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Review article

INTRA NASAL DRUG DELIVERY: THE FASTEST ROUTE TO CROSS THE BLOOD BRAIN BARRIER AND TARGET THE BRAIN: A REVIEW

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ABSTRACT: Intranasal route has potential to target brain and possesses several advantages over parenteral and oral routes in treating CNS disorders such as stroke, Parkinson's disease, multiple sclerosis, Alzheimer's disease, hormone replacement, epilepsy and psychiatric disorders. Many drugs have been developed but they failed in showing the concentration required for action. Therefore various strategies have been proposed to improve the delivery of drug to the tissue. Research has established that the nasal route is a safe, non-invasive, essentially painless and particularly suited for children and acceptable alternative to the parenteral administration of drugs. Nose-to-brain drug delivery of drugs is advantageous as it requires low dose of drug, avoids first pass effect and also it is fast in action and suitable for the drugs that degrades in gastrointestinal tract and improve the patient compliance to use an alternative therapy to conventional dosage form. Nose to brain drug delivery the drug directly enters into the brain through nasal route and has been potentially explored as an alternative route for administration of vaccines and bio molecules such as proteins, peptides and non peptide drugs. The effect is often reached within 5 min for smaller drug molecules. This review intends to detail the recent advances in the field of brain-targeting, rational drug design, approach, factors affecting nasal absorption, devices and formulations. Illustrate the complexity of the problems those have to be overcome for successful brain targeting.

Keywords: Intranasal drug delivery, Barriers (BBB, CSF), Nasal Formulation and devices.

INTRODUCTION:

Drug delivery systems (DDS) are an important component of drug development and therapeutics. It has useful information for pharmaceutical physicians and scientists in many disciplines involved in developing DDS such as chemical engineering, protein engineering, gene therapy, and so on. Drugs may be introduced into the human body by various anatomical routes. They may be intended for systemic effects or targeted to various organs and diseases. The choice of the route of administration depends on the disease, the effect desired, and the product available. Drugs may be administered directly to the organ affected by disease or given systemically and targeted to the diseased organ (Choi et.al. 1998). This review is generally focused on intranasal drug delivery system.

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A classification of various anatomical routes for systemic drug delivery

- **Gastrointestinal system:** Oral, Rectal
- **Intra-osseous infusion**
- **Parenteral:** Subcutaneous injection, Intramuscular injection, Intravenous injection,
- **Intra-arterial injection**
- **Pulmonary:** Drug delivery by inhalation
- **Tran mucosal:** Buccal and through mucosa lining the rest of gastrointestinal tract.
- **Intranasal**
- **Transdermal drug delivery**

Intranasal drug delivery: Nose-to-brain drug targeting is attracting attention of many researchers to develop efficient drug delivery systems to target brain using novel drug delivery systems (Kamble et.al. 2012)**.** Nasal route is an administration route for targeting the central nervous system; the brain. Nasal therapy also called 'Nasya karma' has been recognized form of treatment in the Ayurvedic system of Indian medicines (Appasaheb et.al. 2013). Over the last years, due to the understanding of the positive attributes and appropriate characteristics of the nasal cavity, intranasal route has been increasingly considered for drug delivery when developing new chemical entities or improving the therapeutic profile of existing drugs. Nasal route is the route of choice for rapid mass immunization in developing countries (Jadhav et.al. 2014)**.** Intranasal route is considered for drugs that are ineffective orally, are used chronically require small doses and where rapid entry into the circulation is desired. Nose to brain drug delivery the drug directly enters into the brain (Parvathi 2012)**.** In contrast, this is particularly important to treat or control chronic medical conditions. Nose-to-brain drug delivery of drugs is advantageous as it requires low dose of drug, avoids first pass effect and also it is fast in action and suitable for the drugs that degrade in gastrointestinal tract (Jadhav et.al. 2014). Improvement of the patient compliance to use an alternative therapy to conventional dosage form (Desai et.al. 2011). Nasal route is easily accessible, convenient, and a reliable with a porous endothelial membrane and a highly vascularised epithelium that provides a rapid absorption of compounds into the systemic circulation (Appasaheb et.al. 2013). It was reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles and the absorption of hydrophilic drugs can be increased by means of absorption enhancers. The range of Drugs from small chemicals to large macromolecules including peptide/protein therapeutics, hormones, and vaccines, are being delivered through the nasal cavity (Choi et.al. 1998).The nasal delivery seems to be a favorable 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 (CIllum 2002, Graff et.al. 2005). Buserelin, desmopressin, calcitonin, insulin, and luteinizing hormone releasing hormone, growth hormone and adreno-corticotrophic hormone are some of the peptides that have been successfully administered through the nasal route. Apart from these, steroids (corticosteroids, estradiol, progesterone, testosterone, and so on) antihypertensives (nifedipine, nitroglycerine, propranolol, hydralazine, and so on), analgesics (buprenorphine), antibiotics and antiviral have been shown to produce considerable systemic effects when administered via the nasal cavity (Lipworth et.al. 2000, Wiseman 2001)**.**

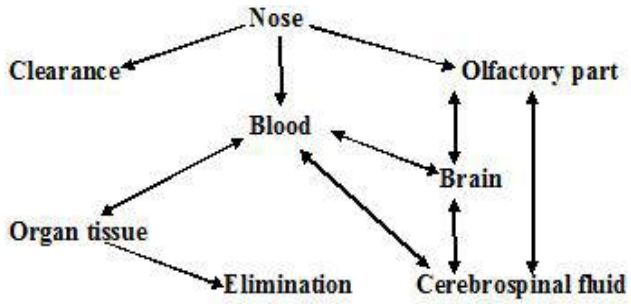

Fig 1: Different pathways for reaching the brain after intranasal administration

Advantages of intranasal drug delivery system (Appasaheb et.al. 2013)

- Via highly vascularised mucosa the absorption of drug is fast.
- By absorption enhancers, increase the bioavailability of large drug molecules.
- On the long term therapy route for the patient is expedient
- Drug directly entered in brain through the nasal route, are more effective.
- Fewer side effects.
- Intranasal drug delivery enables dose reduction.

- Lower risk of over dose (below 25 mg per dose.)
- Nasal bioavailability of small drug molecules better than other route.
- No Degradation effect in GIT.
- No hepatic first pass metabolism.
- Non invasive and easy for administration.
- Quicker onset of pharmacological activity.
- Rapid attainment of therapeutic blood levels.
- Rapidly cross the BBB, Self-administration, patient comfort, and patient compliance.

Disadvantages of intranasal drug delivery (Parvathi 2012, Bhowmik et.al 2010)

- Adversely affected by pathological conditions.
- "Budesonide, Azilactine" may produce irritation in nasal mucosa.
- Changes of immunologic reactions.
- Frequent use of this route leads to mucosal damage.
- Increasing the molecular weight decreasing the drug delivery because the delivery volume in nasal cavity is restricted to 25–200µLand mass cut off ~ 1kDa.
- Nasal congestion due to cold or allergies may interfere with absorption of drug.
- Rapid mucocillary clearance.
- The amount of drug reaches to different regions of the brain and spinal cord varies with each agent.

Mechanism of drug absorption from Nose (Dodane et.al. 1999)

The initial step in the absorption of drug from the nasal cavity is passage through the mucus; large charged particles may find it more difficult to cross. But Small unchanged particles easily pass through this layer.

Mechanisms of absorption which are include paracellular transport via movement between cell and transcytosis by vesicle carrier's transcellular or simple diffusion across the membrane.

The first mechanism includes aqueous route of transport, which is also called as the paracellular route. This is slow and passive route. Inverse log-log relationship between intranasal absorption and the molecular weight of water-soluble compounds.Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons.

The second mechanism is transport through a lipoidal route is known as transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. For example, Chitosan, a natural biopolymer opens tight junctions between epithelial cells to facilitate drug transport.

Factor affecting the nasal drug absorption (Chajed et.al. 2011)

Various factors affect bioavailability of nasally administered drugs as follows;

[1] Biological Factors
- Structural features
- Biochemical changes

[2] Physiological factors
- Blood supply and neuronal regulation
- Nasal secretions (Mucus production is approximately 1.5–2 ml daily).
- Mucociliary clearance and ciliary beat frequency
- Pathological conditions
- Environmental conditions.(24^0 C)
- Membrane permeability.

[3] Physicochemical Properties of Drugs
- Molecular weight and Size (MW 300 Dalton rate of permeation is highly sensitive).
- Solubility
- Lipophilicity
- pka and Partition coefficient
- Chemical form of drug.
- Polymorphism.
- Chemical state.
- Physical state(particles in the 5–10µ range are deposited in the nostrils)

[4] Physicochemical Properties of Formulation
- Physical form of formulation
- pH (pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants.)
- Osmolarity (0.462 M sodium chloride concentration.)
- Volume of solution applied and drug concentration
- Viscosity.

Strategies to improve nasal absorption (Appasaheb et.al. 2013)[3]

There are many barriers present in nasal cavity which interfere with absorption of various drugs

.There are some methods which have been successfully used for the improvement of nasal drug absorption.

- Nasal enzymes inhibitors (enzymes are protease and peptidase etc.)
- Structural modification
- Permeation enhancer (surfactants, fatty acids, phospholipids, bile salts, etc.)
- Particulate drug delivery (carriers are liposomes, microspheres, nanoparticles and niosomes.)
- Prodrug approach (used to improve taste, odour, solubility and stability)
- Bio adhesive polymer (improve the nasal residence and absorption of the drug).

Blood brain barrier (BBB) BBB is the major barrier to the passage of active molecules from the blood component to the brain .it is a unique membranous barrier that tightly segregates the brain from the circulating blood. The CNS consist blood capillaries which are structurally different from the blood capillaries in other tissues these structural differences result in a permeability barrier between the blood within brain capillaries and the extracellular fluid in brain tissue (Misra et.al. 2003) (Fig.2).The brain capillaries consist of endothelial cell which are joined to one other by continuous tight intracellular junction comprising what is called as a blood brain barrier. The tight junctions between endothelial cells results in a very high trans-endothelial electrical resistance of 1500-2000W.cm^2 compared to 3-33W.cm^2 of other tissues which reduces the aqueous based Para-cellular diffusion that is observed in other organs (Kumar et.al. 2012). The drug administered intranasally may diffuse directly in to CNS because of the continuity between subdural area of the nose and the subarachnoid space of the olfactory lobe. since the BBB is the lipoidal barrier, it allow only the drug having high o/w partition coefficient to diffuse passively whereas moderately lipid soluble and partially ionized molecules penetrate at slow rate. There are three different approaches have been utilized successfully to promote crossing the BBB by drug.

- Use of permeation enhancer such as dimethyl sulfoxide(DMSO)
- Osmotic distribution of the BBB by infusing internal carotid artery with mannitol.
- Use of dihydropyridine redox systems drug carrier to the brain.

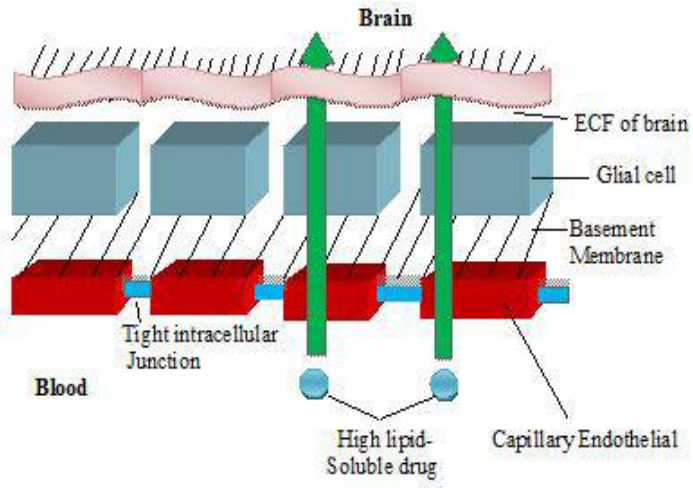

Fig 2: Blood Brain Barrier

Blood cerebrospinal fluid barrier: The second barrier that a systemically administered drug molecule encounters before entering the CNS is the blood-cerebrospinal fluid barrier (BCB). As the CSF has the ability to exchange molecules with the interstitial fluid of the brain parenchyma, the passage of blood-borne molecules into the CSF are also carefully regulated by the BCB (Kumar et.al. 2013).The BCB is found in the epithelium of the choroids plexus, and is arranged in such a manner that it limits the passage of molecules and cells into the CSF. For any given drug, its concentration in the brain will always be higher than in the CSF (Garcia-Garcia et.al. 2005).

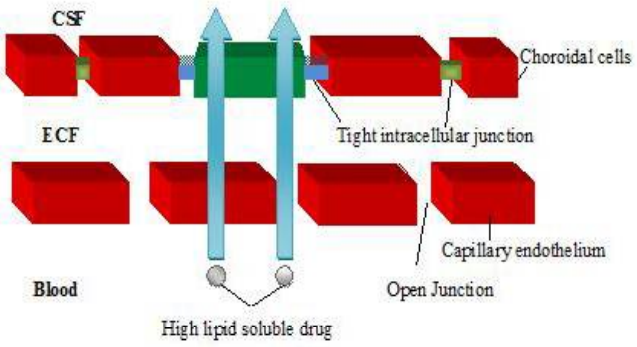

Fig 3: The blood-CSF barrier

Although the mechanism for diffusion of drug into the CNS and CSF are similar, the degree of uptake may vary significantly, CSF drug concentration may be higher than its cerebral concentration e.g. sulfamethxazole and trimethoprime

Parkinson disease [PD]: Ever since PD was first described in 1817**,** in the early 1960s, scientists identified the primary problem underlying the disease: the loss of brain cells that produce a chemical called dopamine, which helps to coordinate and control muscle activity (Singh 2012)**.** Today, the term *parkinsonism* is defined by any combination of six specific motoric features: tremor at rest, bradykinesia, rigidity, loss of postural reflexes, flexed posture, and the freezing phenomenon (where the feet are transiently "glued to the ground") Not all six of these cardinal features need be present, but at least two should be before the diagnosis of parkinsonism is made, with at least one of them being tremor at rest or bradykinesia.

There are currently two main types of treatment for Parkinson disease namely drug treatments and surgery.

[1] Drug Treatments:

Medications for PD fall into three categories.

The first category includes drugs that work directly or indirectly to increase the level of dopamine in the brain. People cannot simply take dopamine pills because dopamine does not easily pass through blood vessels into the brain. The most common drugs for PD are dopamine precursors – substances such as levodopa that cross the blood-brain barrier and are then changed into dopamine. Other drugs mimic dopamine, prevent or slow its breakdown, or increase the amount of it that is released. **The second** category of PD drugs affects other neurotransmitters in the body in order to ease some of the symptoms of the disease. For example, anti cholinergic drugs decrease the activity of the neurotransmitter acetylcholine. These drugs help to reduce tremors and muscle stiffness, which can result from having more acetylcholine than dopamine. **The third** category of drugs prescribed for PD includes medications that help control the non- motor symptoms of the disease. For example, people with PD-related depression may be prescribed antidepressants.

[2] Surgical Treatments

At present, there are two commonly used surgical treatments for PD: pallidotomy and deep brain stimulation. Because these procedures are invasive, they are usually reserved for severely afflicted Parkinson's patients who do not get adequate relief from medications. Brain surgery was one of the first treatments for PD. Surgeons discovered that, by removing or destroying parts of the brain that were "misfiring," some of the symptoms of PD could be alleviated. The most common early brain operations for PD were pallidotomy, which destroyed part of the globus pallidus, and thalamotomy, which destroyed part of the thalamus. These procedures were irreversible and often led to complications. Clinicians have improved these techniques a great deal, but while they are much safer now, they are still irreversible. In recent years, scientists have found that they can mimic the effects of pallidotomy and thalamotomy by deep brain stimulation (DBS). With DBS, an electrode is implanted in the brain in a way that calms the abnormal neuronal firing.

Formulations based on Intranasal Drug Delivery System

Dosage form is the conclusion of the effort of the formulation and product development. It is highly sophisticated drug delivery system and provides a mechanism for safe and constant delivery of accurate dosage.

Classification of dosage forms

Dosage form is classified in several ways on the basis of their physical state, route of administration, intended purpose or site of application etc.

- **Physical state:** Solid, Semi solid, Liquid, Gaseous.
- **Route of administration:** Parental, Oral, Rectal, and Nasal.
- **Site of application:** Skin, Eye, Nose, Tooth, Hand, Foot, Hair.
- **Use:** internal, external.

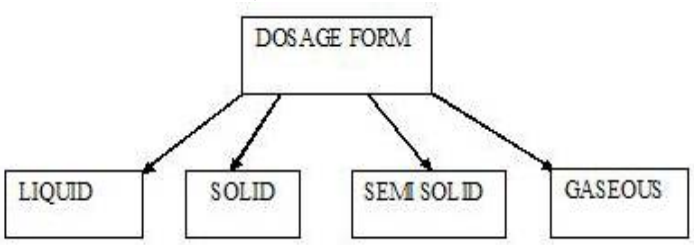

Fig 4: Classification of dosage forms

[1] Liquid dosage form

- **Nasal drops:** Nasal drop are aqueous or liquid paraffin solution meant for instillation into the nostrils. Nasal drop often contain vasoconstrictor drug to relief nasal congestion. Oily solution is not preferred since the oil may retard the ciliary action of the mucosa and even cause lipoid phenomena, if drop of the oil enter the trachea.
  A vehicle for formulating nasal drop should have
  [1] The pH between 5.5and 7.5
  [2] Buffering capacity
  [3] Tonicity equivalent to normal saline
  [4] Viscosity not exceeding the normal viscosity of nasal mucosa.

- **Nasal sprays**: Conventional nasal formulation like solution and suspension in the form of spray and drops have used delivery system like the rhinyle catheters, single dose pipettes, metered dose spry pumps(non pressurized)and metered dose aerosol valve device. Out of these the spray pumps and the aerosol valve orifice lend themselves to controlled delivery of nasal formulation. Both systems are simple to use and provide multiple dosing facilities. A nasal spray can deliver an exact dose anywhere from 25 - 200µL (Appasaheb et.al. 2013). They also provide ease of administration, rapid absorption and onset of action, and bypass of presynaptic clearance. Nasal spray is used intranasally to relieve nasal congestion and inflammation and to treat infection. These sprays may contain antihistaminic, sympathomametic agent and antibiotic substance.
- **Nasal emulsions and micro emulsions:** Intranasal emulsions have not been studied as extensively as other liquid nasal delivery systems. Nasal emulsions offer the advantages for local application mainly due to the viscosity (Appasaheb et.al. 2013). Mucoadhesive Nanoemulsion of Resperidone indicated more effective and best brain targeting approach (Kumar et.al. 2008). The poor absorbable fexofenadine, microemulsion system composed of oil, surfactant & co-surfactant was developed for intranasal delivery to enhance the solubility and bioavailability (Kulkarni et.al. 2013).

[2] Solid dosage forms

- **Nasal powders:** Solid dosage forms are also becoming popular for intranasal drug delivery, although these formulations are more suitable for pulmonary drug delivery and similar applications, since it can cover the vasculature within the epithelium of nasal mucosa (Appasaheb et.al. 2013). Intranasal vaccination represent attractive non-invasive and alternative to needle based injection and provide superior protection at mucosal surface Powder formulation of whole inactivated influenza virus provides a novel intranasal delivery platform (Kulkarni et.al. 2013). SNBL technology is the best technique for vaccine.

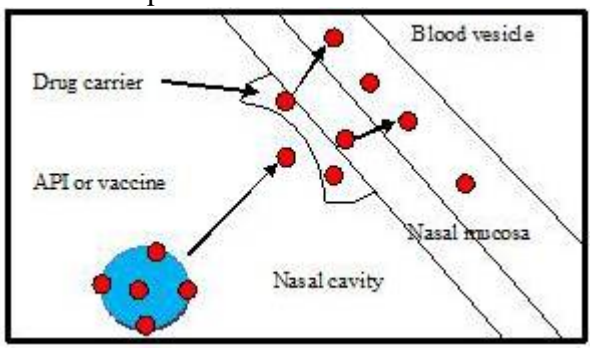

Fig 5: SNBL carrier technology-dry powder formulation

[3] Semi-solid dosage forms:

- **Nasal gels:** Nasal gels are high-viscosity thickened solutions or suspensions. The advantages of a nasal gel include the 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 soothing excipients and target delivery to mucosa for better absorption (Desai et.al. 2011). Zedovudine is transferred to brain via intra nasal route through olfactory route by using thermo reversible gelling system (Parag et.al. 2011).

[4] Novel drug formulations

- **Liposome**: liposome is artificial microscopic bilayer vesicles or sacs made of phospholipids and enclosed with an aqueous compartment. They look like as a cell membrane in structure and composition. Drug are incorporate in liposome and then administered into the body

which are delivered at the desired site in desired concentration with no being toxic with a wide range of hydrophilicity and pKa values. Liposomes are often used as non-viral carrier for DNA delivery because of their dynamic properties of cellular membrane that interact with the biological environment (Kulkarni et.al. 2013, Balazs et.al. 2011). Their size range from 25 to 5000nm. The first injectable liposome drug (AmBisome) is already available in the market.

- **Microspheres:** Microsphere technology has been widely applied in designing formulations for nasal drug delivery. Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect (Appasaheb et.al. 2013). In vaccines delivery chitosan micro-spheres prepared in the presence of selected immune modulator pluronic block copolymer F127 (Kulkarni et.al. 2013). In vitro drug release studies from microsphere were achieved according to USP XXIV nasal administration of microparticles to rat obtained by spray drying can be perform to obtained the selective CNS targeting of anti-ischemic drugs (Illum 2000).
- **Nanoparticles**: Nanoparticles are solid colloidal particles. The diameters raging from 1-1000 nm. It consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles may offer a number of advantages due to their small size, but only the smallest nanoparticles enter the mucosal membrane by paracellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4 Å (Appasaheb et.al. 2013). In order to improve the absorption of nanoparticle in the Brain following nasal administration a novel protocol to conjugate biorecognitive ligand-lectins to the surfaces of poly (ethylene glycol), poly (lactic acid), (PEG-PLA), nanoparticles was established (Kulkarni et.al. 2013). Odorranolectin nanoparticles could be potentially used as carrier for nose to brain drug delivery, especially macro-moleculacular drug, in the treatment of CNS disorders. UAE-I modified nanoparticles indicated their higher affinity to the olfactory mucosa than to the respiratory one. So it becomes the potential carrier for brain drug delivery (Kulkarni et.al. 2013).

Various devices which are used in intranasal drug delivery system:

There is the various number of devices are given below which are frequently used to treat the various diseases, using the intranasal route, and they are successfully deliver the drug and reached on the targeted site.

[1] Direct Haler pulmonary and nasal delivery device: Direct-Haler A/S is the first company to initiate development of second-generation combinations as an integrated treatment for the combined disorder. Drug delivery has an important role in this novel multiple-route combination therapy. Direct-Haler's new concept – second-generation respiratory combination therapy – integrates pulmonary, nasal and oral dosing in fixed-dose combinations for simultaneous delivery. This takes advantage of the patient's anatomy with the aim to improve delivery effectiveness and convenience. The nasal device has successfully been used in clinical trials, and has confirmed patient acceptability. To use Direct Haler Nasal, the cap is taken off leaving both ends of the tube open and the dose resting at the bottom of the "U". Holding and pressing the mouthpiece between the thumb and forefinger, the patient inserts the nostril piece into a nostril and the mouthpiece into their mouth. They then blow into the mouthpiece and thereafter completely release the finger pressure on the tube. The blow of the patient will then disperse the dose and transport it via the nostril piece to the nasal mucosa (Fuhlbrigge et.al. 2003).

There have the various parts:

- **Inhaler cap**: Give protection again the moisture
- **Mouth piece**: Provide protection of mouth and tong.
- **Powder whirl chamber**: Dispersion of dose is turbulent
- **Valves:** It controls the air flow.

- **Air inlet**: Dimensioned for balanced inspiratory resistance.
- **Pharma blister pack**: Give extra protection

Advantages:

- Most excellent technology for pulmonary delivery.
- Patient acceptability is confirmed and successfully used in clinical trials.
- Device offers precise, effectual, repeatable and disinfected dosing.
- Improve successful and convenience delivery.
- Intended for nasal delivery of dry- powder formulations

Company name	Key respiratory product
AstraZeneca	Accolate, Pulmicort, Symbicort, Rhinocort
Aventis	Allegra/Telfast, Nasacort
GlaxoSmithKline	Flixotide/Flovent, Seretide/Advair

[2]The ViaNase™ electronicatomizer: Nasal drug delivery system called ControlledParticle dispersionthat "delivers aerosolized particles to the n ose and imparts a turbulent flow to the particles ofte n in the form of one or more vortices." In addition to drugs designed for treatment of intra- nasalprobles, t he company touts its controlled particle dispersion technology for systemic delivery of meds, nose to brain delivery and intranasal vaccine administration (Teleflex 2012, Djupesland et.al. 2003).

[3]OptiNose AS: The single-use device: Optinose patented technology to deliver highly effective and well-unabsorbed topical steroid medication (fluticasone) into the nasal cavity in a deeply distributed manner that improve upon prior appraches to intranasal drug delivery. Treatment of serious chronic nasal inflametry diseases like chonic rhinosinusitis with nasal drug polyps. Optinose is focused on the development of break through bi-directional nasal drug delivery technology which significantly improves drug transport to targeted site deep into the nasal cavity (Yardley 2014, Yardley et.al. 2004).

Working: Optinose is proceding rapidly with the development of several ground break breath achuated bi-directional nasal drug delivery for both liquid and powder. All of thease system apply bi-directional drug delivery in the same way. A sealing nozzal is inserted in to nostrile and the patient blows into the mouth piece.The blowing action closed the soft palate and creates an air flow, which carries the formulation out of the device through the pump,which tend to move during actuation. Second, the devices are breath actuated. Third, the airflow through the nose at actuation reduces the discomfort often experienced when the spray is released. Finally, there may be a reduction in the aftertaste at the back of the throat due to a different deposition and clearance pattern. Recent clinical studies comparing delivery from a traditional spray pump with delivery from an initial multi-use liquid bi-directional delivery device design (with the same spray pump incorporated inside), have shown significantly improved delivery beyond the nasal valve and in particular to the upper remote and clinically important nasal segments (Yardley et.al. 2004).

[4] The multi-use liquid reservoir device: The multi-dose liquid device has been designed to incorporate existing nasal spray pump technology and to incorporate proven breath actuation technology in order to reduce risk. Recent clinical studies comparing delivery from a traditional spray pump with delivery from an initial multi-use liquid bi-directional delivery device design (with the same spray pump incorporated inside), have shown significantly improved delivery beyond the nasal valve and in particular to the upper remote and clinically important nasal segments. Reproducibility of dosing was also improved with the bi-directional delivery device (Yardley et.al. 2004).

[5] Mucosal atomization device [MAD]: MAD Nasal™ Intranasal Mucosal Atomization Device—the safe and painless way to deliver medication with rapid absorption across mucosal membranes to your patient's blood stream without an intravenous line. This intranasal mucosal atomization device delivers a mist of atomized medication that offers rapid absorption across mucosal membranes to the blood stream. So you spend more time caring for your patient, and less time starting a painful IV line (Teleflex 2012).

[6] SNBL powder drug devices:

In this technology Dry powder formulations are use which are more effective mucoadhesive carrier, consist of generally recognised as safe "GRAS" component. Excellent safety profile demonstrated.

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