to be influenced by the size distribution, shape, and the density of particles. A problem related to the formulation of DPIs is that their particles tend to stick to each other and to other surfaces due to the relatively high adhesive and cohesive interactions , which results in an inefficient filling into the inhalation device (Kawashima et al., 1998). Particles adhere to carriers as a result of the physicochemical properties between the drug and the carrier as well as the manufacturing processes applied. Many technologies were developed to enhance the efficiency of particles deposition on carrier systems, which concentrated on the reduction of adhesion forces that can beachieved by the proper manipulation of the microscopic properties of particles including their sizes, shapes, and surface morphology. Figure shows the difference between large and small carrier systems.[40,41]

Preparation methods of dry powder inhaler (DPI) systems, in which the first method involves an additional step that requires the dispersion of solid particles in a suitable solution in order to introduce particles within the carrier, whereas in the second method, adhesion of particles takes place at the surface of the carrier. [42]

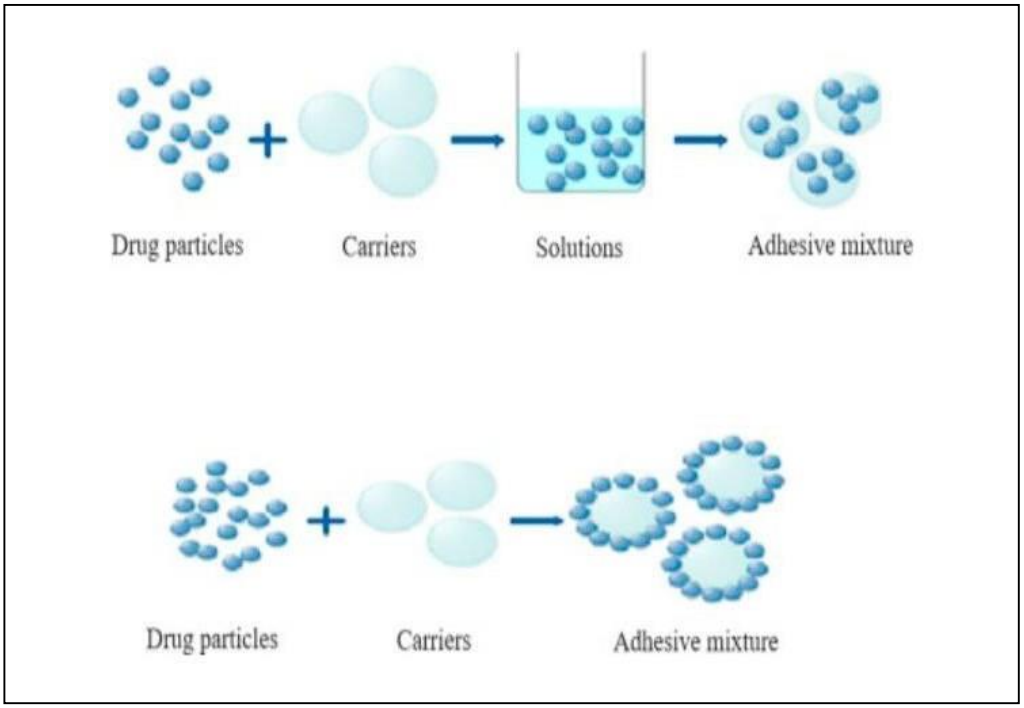

Drug particles
Carriers
Solutions
Adhesive mixture
Drug particles
Carriers
Adhesive mixture

Fig. 2

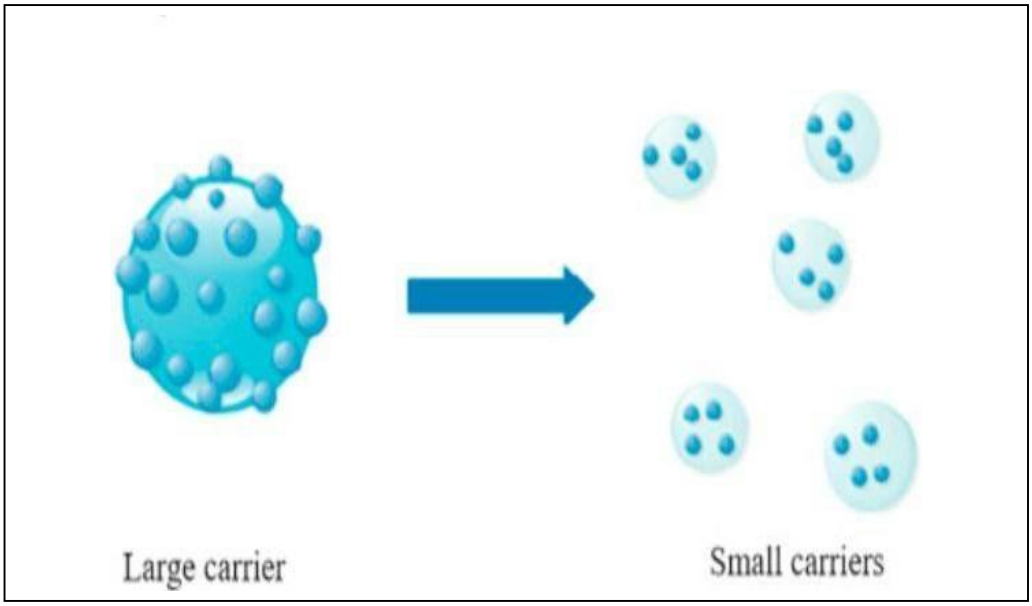

Large carrier
Small carriers

Fig. 3

Approaching the ideal dpi :
There is now clear evidence that many major players in inhaled drug delivery are prioritizing development of DPI products in preference to reformulation of pMDIs with HFA propellants.

However, companies developing DPIs face many challenges, and must often make compromises. For instance, seeking solutions to technical problems associated with optimizing pharmaceutical performance may introduce incompatibilities with patient compliance issues. Multidose (reservoir) devices tend to target drug to the lungs more e¢ciently than multiple unit dose devices but tend to have poorer dose uniformity.While it is unlikely that an ideal DPI will ever appear, it is at least possible to list some of the characteristics of an ideal DPI.A range of DPIs is already marketed, and many others are in development. Not all new DPI devices and formulations will reach the market, but many of those that do are likely to have successfully addressed perceivedlimitations in earlier systems. As we go forward into the 21st century, DPI delivery systems are likely to contribute signi¢cantly to successful drug delivery by the inhaled route, not only to treat asthma, but also to deliver a wider range of drugs intended both for local and systemic application. [43]

Currently, researchers have made enormous strides in the progress of pulmonary delivery technologies, both in terms of inhaler design and progresses in nanoscale carrier engineering. At present there are three main different classes of devices for pulmonary drug delivery: metered dose inhalers, nebulizers, and dry powder inhalers.

Techniques of making particulate matter for lung delivery :
Many conventional techniques have been reported to produce DPI formulations. However, these methods have number of limitations, such as particle size, size distribution, shape and poor control over powder crystallinity. These problems can be rectified by specialized milling techniques. Jet-milling of drug under nitrogen gas with new nanojet milling instrument is the most suitable method for creating nanoparticles meant for pulmonary drug delivery. Here, some of the important techniques are discussed in brief. [44]

Spray drying technique :
Spray drying is an advanced pharmaceutical manufacturing process used to efficiently produce respirable colloidal particles in the solid state. Spray drying was explored in the 1980s as an alternative means of producing fine particles for pulmonary delivery. In this process, the feed solution is supplied at room temperature and pumped to the nozzle where it is atomized by the nozzle gas. The atomized solution is then dried by preheated drying gas in a special chamber to remove water moisture from the system, thus forming dry particles. This method is more promising in producing the particles of above 2-µm size. This method is reported to have better control on particle formation and hence can be easily translated to large scale production. This process is also suitable for thermolabile materials, such as proteins and peptides, because mechanical high-energy input is avoided in this process. More importantly, spray-drying can result in uniform particle morphology. [45]

Spray freeze drying method :
This method was explored for pharmaceutical application in early 1990s. It is an advanced particle engineering method, which combines spray-drying and freeze-drying processing steps. It involves spraying the drug solution into liquid nitrogen as a freezing medium followed by lyophilization. This method produces light and porous particles and high fine particle fraction with improved aerosol performance and almost 100% yield at subambient temperatures. [46] Thermolabile protein and peptide substances, such as insulin and plasmid DNA, can also be formulated into dry powder inhalation products. However, this is an expensive process restricted for only expensive drug.

Supercritical fluid technology :
The basic feature of this process is the controlled crystallization of drugs from dispersion in supercritical fluids, carbon dioxide. This method has been used in the pharmaceutical field for production of microparticles, nanoparticles, liposomes, and inclusion complexes. This method is used for the production of particulate pulmonary drug delivery systems containing proteins and peptides, and also used to improve the formulation properties of certain drug candidates. [47]

Solvent precipitation method :
This method involves sono-crystallization and micro-precipitation by opposing liquid jets. Crystalline drug particles with narrow size distribution could be prepared by direct controlled crystallization. Inhalable particles can be produced by rapid precipitation from aqueous solutions using antisolvents. Recently, ultrasonic radiation has been applied to control the precipitation. Various antiasthmatic drugs were prepared using the sono-crystallization technique. [48]

Double emulsion/solvent evaporation technique :
This method involves preparation of oil/water emulsion with subsequent removal of the oil phase through evaporation. The organic solvent diffuses out of the polymer phase and into the aqueous phase, and is then evaporated, forming drug- loaded polymeric nanoparticles. By this method, biodegradable polymers have been intensively investigated as carriers for respiratory solid drug nanoparticles.

Particle replication in nonwetting templates :
Particle replication in non wetting templates (PRINT) is top-down particle fabrication technique developed by Dr. Joseph DeSimone and his group. This technique is able to produce uniform-sized organic micro- and nanoparticles with complete control of size, shape, and surface functionality, and helps in loading of small organic therapeutics, proteins, peptides, oligonucleotides, siRNA contrast agents, radiotracers, and flurophores. [49]

Formulation of Pressurized Metered Dose Inhalers :
A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD. Pressurized metered aerosols may be formulated as either solutions or suspensions ofdrug in the liquefied propellant. MDIs can be formulated with the drug completely dissolved in the formulation, rendering a solution formulation, or with the drug practically insoluble in the formulation, rendering a suspension formulation. Compared with suspensionformulations, solution MDIs offer the benefits of homogenous formulation (i.e., patients do not need to shake the vial immediately prior to use and there is no concern related to sampling homogeneity), a finer residual aerosol. When formulating solution MDIs, the total amount of fine particle drug delivered cannot simply be increased by increasing the drug concentration in a formulation. Many drugs are not readily soluble in HFA propellants, which frequently limits the amount of drug that can be dosed using MDIs. Previously, surfactants or complexation aids were used in MDIs to increase drug solubility in CFC systems .However, many of the conventional excipients used in CFC formulations and approved for human use, are insoluble in HFA system.

The method for preparing drug particles for MDI formulations needs to be selected based on the chemical stability of the drug. Proteins, for instance, require additional care when micronizing, due to being heat-labile and need to preserve any three-dimensional conformation. Frequently, spray-drying with another agent (i.e., sodium carboxymethylcellulose, polyvinyl alcohol, and/or polyvinylpyrrolidone (PVP)) is utilized for protein drugs due to the need to preserve the three-dimensional conformation and biological activity of the protein. The basic requirements for formulation of MDIs are containers, propellants, and metering valve. Filling Metered Dose inhaler canister: canister is filled by liquefying the propellant at reduced temperature or elevated pressure. In cold filling , active compound , excipients and propellant are chilled and filling at about-60oc. additional propellant is then added at the same temperature and the canister sealed with the valve. In pressure filling, a drug/propellant concentrate is produced and filled at effectively room temperature and pressure (in fact, usually slightly chilled to below 20oc). [50] Thevalue is crimped on to the canister and additional propellant is filled at elevated pressure through the valve, in a process known as gassing. Pressure filling is most frequently employed for inhalation aerosols.

Nebulizers :
A device converts liquids into aerosols that can be inhaled into the lower respiratory tract. Nebulizers are used in aerosol drug delivery produce a poly-disperse aerosol where the drug delivered in the particles size range 1–5 μm in diameter. Most Nebulizers use compressed air for atomization, but some use ultrasonic energy.

Nebulizers are generally used for the treatment of cystic fibrosis, asthma, COPD and other respiratory diseases or disorders. There are following three main types of nebulizerscommercially available. [51]

Nebulizers have been available since the beginning of the twentieth century. Nebulization from a drug solution is a common method of medical aerosol generation. To deliver a drug by nebulization, the drug must first be dispersed in a liquid (usually aqueous) medium. After application of a dispersing force (either a jet of gas or ultrasonic waves), the drug particles are contained within the aerosol droplets, which are then inhaled. At present all commercially available nebulizers can be categorized into two types: (i) jet (or pneumatic) small-volume nebulizers and (ii) ultrasonic nebulizers. Jet nebulizers are based on the venturi principle, whereas ultrasonic nebulizers use the converse

piezoelectric effect to convert alternating current to high-frequency acoustic energy (Rau, 2002). The major features of both types of nebulizer are duration of treatment at each time of use, particle size distributions produced, and aerosol drug output.

The formulation of drug solution is usually designed to optimize drug solubility and stability; small changes in formulation may also affect inhaled mass, particle size distribution, and treatment time. The differences between nebulizer brands probably has a greater impact than differences in formulation (O'Riordan, 2002). There are several advantages to jet nebulization, including the fact that effective use requires only simple, tidal breathing, and that dose modification and dose compounding are possible. Disadvantages include the duration of treatment time and equipment size. Design modifications to the constant-output nebulizer have resulted in breath-enhanced, open-vent nebulizers such as the Pari LC Plus and the dosimetric AeroEclipse.

Jet Nebulizer :

This uses compressed gas to make an aerosol (tiny particles of medication in the air). Jet nebulizers are applicable for acute and domiciliary treatment of various respiratory diseases, pediatric and adult medical practices. These types of nebulizers required 2-10 L\min withdraw medication a capillary tube from the reservoir of the nebulizer. It may cause generate a wider range of particles which blasted into one or more baffles (to convert larger particles to smaller particles) out of suspension and return them to nebulizer.[52]

A jet nebulizer delivers aerosol continuously while the patient inhales and exhales. During thisprocess, as much as 30% to 40% of the nominal dose is trapped in the nebulizer, and more than 60% of the ED is wasted to the atmosphere during exhalation, translating to an availability of less than 10% of the nebulizer contents to the patient. The advantage of these nebulizers is their low cost and the production of aerosol with little effort on the part of the patient.

As a result of the high flow of gas through a jet nebulizer, solvent evaporates during nebulization, reducing the volume delivered and concentrating the aerosol. The rate of evaporation depends on the volume of fluid placed in the reservoir. With a reservoir fill volume of 3 to 5 mL, compared with the 2 mL in unit dose “nebules,” a greater total amount of drug is aerosolized and delivered to the patient, albeit for a longer treatment time. At the end of nebulization, when no further aerosol is produced, approximately 0.5 to 1.5 mL of concentrated solution is left in the nebulizer reservoir. This is referred to as thedead volume, representing drug that is unavailable to the patient. The greater the dead volume, the less the amount of drug available to the patient.

The driving pressure or the flow rate of compressed air applied to the jet affects aerosol output and particle size from jet nebulizers. The higher the pressure or flow rate, the greater the output over time in terms of total solution aerosolized, and the smaller the particle size. The time required to deliver the medication varies with the airflow rate used to drive the nebulizer. Typical treatment for traditional jet nebulizers ranges between 10 and 25 minutes. [53]

Fig. 4: Jet Nebulizer

Ultrasonic Nebulizer :
This makes an aerosol through high-frequency vibrations. The particles are larger than with a jet nebulizer. Ultrasonic nebulizers incorporate a piezoelectric crystal vibrating at high frequencies (1-3 MHz) to produce an aerosol. Ultrasonic nebulizers work on the principle that converts electrical energy to highfrequency vibrations using a transducer. This nebulizer generates vibrations, which are transferred to solution surface that would create waves, and thosewaves produce aerosol; we can say that these types of nebulizers are large volume nebulizers to deliver hypertonic saline for sputum inductions.

Fig. 5 Ultrasonic Nebuliz

Ultrasonic nebulizers incorporate a piezoelectric crystal, which is vibrated at a high frequency with sufficient intensity to create standing waves on the surface of the liquid overlying the crystal. Droplets are formed that remain within the nebulizer until they are swept out by a fan or the patient's inspiratory breath.[54]

Most current ultrasonic nebulizers operate at frequencies above 1 MHz, producing aerosols with MMADs between 2 and 12 µm, with an output that is two to three times higher than with most jet nebulizers.41 Heat is produced along with the aerosol, however, because the ultrasonic nebulizer solution is sonicated, and the temperature can rise 10° to 15° C over a 10-minute.

Mesh Nebulizer :
Mesh nebulizers contain apertures or aperture plate; when we applied force, it will generate aerosol. They force liquid medications through multiple apertures in a mesh or aperture plate to generate aerosol. Comparisons of mesh and ultrasonic nebulizers demonstrated similar drug delivery in simulated ventilator-dependent patients. Mesh nebulizers are more efficient than jet nebulizers and can provide higher drug doses to patients. The efficiency of mesh nebulizers is affected by various factors like size of the pore, aerosol chamber, and reservoir. [55]

Fig. 6 Mesh Nebulizer

Formulating Nebulizer Fluids :

Nebulizer fluids are formulated in water, occasionally with the addition of co-solvents such as Ethanol or propylene glycol and with the addition of surfactants for suspension formulations. Because hypo-osmotic and hyper-osmotic solutions may cause bronchoconstriction, as may high hydrogen ion concentrations, iso-osmotic solutions of PH greater than 5 are usually employed. Stabilizers such as antioxidants and preservatives may also be included, although these may also cause bronchospasm and for this reason sulfites in particular are generally avoided as antioxidant in such formulations. Whilst most nebulizer formulations are solutions, suspensions of micronized drug are also available for delivery from nebulizers. In general, suspensions are poorly delivered from ultrasonic nebulizers, whereas with jet nebulizer the efficiency of drug delivery increases as the size of suspended drug is decreased, with little or no release of particles when they exceed the droplet size of the nebulizer aerosol.[56]

Recent advances in formulation of pulmonary drugdelivery:

Effective inhalable medication are produced by drug formulation. Formulation stability is another challenge in producing pulmonary drug delivery. Formulation is responsi ble for keeping drug pharmacologically active, it must be efficiently delivered into the lungs, to the appropriate site of action and remain in the lungs until the desired pharmacological effect occurs. Depending upon disease condition effective formulation release drug, such as insulin for diabetes, must be deposited in the lung periphery to ensure maximum systemic bio availability. . Thus, a formulation that isretained in the lungs for the desired length of time and avoids the clearance mechanisms of the lung may be necessary. Research into dry powder formulations ha s been an area of growth in recent years and will be the focus of this section. Various techniques are used to made advances in dry powders formulation for inhalation involves either ,micronization via jet milling, precipitation, or spray drying using various exci pients, such as lipids and polymers,

or carrier systems like lactose. [57]

Lactose carrier systems:

Recent advances in inhalation therapy have sparked considerable biomedical interest in the development of novel particle technologies for respiratorydr ug formulation .The cohesive powders with poor flow arises if the surface electric forces associated with the particles exceed the gravitational force acting upon them '. To overcome this problem, the drug is blended with a coarse carrier system (30100 µm), such as lactose. At present,marketed dry powder inhalers contain eithe r the drug alone or mixed with a bulk carrier, usually lactose (α-lactose monohydrate). La ctose has an established safety profile and improves the flow properties of the formulation necessary for reproducible filling and promoting dosing accuracy.[58,59]

Advances in propellants used in pulmonary drug delivery devices:

Recently HFA propellants are a new alternative for CFC propellants in pulmonary drug delivery devices. Generally the higher vapor pressures of the HFAs (particularly 134a) have the potential to generate aerosols of higher quality than the "old" CFC formulations. However, except in a few notable instances, potential product improvements have been sacrificed for development costs and time as per market need. [60]

Recent trend in applications of pulmonary drug delivery:

New applications of pulmonary drug delivery

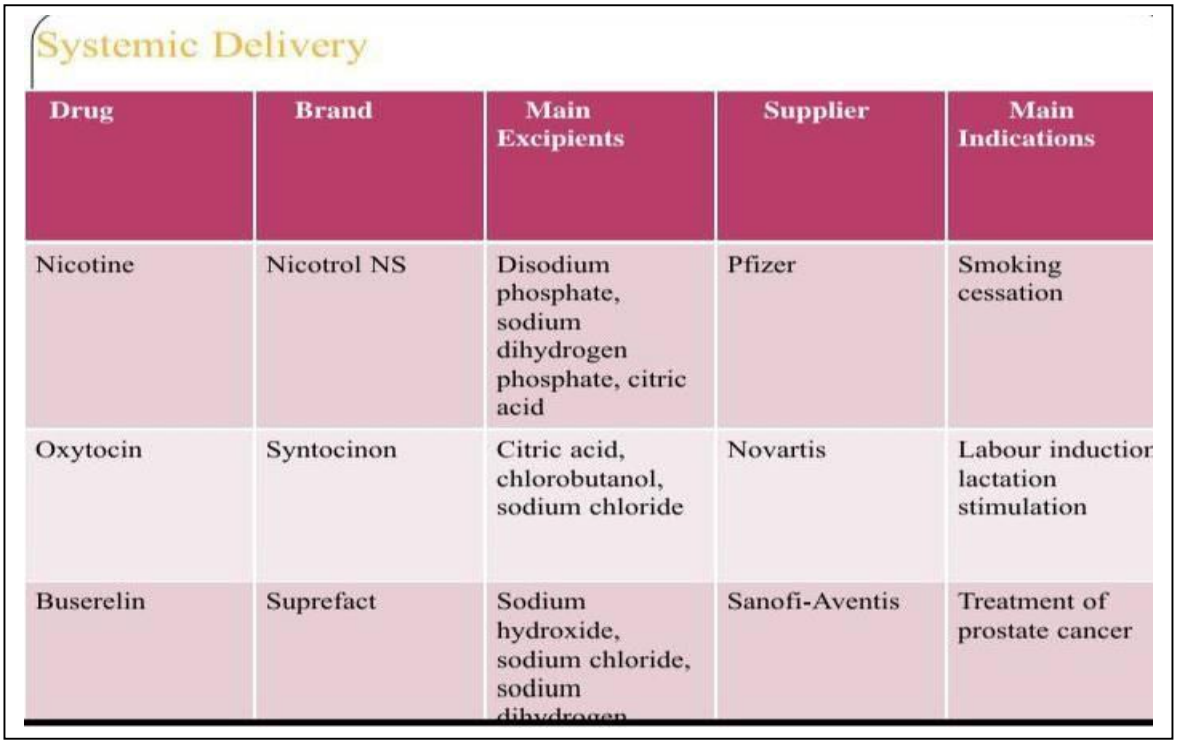
Apart from asthma and COPD recentaly pulmonary drug delivery is used for following indication

- Insulin by Aerosol
- Treatment of Migraine
- Nicotine Aerosol for Smoking Cessation
- Aerosols for Angina.
- Aerosol Vaccination.
- Alpha 1 Antitrypsin
- Aerosols in Transplantation
- Pulmonary arterial hypertension
- Acute Lung Injury
- Surfactant Aerosol
- Gene Therapy via Aerosol
- In Cancer chemotherapy
- Pentamidine Aerosol
- Gentamycin aerosol
- Ribavirin Aerosol
- Zanimivir with revolizer for swine flue
- Aerosols used in clinical investigations of disease
- Inhaled Drug Delivery for Tuberculosis Therapy
- Pulmonary delivery of lower molecular weight Heparin
- Controlled delivery of drugs to lungs
- Pulmonary delivery of drugs for bone disorders
- Pulmonary delivery of opioids as pain therapeutics

MARKETED DRUGS Local Delivery

Drug	Brand	Main Excipients	Supplier	Main Indications
Azelastine	Astelin	Benzalkonium chloride, edetate disodium,	Meda Pharmaceuticals	
Beclometasone	Beconase	Microcrystalline cellulose, carboxymethyl cellulose sodium, benzalkonium chloride	GlaxoSmithKline	
Levocabastine	Livostin	Benzalkonium chloride, edetate disodium, disodium phosphate	Jansen-Cilag	Management/ treatment of symptoms of seasonal and perennial rhinosinusitis
Olapatadine	Patanase	Benzalkonium chloride, dibasic sodium phosphate, edetate disodium	Alcon Laboratories	
Sodium cromoglicate	Nasalcrom	Benzalkonium chloride, edetate disodium	Sanofi-Aventis	
Mupirocin	Bactroban	Paraffin and a mixture of glycerin esters (Softisan 649)	GlaxoSmithKline	Eradication of nasal staphylococci
Triamcinolone acetonide	Nasacort	Microcrystalline cellulose, CMC sodium, polysorbate 80	Sanofi Aventis	

Table. 1



Systemic Delivery

Drug	Brand	Main Excipients	Supplier	Main Indications
Nicotine	Nicotrol NS	Disodium phosphate, sodium dihydrogen phosphate, citric acid	Pfizer	Smoking cessation
Oxytocin	Syntocinon	Citric acid, chlorobutanol, sodium chloride	Novartis	Labour induction lactation stimulation
Buserelin	Suprefact	Sodium hydroxide, sodium chloride, sodium dihydrogen	Sanofi-Aventis	Treatment of prostate cancer
Salmon calcitonin	Miacalcin	Sodium chloride, benzalkonium chloride, hydrochloric acid	Novartis	Treatment of postmenopausal osteoporosis
Sumatriptan	Imigran	Potassium dihydrogen cluster headaches phosphate, dibasic sodium phosphate anhydrou	GlaxoSmithKline	Treatment of migraine and Sumatriptan Imigran Potassium dihydrogen cluster headaches
Estradiol	Aerodiol	Methylbetadex, sodium chloride	Servier laboratories	Hormone replacement therapy

Table. 2

Fig. 7

PATENTED DRUGS FOR NASAL DELIVERY

Cited Patent	Filing date	Issue date	Original Assignee	Title
US3874380	May 28, 1974	1975		Dual nozzle Intranasal drug delivery
US4895559	Oct 11, 1988	Jan 23, 1990		Nasal pack syringe
US6610271	Feb 21,2001	Dec15,2002	Intranasal Tech.Inc.(ITI)	The lorazepam nasal spray
US4767416	Dec 1, 1986	Aug 30, 1988	Johnson & Johnson Patient Care, Inc.	Spray nozzle for syringe
US5064122	Aug 10, 1990	Nov 12, 1991	Toko Yakuhin KogyoKabushii Kaisha	Disposable nozzle adapter for intranasal spray containers
US5601077	Aug 7, 1991	Feb 11, 1997	Becton, Dickinson and Company	Nasal syringe sprayer with removable dose limiting structure
US8118780	Aug 23, 2004	Feb 21, 2012	Liebel-Flarsheim Company	Hydraulic remote for a medical fluid injecto

Table. 3

CONCLUSION :

There have been a number of significant achievements in technologies to express and deliver drugs by pulmonary route. Improvements in the aerosol's velocity, particle size, or moment of release have been achieved. But drug administration via pulmonary route is a difficult and complex process, comprising not only aspects from technology but also from physiology, clinical application or patient use.. This shows that for different diseases or even for each individual drug, the required conditions for optimal administration differ substantially and that a perfect inhaler (plat-form) suitable for all types of drugs and diseases is a fiction.

Advantages of DPIs such simple and cheap devices, their robustness, portability, easy of use as but systems that can disperse larger amounts of powder (upto 50 mg) within one breath is Major challenges that remain for dry powder inhalation. To maintain stability of powder formulation is another challenge associated with DPI.

As compare to classic nebulizers or MDIs the new liquid inhalation systems are certainly better option but many liquid aerosol generation systems require an external energy source and contain complex electronics. Due to this there is increase failure risk and reduce the freedom of the patient. Further relevant aspects are the dependency of the device's performance on the physicochemical characteristics of the liquid formulation. Advancements in pulmonary drug delivery should not only focus on only one technological aspect, but also need to focus on other aspects. And there is a wide scope for the researchers to investigate and demonstrate good agreement between in-vitro, ex-vivo, and in-vivo tests used to predict drug absorption from the intact animal and, which may therefore present a solid basis for future advancement in nanomedicine strategies for pulmonary drug delivery.

Considering the wide unfold interest in nasal drug delivery and also the potential advantages of intranasal administration, it's expected that novel nasal merchandise can still reach the market. They'll embrace not solely medicine for acute and long run diseases, however conjointly novel nasal vaccines with higher native or general protection against infections.

Within the treatment of preventative metabolism diseases, respiratory organ delivery will minimize general facet effects, offer fast response and minimize the desired dose since the drug is delivered on to the conducting zone of the lungs. Within the treatment of preventative metabolism diseases, respiratory organ delivery will minimize general facet effects, offer fast response and minimize the desired dose since the drug is delivered on to the conducting zoneof the lungs.

REFERENCES:

1. Ansel HC, Popovich NG and Allen LV. Pharmaceutical dosage forms and drug delivery systems. Lea & Febiger, Philadelphia; *1990.*
2. Chien YW and Banga AK. Iontophoretic (transdermal) delivery of drugs: overview of historical development. Journal of Pharmaceutical Sciences.**78 (**5**);** 353-354, *1989*
3. Aulton. M. E. Pharmaceutics; The science of dosage form design, second edition, Churchill Livingston, Harcourt publishers-*2002*.
4. Jain.N.K, Controlled and novel drug delivery, first edition, CBS publishers and distributors, New Delhi. *1997*.
5. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastro-retentive dosage forms. J Control Release**; 90:** 143-62, *2003*
6. Thorat and Santosh: Formulation and product development of nebulizer inhaler: An overview. Inc Pharmaceut Sci Res*;* **5:** 30-35, *2016*
7. Perkins W: Performance of PARI eFlow® To the Editor. Journal of Aerosol Medicine And Pulmonary Drug Delivery*;* **23:** 113-14, *2010*
8. Shubham Prajapati, Sanjay Saha, C. Dilip Kumar: Nebulized Drug delivery:An overview
9. ,International Journal of Pharmaceutical Sciences and Research*;* **10(8):** 3575-3582, *2019*
10. Aijaz A.Sheikh, subhash V.Deshmane, Kailash R.Biyani: A Text Book of Novel Drug
11. ChienY.W., Su K.S.E., Chang S.F., Nasal Systemic Drug Delivery, Ch. Marcel-Dekker, New York, 1: 1-77.
12. Illum.L, Jorgensen. H, Bisgard. Hand Rossing. N, Bioadhesivemicrospheres as a potential nasal drug delivery system. Int. J. of Pharmaceutics, 189-199.
13. Akwete, A.L., Gupta, P.K., Eds.; Niven, delivery of biotherapeutics by inhalation aerosol. In Inhalation Delivery of Therapeutic Peptides and Proteins; Marcel Dekker, Inc., NewYork*;* 151–231, *1997*
14. Patton, J.S. Mechanisms of macromolecule absorption by the lungs: Adv. Drug DeliveryRev*;* 3–36, *1996*np,https://en.m.wikipedia.org/wiki/Lung)
15. Aulton ME. Pharmaceutics – The Science of Dosage form Design. New York: Churchill Livingston*;* 494, *2002*
16. Johnson NJ, Hanson LR, Frey WH. Trigeminal pathways deliver a low molecular weight drug

from the nose to the brain and orofacial structures. Mol Pharm*;* **7:** 884-93, *2010*
17. Svensson S, Olin AC, Hellgren J. Increased net water loss by oral compared to nasalexpiration in healthy subjects. Rhinology*;* **44:** 74-7, *2006*
18. Rudman KL, O'Brien EK, Leopold DA. Radiographic distribution of drops and sprays within the sinonasal cavities. Am J Rhinol Allergy*;* **25:** 94-7, *2011*
19. Hammarlund-Udenaes M, de Lange E, Thorne RG. Pharmacokinetic concepts in brain drug delivery in drug delivery to the brain. In: Physiological Concepts, Methodologies and Approaches. New York: Springer*;* 127-61, *2014*
20. Harmon BT, Aly AE, Padegimas L, Sesenoglu-Laird O, Cooper MJ, Waszczak BL, et al.
21. Intranasal administration of plasmid DNA nanoparticles yields successful transfection and expression of a reporter protein in rat brain. Gene Ther*;* **21:** 514-21, *2014*
22. Kaye RS, Purewal TS, Alpar OH. Development and testing of particulate formulations for the nasal delivery of antibodies. J Control Release*;* **135:** 127-35, *2009*
23. Hardy JG, Lee SW, Wilson CG. Intranasal drug delivery by spray and drops. J PharmPharmacol*;* **37:** 294-7, *1985*
24. Haque S, Md S, Sahni JK, Ali J, Baboota S. Development and evaluation of brain targeted intranasal alginate nanoparticles for treatment of depression. J Psychiatr Res*;* **48:** 1-2, *2014*
25. Watson J, Wright S, Lucas A, Clarke KL, Viggers J, Cheetham S, et al. Receptoroccupancy and brain free fraction. Drug Metab Dispos*;* **37:** 753-60, *2009*
26. Dinanath G, Padmini K, Dipak M, Namdeo J. Development of particulate mucoadhesive gel for intranasal delivery. Asian J Pharm Clin Res*;* **10:** 222, *2017*
27. Kritika S, Bhupen K, Banasmita K. Development and characterizationof mucoadhesive microsphere-loaded intranasal gel of venlafaxine hydrochloride. Asian J Pharm Clin Res *;* **9:**139-44, *2016*
28. Giuliani A, Balducci AG, Zironi E, Colombo G, Bortolotti F, Lorenzini L, et al. In vivo nose-to-brain delivery of the hydrophilic antiviral ribavirin by microparticle agglomerates. Drug Deliv*;* **25:** 376-87, *2018*
29. Ravikumar R, Balan R, Ganesan N, Thiruvengadam D. Recent modalities in drug delivery via inhalation therapy – An advanced treatment strategy for pulmonary carcinoma. Int J Pharm Pharm Sci*;* **7:** 8-21, *2015*
30. Mosab A. Approaches to achieve an oral controlled release drug delivery system using polymers: A recent review. Int J Pharm Pharm Sci*;* **7:** 16-21, *2025*
31. Özer AY. The importance of intranasal route for application of drugs and nasal drug delivery systems. Pharm JTPA*;* **30:** 136-47, *1990*
32. Hughes B.L., Allen D.L., Dorato M.A., Wolff R.K., Effect of devices on nasal deposition and mucociliary clear-ance in rhesus monkeys, Aerosol Sci. Technol*;* **18:** 241–249, *1993*
33. Knoch, M. & Finlay, W. H. "Nebulizer Technologies", Chapter 71 in Modified-Release Drug Delivery Technology, ed. Rathbone/Hadgraft/Roberts, Marcel Dekker*;*849-856, *2002*
34. A J. Hickey, Pharmaceutical Inhalation Aerosol Technology, Marcel Dekker, NY, **2:**558
35. Mygind N., Vesterhauge S., Aerosol distribution in the nose, Rhinology*;* **16:** 79–88, *1978*
36. Hughes B.L., Allen D.L., Dorato M.A., Wolff R.K., Effect of devices on nasal deposition and mucociliary clear-ance in rhesus monkeys, Aerosol Sci. Technol*;* **18:** 241–249, *1993*
37. Alagusundaram M., Deepthi N., Ramkanth S., Angala-parameswari S., Mohamed Saleem T.S., Gnanapra-kash K.. Thiruvengadarajan V. S, Madhusudhana Chetty C, Dry Powder Inhalers - An Overview ,Int. J. Res. Pharm. Sci**; 1(1):** 34-42, *2010*
38. Finlay, Warren H. The mechanics of inhaled pharmaceutical aerosols: an introduction.Boston: Academic Press*;* **ISBN** 0-12-256971-7, *2001*
39. Newhouse M.T., Advantages of pressured canister me-tered dose inhalers, J. Aerosol Med*;* **4:** 139–150, *1991*
40. Coro DC, Liu JC, Chien YW. Characterization of the barrier properties of mucosal membranes. J Pharm Sci*;* **79:** 202-206, *1990*
41. Bawarshi RN, Hussain A, Crooks PA. Nasal absorption of 17a- ethinyloestradiol in the rat. J Pharm Pharmacol*;* **41:** 214-215, *1989*
42. Lee V.H.L., Enzymatic barriers to peptide and protein absorption, CRC Crit. Rev. Ther. Drug Carrier Syst*;* **5:** 69–97, *1988*
43. Inagaki M, Sakakura Y, Itoh H, Ukai K, Miyoshi Y. Ma-cromolecu- lar permeability of the tight junction of human nasal mucosa. Rhinology*;* **23:** 213-221, *1985*
44. Franz, M.R., Oth, M.P., U.S patent*;* 5232704, *1993*
45. Jorissen, M., AND Bessems, A., Eur. Arch. Otorhinolar ngol*;* **252:** 451-454, *1995*
46. Arora P, Sharma S, Garg S. Permeability issues in nasal drug deliv- ery. Drug Discov Today*;* **7(18):** 967-975, *2002*
47. Satish BB, adhikrao VY, Amelia MA, Rajkumar

M, Bio availability of intranasal drug delivery system, Asian J of Pharmaceutics*;* 201-15, *2008*
48. Ohwaki K, Ando H, Watanabe S, Miyake Y, Effects of dose, pH and osmolarity on nasal absorption of se-cretin in rats, J Pharm Sci*;* **74:** 550-2, *1985*
49. Gizurarson S, Bechgaard E. Intranasal administration of insulin to humans. Diabetes ResClin Prac*;* **12:** 71-84, *1991*
50. Rohan Bhavane, Efstathios Karathanasis, Ananth V. Annapragada, "Agglomerated vesicle technology": a new class of particles for controlled and modulated pulmonary drug delivery, Journal of Controlled Release*;* 15– 28, *2003*
51. P.P.H. Le Brun, A.H. de Boer, H.G.M. Heinemann and H.W. frijlink "A review of the technical aspects of drug nebulization", Pharm World Sci*;* **22(3):** 75-81, *2000*
52. CheinYW, KSE.Su and S.F.Chang. Nasal systemic drug delivery. Dekker*;* **1-77**, *1989*
53. Hicke AJ. Pharmaceutical Inhalation Aerosol Technology. 2nd ed. New York: Marcel Dekker, Inc.; *2004.*
54. Sharma PK, Chaudhari P, Kolsure P, Ajab A, Varia N. Recenttrends in nasal drug delivery system - An overview. ARPB*;* **5:**4, *2006*
55. Ramadan HH, Sanclement JA, Thomas JG. Chronic rhinosinusitis and biofilms. Otolaryngol Head Neck Surg **132:**414-7, *2005*
56. Mahita B, Vinod K. A clinic opathological study of allergic rhinitis. Asian J Pharm Clin Res*;***10:**186-91, *2017*
57. Shanu T, Nitin S, Sharma PK. A review on application of natural bio adhesive polysaccharides for intranasal drug delivery. Int J A.PS.BMS*;* **1:**80-94, *2012*
58. Zaheer A, Swamy S. Mucoadhesive polymers: Drug carriers for improved nasal drug delivery. Indian J Novel Drug Deliv*;* **4:**2-16, *2012*
59. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery Novel Carrier System. 1st ed.New Delhi: CBS Publishers and Distributors; p. **173,** *2006*
60. Mahalaxmi R, Kumar DS, Shirwaikar A. preparation of mucoadhesive microsphere for nasal delivery by spray drying. Indian J Pharm Sci; **69:**651-7, *2007*
61. Pires A, Fortuna A, Alves G, FalcÃ£o A. Intranasal drug delivery: How, why and what for? JPharm Pharm Sci; **12:**288-311, *2009*