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INTRANASAL THERMOREVERSIBLE MUCOADHESIVE GELS: A Review

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ABSTRACT

Almost 40% of active Pharmaceutical ingredients have low oral bioavailability, high hepatic first-pass metabolism and also less efficient in crossing the blood brain barrier for brain targeting through oral delivery. To overcome this problem the various system such as: nasal spray, gels, emulsions, droplets, suspensions, powders and thermoreversible mucoadhesive gels etc have been studied for nasal delivery. Thermoreversible mucoadhesive gels have promising results in nasal drug delivery. Thermoreversible mucoadhesive gels are those which convert into gel in nasal cavity after administration at body temperature with suitable gel strength, results in enhancement of the residence time in the nasal cavity. These formulations contain thermoreversible polymers (Pluronic F127 or Poloxamer) and mucoadhesive polymers. Thermoreversible polymers are a novel state of matter having both solid and liquid like properties which can be delivered as a fluid and solidifies within the body's microenvironment where the temperature is higher than the sol-gel transition temperature. The formulation has the advantage to prevent the anterior leakage of dosage form, reduce the taste impact, and enhance the nasal bioavailability. Thermoreversible gels are formulated by two methods: simple stirriring and cold method. This abstract gives an overview of Thermoreversible mucoadhesive gels as a promising approach to effectively tackle the problem of low oral bioavailability of drugs.

Keywords: Thermoreversible Mucoadhesive gels, Nasal drug delivery, Brain targeting

INTRODUCTION

Almost 40% of active pharmaceuticals ingredients have low oral bioavailability, high hepetic first pass metabolism and also less efficient in crossing the blood brain barrier for brain targeting through oral delivery. To overcome these problems the nasal drug delivery system has been studied because the nasal drug delivery system comprises of targeting a drug through nasal epithelium. This mode of drug delivery has tremendous absorptive potential of the nasal mucosa owing to its high permeability because of high perfusion rate. This route can be selectively exploited for delivery of small molecules, peptides and proteins that are not easily administered by routes other than i.v. where immediate response is desired [1,2]. Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents [3,4]. For nasal drug delivery various systems such as: nasal spray, nasal pumps, gels, microemulsion, suspensions, powders and thermoreversible mucoadhesive gels have been studied.

Thermoreversible mucoadhesive gel may be liquid or solid in nature converts into gel in nasal cavity at the body temperature after administration. Thermoreversible gels can be formulated using enviornmentally responsive polymers such as poloxamers and Pluronic F127 [5] and mucoadhesive polymers. Lutrol F grades are block copolymers referred to as poloxamers, consisting of polyoxyethylene (POE) and polyoxypropylene (POP) units. Higher moleculer weight poloxamer has the ability to form thermoreversible gels. In particular poloxamer 407(Lutrol F 127) has been used in

number of applications including nasal drug delivery, where the increase in the viscosity at the body temperature, increase the residence time of drug in the nose [6]. As Pluronic F-127 is fulfilling all the properties required form successful nasal formulation, with increased contact time [7]. Thermoreversible polymers are a novel state of matter having both solid and liquid like properties. This polymer can be delivered as a fluid and solidifies within the body's microenvironment where the temperature is higher than the sol-gel transition temperature. Such a system has both fluidity and elasticity [8]. A thermoreversible polymer, when used as a drug carrier for nasal administration, might achieve (i) Quick transition from liquid to solid upon temperature change: this permits the gel to stay at the injected site without being washed away by the bloodstream, (ii) Prevent the wastage of dosage form the site of application, (iii) Solid-to-gel state reversible property of polymer may be adjusted from temporary to permanent by changing its chemical composition. and (iv) Increase drug concentration at the site of deposition [9-10].

Mucoadhesive polymers have been used to improve the nasal bioavailability of several drugs [11]. The mucoadhesive polymers provide a relatively short term adhesion between the drug delivery system and mucus and/or the epithelial cell surface. They have the advantage of not being absorbed and therefore would not be expected to display systemic toxicity. Mucoadhesive polymers, when used as drug carriers for nasal delivery, may increase the residence time within the nasal cavity, intensify the contact between the nasal mucosa and the drug, increased drug concentration at the site of deposition and facilitate drug permeation through the mucosa by opening the tight junction between the epithelial cell [12-13].

Thermoreversible mucoadhesive gel can be prepared by two methods: simple and cold method. Both methods required stirriring for gentle mixing of ingredients.These gels have promising results in case of low oral bioavailable drugs.

Material and Method:

Polymers: Thermoreversible polymers:- Pluronic and poloxamers are two main polymers.

Mucoadhesive polymers:- which compatible with given drug.

Formulation excipients:-

Formulation excipients are chosen for various reasons. The most common reasons follow-

I. ***Solubolizers:*** co-solvents (glycols, alcohols, Transcutol etc), surfactants and cyclodextrins are used to improve the solubility of insoluble drugs.
II. ***Buffer components:*** various conventional buffer systems can be used to buffer nasal formulations. A high buffer capacity is important to maintain in situ formulation pH.
III. ***Antioxidants:*** according to stability of drug the antioxidants are used to prevent drug degradation in small quantities.
IV. ***Flavour/taste:*** some drugs may present problems with regard to aroma and taste. To avoid this problem particular flavor and taste masking agents are used.
V. ***Preservative:*** Nasal formulation usually contains preservatives to protect them from microbial contamination. Parabens, benzalkonium chloride, benzoyl alcohol are typicaaly used as preservative.
VI. ***Humectant:*** To avoid any nasal irritation by formulation components, humectants are usually added to formulations. Example- glycerin, sorbitol, mannitol.
VII. ***Gelling/viscofying agents:*** commonly used agents for this purpose are methyl cellulose, carboxymethyl cellulose, carbopols, polyvinylalcohol.

Methods: There are main two methods used in prepration of thermoreversible mucoadhesive gels which following are-

Simple and Cold method:- both include the megnetic stirring of excipients. In cold method liyophilization is also used.

NASAL ANOTMY:

Nose is the most prominent feature located in the middle of the human face. It is the beginning part of the respiratory system that is involved in inhalation. The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril.

The nasal cavity consists three main regions are:

- nasal vestibule,
- olfactory region and
- respiratory region.

The surface area in the nose can be enlarges about 150cm^2 by the lateral walls of the nasal cavity includes a folded structure, it is a very high surface area compared to its small volum.

This folded structure consists of three turbinates: the superior, the median and the inferior [14].

The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area

includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, where as respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport [15].

Nasal delivery is considered to be a promising technique for the following reasons:

The nose has a large surface area available for drug absorption due to the coverage of the epithelial surface by numerous microvilli, the sub epithelial layer is highly vascularized, the venous blood from the nose passes directly into the systemic circulation and therefore avoids the loss of drug by first pass metabolism in the liver, it offers lower doses, more rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity fewer side effects, high total blood flow per cm^3, porous endothelial membrane is easily accessible, and drug is delivered directly to the brain along the olfactory nerves [16-18].

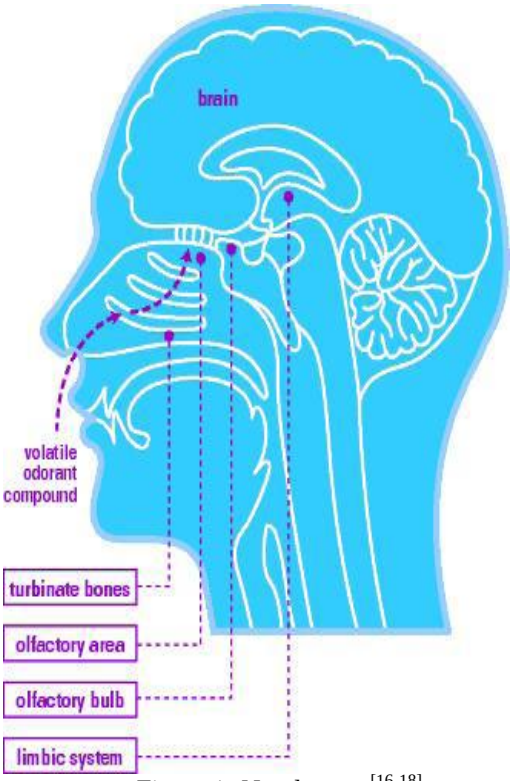

Figure.1- Nasal route [16-18]

FACTORS INFLUENCING NASAL DRUG ABSORPTION

Several factors affect the systemic bioavailability of drugs which are administered through the nasal route. The factors can be affecting to the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drugs delivery system. These factors play key role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. The factors influencing nasal drug absorption are described as follows.

1) Physiochemical properties of drug.

- Molecular size.
- Lipophilic-hydrophilic balance.
- Enzymatic degradation in nasal cavity.

2) Nasal Effect

- Membrane permeability.
- Environmental pH
- Mucociliary clearance
- Cold, rhinitis.

3) Delivery Effect

- Formulation (Concentration, pH, osmolarity)
- Delivery effects
- Drugs distribution and deposition.
- Viscosity

1) Physiochemical properties of drug

Molecular size: The molecular size of the drug influence absorption of the drug through the nasal route**.** The lipophilic drugs have direct relationship between the MW and drug permeation whereas water- soluble compounds depict an inverse relationship. The rate of permeation is highly sensitive to molecular size for compounds with MW $\geq$ 300 Daltons [19].

Lipophilic-hydrophilic balance: The hydrophilic and lipophilic nature of the drug also affects the process of absorption. By increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mu-cosa was found to have some hydrophilic character, it appears that this mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. Lipophilic drugs like naloxone, buprenorphine, testosterone and 17a-ethinyl- oestradiol are almost completely absorbed when administered intranasal route [20-21].

Enzymatic degradation in nasal cavity: In case of peptides and proteins are having low bioavailability across the nasal cavity, so these drugs may have possibility to undergo enzymatic degradation of the drug molecule in the lumen of the nasal cavity or during passage through the epithelial barrier. These both sites are having exo-peptidases and endopeptidases, exo-peptidases are mono-aminopeptidases and di-aminopeptidases. These are having capability to cleave peptides at their N and C

termini and endopeptidases such as serine and cysteine, which can attack internal peptide bonds [22].

2) Nasal effect factors

Membrane permeability: Nasal membrane permeability is the most important factor, which affect the absorption of the drug through the nasal route. The water soluble drugs and particularly large molecular weight drugs like peptides and proteins are having the low membrane permeability. So the compounds like peptides and proteins are mainly absorbed through the endocytotic transport process in low amounts [23].

Environmental pH: The environmental pH plays an important role in the efficiency of nasal drug absorption. Small water-soluble compounds such as benzoic acid, salicylic acid, and alkaloid acid show that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the nonionised form. However, at pH values where these compounds are partially ionized, substantial absorption was found. This means that the nonionised lipophilic form crosses the nasal epithelial barrier via transcellular route, whereas the more lipophilic ionized form passes through the aqueous paracellular route [24].

Mucociliary clearance: Mucociliary clearance is a one of the functions of the upper respiratory tract is to prevent noxious substances (allergens, bacteria, viruses, toxins etc.) from reaching the lungs. When such materials adhere to, or dissolve in, the mucus lining of the nasal cavity, they are transported towards the nasopharynx for eventual discharge into the gastrointestinal tract [25].

Cold, rhinitis: Rhinitis is a most frequently associated common disease, it influence the bioavailability of the drug. It is mainly classified into allergic rhinitis and common, the symptoms are hyper secretion, itching and sneezing mainly caused by the viruses, bacteria or irritants. Allergic rhinitis is the allergic airway disease, which affects 10% of population. It is caused by chronic or acute inflammation of the mucous membrane of the nose. These conditions affect the absorption of drug through the mucus membrane due the inflammation.

3) Delivery effect factors

Factors that affect the delivery of drug across nasal mucosa such as surfactants, dose pH, osmolarity, viscosity, particle size and nasal clearance, drug structure can be used to advantage to improve absorption.

Formulation (Concentration, pH, Osmolarity): The pH of the formulation and nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection. In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bac-teria [26].

Concentration gradient plays very important role in the absorption / permeation process of drug through the nasal membrane due to nasal mucosal damage. Examples for this are nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. Another is absorption of salicylic acid was found to decline with concentration. This decline is likely due to nasal mucosa damage by the permanent [27].

The osmolarity of the dosage form affects the nasal absorption of the drug; it was studied in the rats by using model drug. The sodium chloride concentration of the formulation affects the nasal absorption. The maximum absorption was achieved by 0.462 M sodium chloride concentration; the higher concentration not only causes increased bioavailability but also leads to the toxicity to the nasal epithelium [28].

Drugs distribution and deposition: The drug distribution in the nasal cavity is one of the important factors, which affect the efficiency of nasal absorption. The mode of drug administration could affect the distribution of drug in nasal cavity, which in turn will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms mainly depends on the site of disposition [29].

Viscosity: A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

ADVANTAGES OF NASAL ROUTE:

1) Drug degradation that is observed in the gastrointestinal tract is absent.
2) Hepatic first pass metabolism is avoided.
3) Rapid drug absorption and quick onset of action can be achieved.

4) The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
5) The nasal bioavailability for smaller drug molecules is good.
6) Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
7) Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
8) Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
9) Drugs possessing poor stability in g.i.t. fluids are given by nasal route.
10) Polar compounds exhibiting poor oral absorption may be particularly suited for this route of deli-very [30-31].

LIMITATIONS OF NASAL ROUTE:

1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3) Nasal cavity provides smaller absorption surface area when compared to GIT.
4) There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
5) Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
6) There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration [32-33].

THERMOREVERSIBLE MUCOADHESIVE GELS:

Mucoadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are maintained together for a prolonged time period by means of interfacial forces [34]. During the 1980s, this concept began to be applied to drug delivery systems.

It consists of the incorporation of adhesive molecules into some kind of pharmaceutical formulation intended to stay in close contact with the absorption tissue, releasing the drug near to the action site, thereby increasing its bioavailability and promoting local or systemic effects [35-36].

MECHANISMS OF MUCOADHESION

The mechanism of adhesion of certain macro-molecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water [37]. Thus; the mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage [34-35].

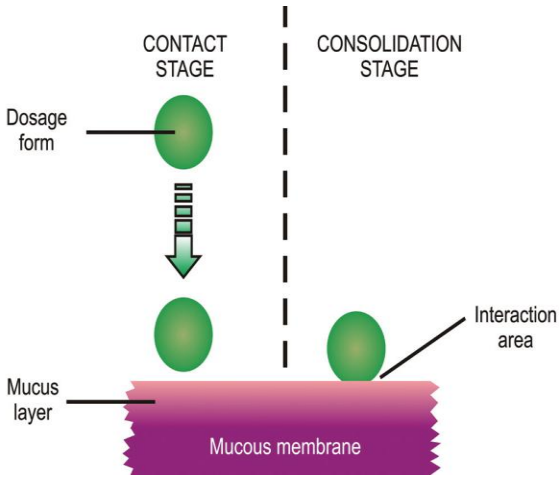

Figure.2-The Two Steps in Mucoadhesion Process [34-35]

Mucoadhesion is currently explained by six theories:

Electronic theory: Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength [38].

Adsorption theory: According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in van der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions. For example, hydrogen bonds are the prevalent interfacial forces in polymers containing carboxyl groups [35,39,37,34]. Such

forces have been considered the most important in the adhesive interaction phenomenon [34] because, although they are individually weak, a great number of interactions can result in an intense global adhesion [38].

Wetting theory: The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity (Figure 3). The contact angle should be equal or close to zero to provide adequate spreadability [38].

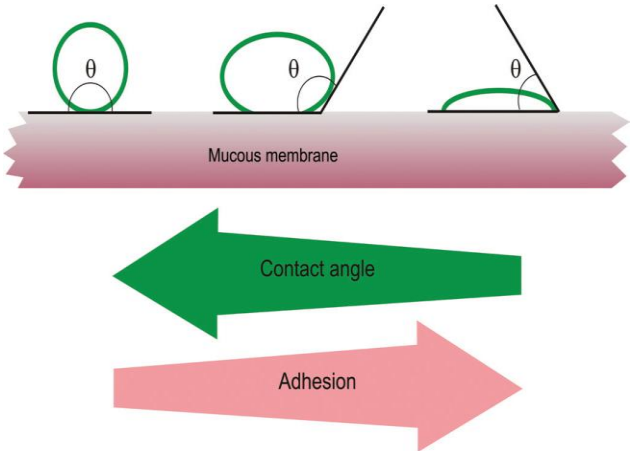

FIGURE 3 – Schematic diagram showing influence of contact angle between device and mucous membrane on bioadhesion.

Diffusion theory:

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond (Figure 4). It is believed that the adhesion force increases with the degree of penetration of the polymer chains [38].

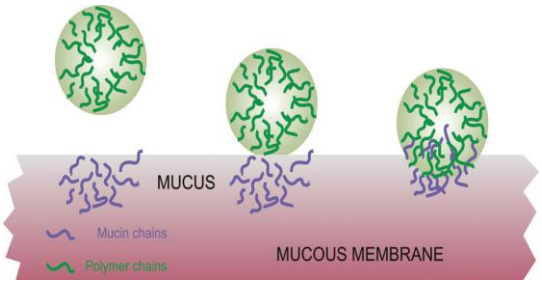

FIGURE 4 – Secondary interactions resulting from interdiffusion of polymer chains of bioadhesive device and of mucus.

Fracture theory: It analyses the force required to separate two surfaces after adhesion is established [34-35]. This force, *Sm*, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, *Fm*, and the total surface area, *Ao*, involved in the adhesive interaction [38].

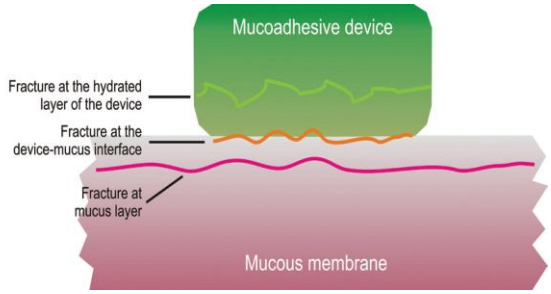

FIGURE 5 – Regions where the mucoadhesive bond rupture can occur [38].

Mechanical theory: Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process [34,40].

THERMO REVERSIBLE MUCOADHESIVE GELS: The gels are the polymeric network which increases the contact time of the drugs at the administered site,hence increasing the absorption of drug,due to its mucoadhesive property. Thermoreversible gels can be formulated using enviornmentally responsive polymers such as poloxamers [38]. Polymer gels and mucoadhesive polymers have been studied for the mucosal delivery of various compounds ranging from small molecule to macromolecular drugs.The nasal bioadhesives enhanced bioavailability compared with oral delivery [39]. A very good example of such system is EnerB(Nature's Bounty Inc, Bohemia,NY),a vitamin B_{12} supplement available in gel form.Application of insitu gelling solutions of tri-block copolymers of poly(ethylene oxide) and poly(propylene oxide) (Pluronic) exhibiting thermoreversible properties have been proposed to lower the viscosity of the nasal formulations below the body temperature [40]. By modulating the gelation temperature of different PF127 solutions,liquid bases for nasal use can be formulated that form a gel in the nasal cavity at body temperature with suitable gel strength resulting in enhancement of the residence time in the nasal cavity [41].

Advantages of Thermoreversible mucoadhesive gels:

- Accuracy of dosing.
- Ease of administration.
- Reduction of taste impact.

- Prolonged nasal residence.
- Improved nasal bioavailability.
- Reduction of irritation.
- Reduction of anterior leakage of formulation.
- Target delivery to mucosa for better absorption.

TYPES OF NASAL FORMULATIONS:
The selection of dosage form depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences. Four basic formulations must be considered, i.e

- LIQUID NASAL FORMULATIONS,
- POWDER DOSAGE FORMS,
- PRESSURIZED MDIs
- NASAL GELS.

LIQUID NASAL FORMULATIONS:
Liquid preparations are the most widely used dosage forms for nasal administration of drugs. They are mainly based on aqueous state formulations. Their humidifying effect is convenient and useful, since many allergic and chronic diseases are often connected with crusts and drying of mucous membranes. Microbiological stability, irritation and allergic rhinitis are the major drawbacks associated with the water-based dosage forms because the required preservatives impair mu-cociliary function [42] and the reduced chemical stability of the dissolved drug substance and the short residence time of the formulation in the nasal cavity are major disadvantages of liquid formulations [43-44]. The several type's dosage forms available in liquid form are described below.

1. Instillation and rhinyle catheter:
Catheters are used to deliver the drops to a specified region of nasal cavity easily. Place the formulation in the tube and kept tube one end was positioned in the nose, and the solution was delivered into the nasal cavity by blowing through the other end by mouth [45-46]. Dosing of catheters is determined by the filling prior to administration and accuracy of the system and this is mainly used for experimental studies only.

2. Compressed air nebulizers:
Nebulizer is a device used to administer medication in the form of a mist inhaled into the lungs. The compressed air is filling into the device, so it is called compressed air nebulizers. The common technical principal for all nebulizers, is to either use oxygen, compressed air or ultrasonic power, as means to break up medical solutions/ suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the device [47]. Nebulizers accept their medicine in the form of a liquid solution, which is often loaded into the device upon use. **Corticosteroids** and **Bronchodilators** such as **salbutamol (*Albuterol* USAN)** are often used, and sometimes in combination with **ipratropium** [48].

3. Squeezed bottle:
Squeezed nasal bottles are mainly used as delivery de-vice for decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This procedure often results in contamination of the liquid by microorganisms and nasal secretion sucked inside. Dose accuracy and deposition of liquids delivered via squeezed nasal bottles are strongly dependent on the mode of administration. Thus the dose is hard to control. Therefore squeezed bottles with **vasoconstrictors** are not recommended to be used by children [49].

4. Metered-dose pump sprays:
Most of the pharmaceutical nasal preparations on the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to generally alleviate cold or allergy symptoms such as nasal congestion or systemically, see nasal administration. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by action of a hand-operated pump mechanism. The three main types available for local effect are: **antihistamines, corticosteroids, and topical decongestants**.

POWDER DOSAGE FORMS
Dry powders are less frequently used in nasal drug delivery. Major advantages of this dosage form are the lack of preservatives and the improved stability of the formulation. Compared to solutions, the administration of powders could result in a prolonged contact with the nasal mucosa. The types of powder dosage forms are described below:

1. Insufflators:
Insufflators are the devices to deliver the drug substance for inhalation; it can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also. The achieved particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient deaggregation of the particles and results in a high coefficient of variation

for initial deposition areas.Many insufflator systems work with predosed powder doses in capsules [45].

2. Dry powder inhaler

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 [50-51].

PRESSURIZED MDIs:

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. Other medications less commonly used but also administered by MDI are mast cell stabilizers, such as **(cromoglicate or nedocromil) [48].**

NASAL GELS

Nasal gels are high viscosity thickened solutions or suspensions.Until the recent development of precise dosing devices, there was not much interest in this system.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/emollient excipients and target delivery to mucosa for better absorption [52].

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