A Review Article on Pulmonary Drug Delivery System

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Abstract*— In present study authors review all aspects of pulmonary drug delivery system; including need of drug delivery, different approaches for drug delivery and recent advancement in pulmonary drug delivery system. Apart from various formulations, different delivery devices such as metered dose inhalers (MDI), dry powder inhalers (DPI), nebulizers, aerosolizers, etc. have also improved drug targeting efficacy and reduced dose size in a more efficient manner. Many drug delivery devices for nasal application of liquid, semisolid and solid formulation are investigated to deliver the drugs to the treat most crisis CNS diseases (i.e., Parkinson's disease, Alzheimer's disease) because it requires rapid and/or specific targeting of drugs to the brain. This review contains mainly the tabulated description of different categories of drugs and devices recently available in the market which makes it easily accessible for the researchers. It can be concluded from whole study that different pulmonary delivery system possesses certain specificity for dosage formulations and serves as an important tool to deliver drugs to the target site.This review sets out to discuss some factors affecting nasal absorption, bioavailability barriers, strategies to improve nasal absorption, new developments in nasal dosage form design and applications of nasal drug delivery system.

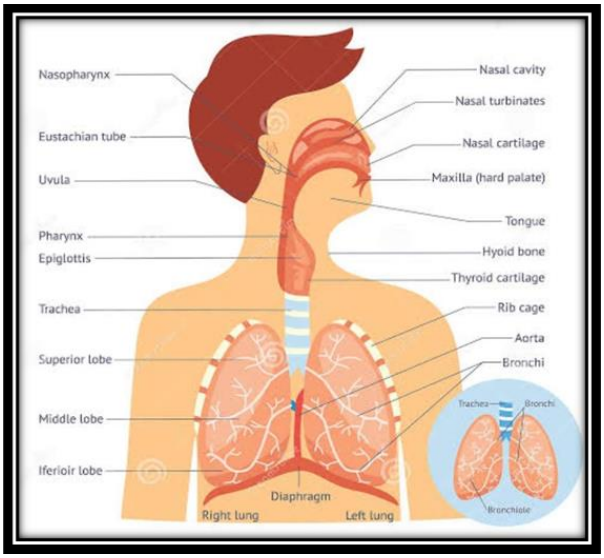
Indexed Terms-- pulmonary drug delivery, nasal drug delivery, targeted drug delivery, delivery devices, formulation approaches, strategies.

I. INTRODUCTION

Respiratory system:

- The respiratory tract is one of the oldest routes used for the administration of drugs.
- 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.

Fig.no 1: human respiratory system



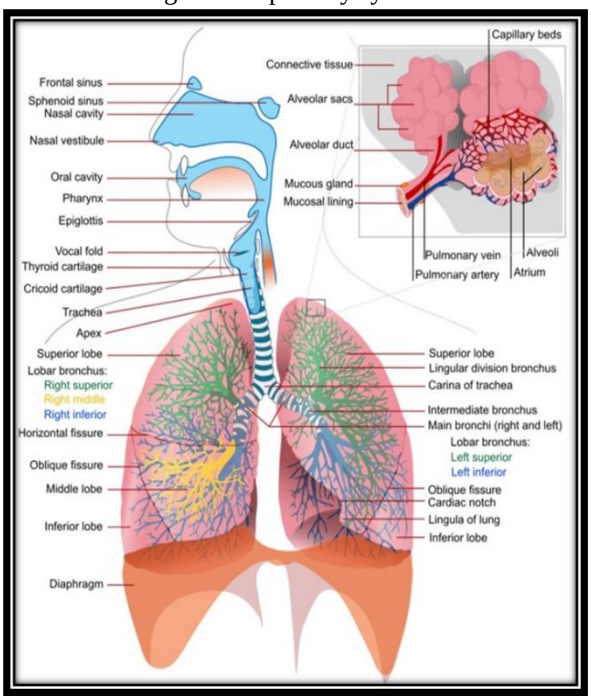
II. ANATOMY AND PHYSIOLOGY OF PULMONARY SYSTEM

Lungs

- The human respiratory system is a complicated organ system of very close structure-function relationships.
- The system consisted of two regions:
- The conducting airway
- 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.

fig.no:2 respiratory system



III. BARRIERS OF PULMONARY DRUG DELIVERY SYSTEM

Table no:1 barriers

Barrier parameters	examples	Description
Less bioavailability	Polar drugs such as proteins and peptides	Less permeability of membrane lowers the bioavailability of large molecular weight compounds
Enzymatic degradation	Natural peptides having molecular weight less than 3,000 D such as somatostatin, VIP, and glucagon.	Various metabolic enzymes appers both extracellulary and intracellularly in secretions, bound to membrane, released by specific cells such as macrophages, lymphocytes, neutrophils and mast cells
Lung clearance mechanisms	Bacteria, macrophages	Deposited particles in the conducting airways exhibit smaller lung residence time and hence get removed rapidly by mucociliary and aleovelar clearance.
Limitation of conventional devices	Venture nebulizers deposit more amount of salbutamol to the lungs than conventional disposable jet nebulizers	Only 10-40% of the drug gets deposited to the target sites by conventional devices which results in wastage of rest of the drug

IV. MEANS OF DRUG DELIVERY SYSTEM

AEROSOLS

- Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium.
- The drugs, delivery by aerosols are deposited in the airways by: gravitational sedimentation, inertial impaction, and diffusion.

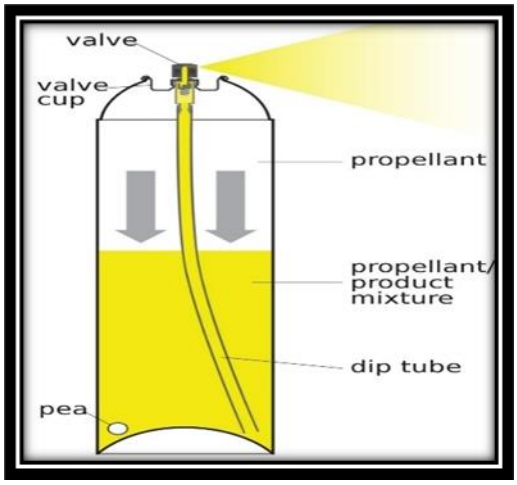


Fig.no: 3 aerosol

- 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.

V. DEVICES

A. 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:

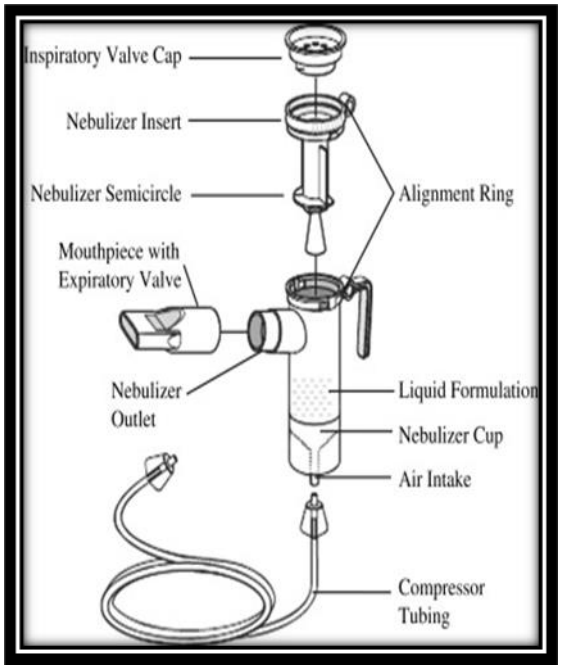
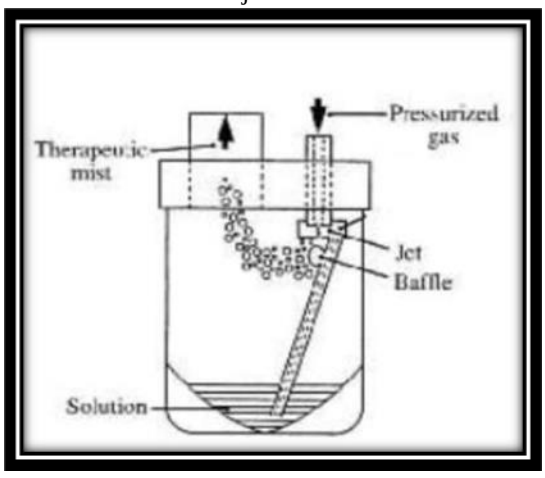


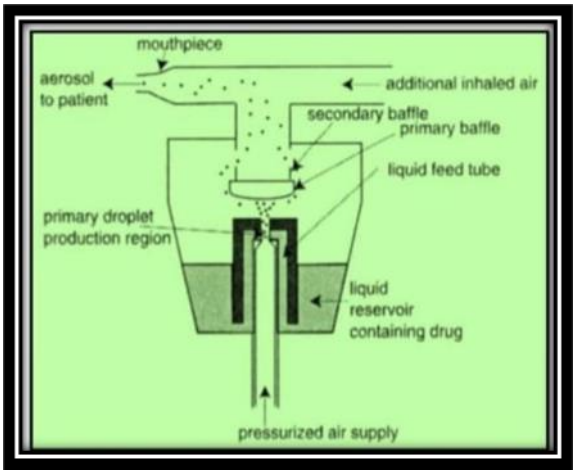
Fig.no: 4 nebulizer

1. Air jet

MECHANISM: - The jet nebulizer functions by the Bernoulli principle by which compressed gas (air or oxygen) passes through a narrow orifice, creating an area of low pressure at the outlet of the adjacent liquid feed tube. This results in the drug solution being drawn up from the fluid reservoir and shattering into droplets in the gas stream.

FIG:5 jet nebulizer





2. Ultrasonic nebulizer

MECHANISM: - The ultrasonic nebulizer uses a piezoelectric crystal, vibrating at a high frequency (usually 1-3 MHz), to generate a fountain of liquid in the nebulizer chamber; the higher the frequency, the smaller the droplets produced.

It is an electric nebulizer.

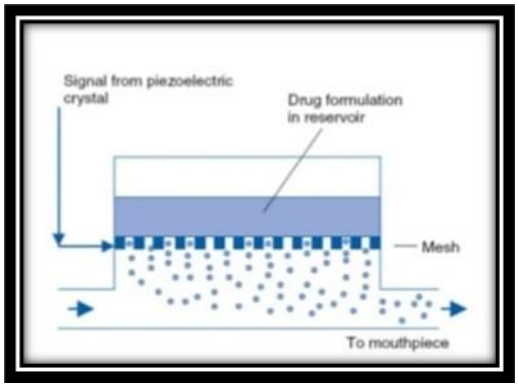
Working principle: - piezoelectric effect

Ultrahigh frequency current
↓
Piezoelectric transducer
↓
Ultrahigh frequency vibration
↓
Disk vibration
↓
Couplant (water bath)

DRUGS FOR NEBULIZATION

Distilled water or normal saline
Mucolytics : mesna, acetylcysteine
Beta 2 agonists: salbutamol, terbutalin, fometerol,salmeterol
Antimuscarinic: ipratropium bromide
Steroids: budesonide

Antibiotics



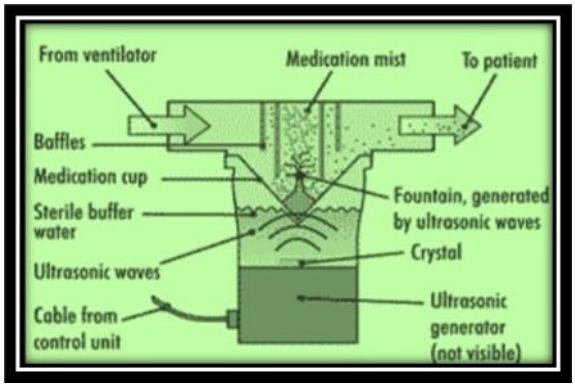
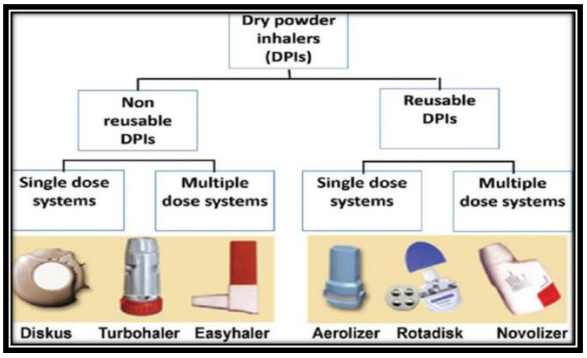


Fig.no: 6 Ultrasonic nebulizer

FIG:7 TYPES OF DRY POWDERS



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.

Disadvantage

- 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.

A. 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.

B. Multidose Devices

This device is truly a metered-dose powder delivery system. The drugIs contained within a storage reservoir and can be dispensed into theDosing chamber by a simple back and forth twisting action on the baseOf the unit.

TABLE:2 MARKETED DRUG DRY POWDER INHALERS

Active ingredient	country	brand	Manufacturer
Terbutaline 0.25mg	UK	bricanyl	Astrazeneca
Fluticasone propionate	United kingdom	Glaxosmith kline	Glaxosmith kline
Salbutamol	india	Salbutamol dry powder capsules	Cipla limited
Xinafoate	UK	Seretide evohaler	Glaxosmith kline
Beclometasone dipropionate 250mcg	India	Beclofort e	Cipla limited
Ipratropium bromide 20mcg	italy	ATEM	Chiesi farmaceutici

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.

FIG:8 METERED DOSE INHALER

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.

TABLE:3 MARKETED DRUG METERED DRUG INHALER

Active ingredients	brand	country	Manufacturer
Formoterol fumurate 12mcg		india	Ultratech
Fluticasone 50g	Flixoide	New zealand	Glaxosmith kline
Levalbutrol HCL	Xopenex	U.S.A	3M pharmaceuticals
Albuterol	Ventolin	India	Glaxosmith kline
Salbutamol pressurized inhalation (100g)	asthalin	India	cipla

VI. FORMULATION APPROACHES

a) Solid dispersion

SD is defined as a dispersion of one or more drugs in an inert carrier or matrix in the solid state, produced from a solution by the fusion, the solvent, or the fusion/solvent method 1971.

A given SD is classified according to whether the drug is dispersed in the carrier at a molecular level, as a solid solution, or a glass solution (drug in a glassy carrier), or at a nonmolecular level, as a eutectic mixture (crystalline drug in crystalline carrier), as amorphous precipitation in a crystalline carrier (amorphous drug in crystalline carrier), as a glass suspension (amorpheus/crystalline drug as a fine precipitate in a glassy carrier), or a combination of the preceding forms.

b) Reduction of size to Micro-/Nanoparticles

- Particle size reduction can be performed by top-down methods, such as milling or high-pressure homogenization (HPH), or by bottom-up technologies such as precipitation/crystallization methods, as well as a combination thereof Micronization results in the reduction of particles to a size range of 2-5 µm.
- Particle size reduction increases the specific surface area (area per unit of mass) und, therefore, the drug dissolution rate, as described by the Noyes-Whitney equation.

c) Nanoclusters

- "Nanoclusters" are micron or submicron-sized agglomerates of drug nanoparticles manufactured using an appropriate surfactant(s) and flocculating agents.
- Dry powders for inhalation are then obtained by employing a drying technique such as lyophilization.
- Nanoclusters were then lyophilized to produce dry powder with good aerodynamic performances (MMAD between 1.22 0.04 and 1603pm).

d) Liposomes

- Liposomal Nasal solutions can be formulated as drug alone or in combination with pharmaceutically acceptable eexcipients
- 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.

e) Nanoparticles

- Nanoparticles are solid colloidal particles with diameter raging from 1-1000 nm. They consist of macromolecular materials which are therapeutically active and can also be used as adjuvant in vaccines in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached.

f) 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.

g) Micelles

- A successful drug carrier system needs to demonstrate optimal drug loading and release : properties, long shelf-life and low toxicity.
- Micelle contains drugs entrapped in the core and transported at concentrations even greater than their intrinsic water solubility. A hydrophilic shell can form around the micelle, effectively protecting the contents.
- Colloidal systems, such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticles dispersions - consisting of small particles of 10-400 mm diameter showed as great promising carriers in pulmonary drug delivery systems.

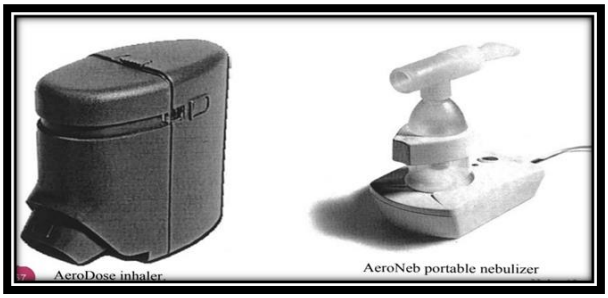
h) NasalGels

- High-viscosity thickened solutions or suspensions.
- Reduction of irritation by using emollient excipients.

VII. RECENT ADVANCES

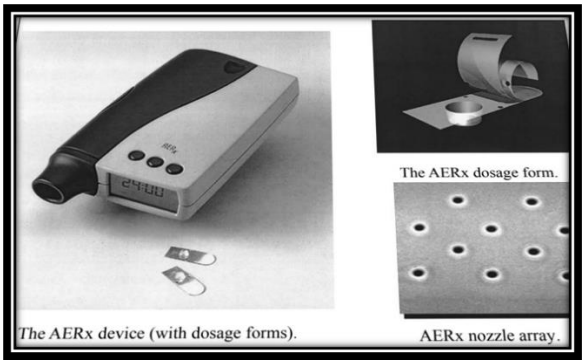
i. The Aerogen Pulmonary Delivery Technology

- 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.
- AeroGentechnologies 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.



ii. The AERx Pulmonary Drug Delivery System

- 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.



iii. The Spiros Inhaler Technology

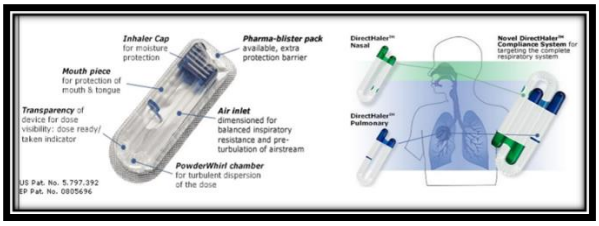
- The inhaler has an impeller that is actuated, when the patient inhales, to disperse and deliver the powder aerosol for inhalation. The core technology was initially developed to overcome the patient coordination required for metered-dose inhalers and the inspiratory effort required for first-generation 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.

iv. The DirectHaler™ Pulmonary device platform

- DirectHalerTM Pulmonary is an innovative and new device for dry powder Each pre-metered, pre-filled pulmonary dose has its own DirectHalerTM Pulmonary device.

- The device is hygienically disposable and is made of only 0,6 grammes of Polypropylene. DirectHalerTM 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 Powder Whirl chamber, before removing the cap and delivering the dose.
- Sensitive powders
- Deep lung delivery
- High drug payloads
- New types of combination dosing

v. Development Dr Reddy's launches "Dose Counter Inhalers' in India Friday, April 16, 2010

- 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 change the inhaler.

VIII. STRATEGIES TO IMPROVE NASAL ABSORPTION

I. Permeation enhancer

TABLE:4 PERMEATION ENHNACERS

Types of compound	Mechanism of action	examples
Bile salts and derivates	Disrupt membrane, open tight junctions, enzymes inhibition, mucolytic activity	Sodium deoxycholate, sodium glycolate, sodium taurodihydrofusidate
Chelating agents	Open tight junction	Ethylenediaminetetracetic acid (EDTA), salicylates
Liquids	Reduce nasal clearance, open tight junction	Chitosan, carbapol
Fatty acids	Disrupt membranes	Sodium caprylate, sodium laurate, phospholipids
Surfactants	Disrupt membranes	SLS, saponin, polyoyethylene-9-lauryl ether
Bioadhesive materials powder	Reduce nasal clearance, open tight junctions	Carbapol, starch microspheres, chitosan

II. Prodrug approach

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

III. Structural modification

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

IV. Particulate drug delivery
Microspheres, nanoparticles and liposomes
Nasal enzyme inhibitors
peptidases and proteases tripsin, aprotinin, borovaline, amastatin, bestatin and boroleucin inhibitor.

TABLE: 5 CHARACTERISTICS OF VARIOUS POLYMERS EMPLOYED IN INTRA NASAL DELIVERY

POLYMER	CHARACTERSTIC
Cellulose derivative: soluble: hydroxypropylmethyl cellulose, carboxymethyl cellulose. Insoluble: ethylcellulose microcrystalline cellulose.	Prolong the residence time of drug in nasal cavity. Sustain the release of drug due to high velocity. Act as absorption enhancer. Effectively increase intranasal bioavailability
Polyacrylates: Carbomers. Polycarbophils	Excellent mucoadhesive and gel forming capability, capable of attaching to mucosal surface hence ensure intimate contact between the formulation and membrane surface
Starch: Maize starch Degradable starch microsphere.	Effectively improve absorption of both small hydrophobic and hydrophilic macromolecular drugs mostly used in micro particulate nasal delivery system
Chitosan	Insoluble of neutral and alkaline PH. It can form water soluble salts with inorganic and organic acids low caused biodegradable and bio compatible

CONCLUSION

Pulmonary:- 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.

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