

**NOVEL NASAL DRUG DELIVERY SYSTEM- A REVIEW****J.Joysa Ruby\* and V.P. Pandey**

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**ABSTRACT**

The last two decades have been marked by the recognition of the nasal cavity as a potential route for drug delivery. The nasal route has attracted increasing attention as a suitable method for delivery. The nasal cavity as a site for systemic absorption of drug has some advantages which include large surface area, porous endothelium basement membrane, highly vascularised epithelial layer; high total blood flow per cm<sup>3</sup>, avoids first pass metabolism and easy access. The novel nasal delivery available is microspheres, microemulsion, liposomes, nanoparticle, *In-situ* gel etc. Even though a number of challenges are still to be overcome, the encouraging results stimulate pharmaceutical researchers to make further efforts in order to develop new novel nasal formulations to replace the conventional nasal products. The present study is an attempt to investigate the possible novel methods of nasal drug delivery system.

**Keywords:** novel nasal delivery, microspheres, microemulsion, nanoparticle, *In-situ* gel.

**INTRODUCTION**

The use of the nasal cavity as a route for drug delivery has been an area of great interest to the pharmaceutical industry, especially for systemically acting drugs that are difficult to deliver via routes other than injection. The nasal route could be important for drugs that are used in crisis treatments, such as for pain, and for centrally acting drugs where the putative pathway from nose to brain might provide a faster and more specific therapeutic effect<sup>1</sup>.

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<sup>2,3</sup>.

The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. Drug delivery systems, such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics which swell easily when in contact with the nasal mucosa. These drug delivery systems have the ability to control the rate of drug clearance from the nasal cavity as well as protect the drug from enzymatic degradation in nasal secretions<sup>4</sup>.

Nasal drug delivery system provides excess of easy application of drug with the possibility of self administration by removing the chance of unwanted painful condition associated with injection form of drug delivery. Furthermore, lipophilic and low molecular weight drugs can easily penetrate through nasal mucosa with less degradation. Fast absorption can be achieved due to large absorption surface area and high vascularisation. Nasal route can be used as an alternative to parenteral in case of emergency therapy<sup>5,6</sup>.

Nasal drug delivery system is a potential route for direct delivery of drug to the central nervous system through olfactory region by bypassing hepatic first pass metabolism.

Side by side nasal drug delivery system has some limitations like large dose cannot be administered by this route conveniently due to administrative problems. Administration of solid formulation is quite difficult by nasal route<sup>7,8</sup>.

Fast clearance of the administered formulation occurs from the nasal cavity as the result of mucociliary clearance causes poor absorption of drug<sup>9</sup>.

Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, *etc.* which modulates the release and absorption characteristics of the drug. To deliver drugs efficiently to specific organs, a range of organic systems (e.g., micelles, liposomes, and polymeric nanoparticles) novel ways have been designed. In recent decades, significant advances in drug-delivery systems have enabled more effective drug administration. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under research and development. Among the several drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic

polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, nanoparticles, Dendrimers and micelles

## **NOVEL STRATEGIES FOR NASAL DRUG DELIVERY**

### **NOVEL DRUG FORMULATIONS**

Nasal formulations containing Liposomes, microspheres and nanoparticles have been used in recent intranasal drug delivery. In fact, it is not clear if those formulations increase drug absorption by transporting encapsulated drug across the membrane or just because they enhance the nasal retention time and stability of the drug. However, their use is in extensive growth and the results have been very capable the novel strategies for nasal drug delivery are

#### **Liposomes**

Liposomes are phospholipids vesicles composed of lipid bilayers enclosing one or more aqueous compartments in which drugs and other substances are included. They have been investigated as a vehicle for sustained-release formulations in the treatment of lung disease, gene therapy and as a method of delivering therapeutic agents to the alveolar surface for the treatment of systemic diseases. Liposomal drug delivery system has various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values. They have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been attributed to increase nasal retention of peptides, provides protection to the entrapped peptides from enzymatic degradation and mucosal membrane disruption. Insulin incorporated in liposomes coated with chitosan and carbapol, when administered them intranasally to rats. The results demonstrated that this formulation was effective and that its mucoadhesive property is a good option for a sustained release of insulin<sup>10, 11, 12</sup>.

#### **Nanoparticles**

Nanoparticles (NPs) were proposed as drug carriers over 30 years ago and have received growing attention since, mainly due to their stability, enhanced loading capabilities and control over physicochemical properties. Nanoparticles are solid colloidal particles with diameter ranging 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. Nanoparticles offer several advantages due to their small size. However only the smallest

nanoparticles penetrate the mucosal membrane by paracellular route and also in a limited quantity. Since the tight junctions are in the order of 3.9-8.4 Å<sup>13</sup>.

### Advantages of Nanoparticles

- Preferably used as a vehicle for sustained release formulations.
- Sustained release from a therapeutic aerosol can prolong the residence of an administered drug
- Minimize the risk of adverse effects
- Decreasing its systemic absorption
- Reduces dosing frequency.
- Increased patient compliance
- Suitable for the delivery of nasal vaccines<sup>14,15</sup>.

### Microspheres

Microsphere is one of the specialized formulations for nasal drug delivery. Mucoadhesive microspheres may help to increase residence time of drug inside the nasal mucosa and thus improve the bioavailability. The range of microspheres for intranasal drug delivery should be 10µ- 100µ<sup>16</sup>.

A. V. Yadav et al., prepared intranasal mucoadhesive microspheres for the delivery of antimigraine drug domperidone by using soluble starch polysaccharide in different concentration. Better bioavailability was found at 73.11% concentration of polysaccharide<sup>17</sup>. All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere's matrix, resulting in swelling of the spheres and the formation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal models. Also, some low-molecular weight drugs have been successfully delivered in microsphere preparations. The residence time in the cavity is considerably increased for microspheres compared to solutions. However, this is not the only factor to increase the absorption of large hydrophilic drugs. Microspheres also exert a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells. Starch and dextran microspheres have been administered repeatedly and can be classified as safe dosage forms<sup>18</sup>.

Recently Microsphere technology has been widely useful in designing of formulations for nasal drug delivery. Microspheres are usually based on muco-adhesive polymers (xanthan gum, Carbopol, polyacrylates, cellulose derivatives etc.), which provide various advantages for intranasal drug delivery. Nasal/ Pulmonary microspheres also protect the drug from enzymatic metabolism which occurs due to harsh environment in GIT and gives sustain drug release, thereby prolonging its effect. Aminated gelatin microspheres as a nasal drug delivery system for insulin has been investigated by Wang et al,. They observed a considerable hypoglycaemic effect when administered intra-nasally in dry powder form to rats. But there is no significant effect when given in a suspension. Gavine et al. have analyzed nasal mucosa after its exposure to microspheres of alginate/chitosan containing metoclopramide. They observed the opening of tight junctions in the epithelium and also observed that these spraydried microspheres have promising properties as mucoadhesive nasal carriers. Many other similar studies have been carried out and positive results are found for nasal delivery of carbamazepine using chitosan microspheres, cyclodextrins using chitosan and alginate as mucoadhesive polymers, Gentamycin using HPMC and carvedilol using alginate mucoadhesive microspheres<sup>19</sup>.

### **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. In addition, the outer chemistry of the shell may prevent recognition by the reticulo endothelial system, and therefore early elimination from the bloodstream. Colloidal systems, such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticles dispersions consisting of small particles of 10–400 nm diameter showed as great promising carriers in nasal drug delivery systems. A feature that makes micelles more attractive is that their size and shape can be changed. Chemical techniques using cross linking molecules can improve the stability of the micelles and their temporal control. Micelles may also be chemically altered to selectively target a broad range of disease sites<sup>20</sup>.

### **Nasal Gels**

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing devices, there is not much interest in this system. The

advantages of a nasal gel include 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. The deposition of the gel in the nasal cavity depends on the mode of administration. Due to its viscosity, the formulation has poor spreading abilities. Without special application techniques, it only occupies a narrow distribution area in the nasal cavity, where it is placed directly. Recently, the first nasal gel containing Vitamin B12 for systemic medication has entered the market<sup>21</sup>.

### Nasomucoadhesive drug delivery systems

It is one of the most important limiting factors for nasal drug delivery, because it reduces the time allowed for drug absorption. Thus, mucoadhesive drug delivery systems improving the nasal drug absorption, and also prolonging the contact time between drug and nasal mucosa. Mucoadhesion as a strategy improves systemic drug delivery via the nasal route. Mucoadhesion indicates the attachment of the drug delivery system to the mucus, involving an interaction between mucin and a synthetic or natural polymer called mucoadhesive. The sequential events that occur in mucoadhesion include.

- Firstly the mucoadhesive system absorbs water from mucus layer and get wet and swells.
- Secondly the polymer intimately penetrates into the mucus and localizes the formulation in nasal cavity, enhancing the drug concentration gradient across the epithelium.

Mucoadhesives are mostly used in intranasal drug delivery are hydrogels, hydrophilic polymers, polyacrylates, starch, chitosan, alginate and cellulose derivatives<sup>14</sup>.

**Table No: 1: Novel Formulation And Active Agent That Have Been Utilized In Nasal Drug Delivery**<sup>23,24,25</sup>

Sr. no.	Formulation	Active agent
1	<i>In-situ</i> nasal gel	Midazolam, Insulin, Triptans , Diltiazem
2	Nasal inserts	Chlorpromazine, Albuterol
3	Microspheres	Beta-amyloid fibril, Starch microspheres, Dextran Gentamicin, Insulin , Desmopressin
4	Microparticles	Serum albumin, Thiolated chitosan microparticles
5	Dry powder	Zolmitriptan
6	Nasal gel	Oxytocin, Metoclopramide Hydrochloride

### CONCLUSION

Nasal drug delivery system is used to minimize the limitation of conventional dosage form.

Bioavailability of pharmaceutical and biopharmaceuticals can be improved with lesser side effects due to localized form of delivery formulations and it will minimize the painful condition and reduce the dependence of patient over technical staff for delivery of drug. The natural mucoadhesive polymer as a carrier for nasal drug delivery can be used to improve the health of all living things and to minimize the unwanted effect of synthetic polymers. This review is highly illustrative of nasal drug delivery system which focuses on the modern advancement in nasal drug delivery system along with its challenges. This review also gives deep insight of requirements in upcoming future prospectus. In situ gel, nasal inserts, microspheres, microparticles and nanoparticles are being used to bring novelty in nasal drug delivery system.

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