ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2014; 5(3): 29 - 40

REVIEW ARTICLE

A Holistic Review on Nasoadhesive Microsphere

Neha Kashyap, Roshni Dhurve, Ashwani Mishra*, Anupam Kumar Pathak

Department of Pharmacy, Barkatullah University, Bhopal (M.P), India

Received 21 Feb 2014; Revised 02 May 2014; Accepted 14 May 2014

ABSTRACT

Nasal route has been demonstrated as a possible alternative to the intravenous route for the systemic delivery of drugs. It has been demonstrated that low absorption of drugs can be enhanced by increasing the drug residence time in the nasal cavity, by using mucoadhesive microspheres. The present review holds the brief introduction of the role of mucoadhesive microspheres in the nasal drug delivery, the interaction between the mucoadhesive microsphere and mucus, different theories of mucoadhesion and the researches done on nasoadhesive microspheres till date. As its Nasal route is being widely looked forward for the delivery of various drug categories for getting systemic as well as local effect and also for targeting drugs to brain

Key words*:* Nasoadhesive, Mucoadhesive, Mucus, Targeting, Systemic, Microsphere, Nasal route, Polymer, Brain.

INTRODUCTION

Nasal route has been demonstrated as being a possible alternative to the intravenous route for the systemic delivery of drugs. Along with the rapid absorption and avoidance of hepatic first-pass metabolism, the nasal route also allows the preferential delivery of drug to the brain via the olfactory region, and is thus, a promising approach for the rapid-onset delivery of medications [1].

Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called "NASAYA KARMA" [2]. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration [3].

The nose had been considered primarily as a route for local drug delivery. Advances in biotechnology have made available a large number of protein and peptide drugs for the treatment of a variety of diseases. These drugs are unsuitable for oral administration because they are significantly degraded in the gastrointestinal tract or considerably metabolized by first pass effect in the liver. The parenteral route is inconvenient for long term therapy as it is invasive. Among the various alternative routes tried, intranasal drug delivery is found much promising for administration of these drugs [4].

The larger drug molecules showed poor bioavailability, typically in the order of 5–10%. On the other hand, very good results were obtained with small organic molecules [5]. The causes of failure led to the conclusion that the short residence time of the formulation within the nasal cavity is the reason for the low permeability. Consequently, the attention shifted towards the mucoadhesive polymers, some of which would also demonstrate permeation- enhancing property [6]. The encouraging results stimulated the development of new generations of polymers based on pH or thermal responsiveness or modified existing polymers having improved bioadhesive or permeation-enhancing properties [7,8,9]. Even though a number of challenges are still to be overcome, especially with respect to toxicity, the potential of nasal drug delivery (NDD), including the ability to target drugs cross the blood–brain barrier (BBB), are very high and continues to stimulate academic and industrial research groups so that we will keep witnessing increasing number of advanced nasal drug delivery products.

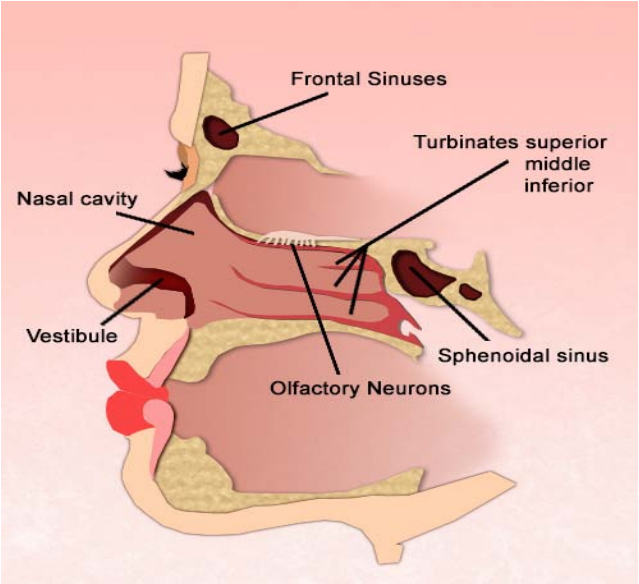
NASAL ANATOMY AND PHYSIOLOGY

The nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption. The reason for this is the large surface area, porous nature of

***Corresponding Author:** Ashwani Mishra, **Email:** ashwanipharma@gmail.com

endothelial membrane, high total blood flow to the nasal cavity and the avoidance of first-pass metabolism. Various drugs including peptides and proteins had been administered nasally for getting systemic effect and investigated widely in recent years.

In the recent past many researchers have also attempted to deliver the drugs to the CNS through the nose [10-17]. The nose is divided into two nasal cavities by septum. The volume of each cavity is around 7.5mL and has a surface area approximately 75 cm^2 [18,19,20]. There are three distinct functional regions in the nose- the vestibular, respiratory and olfactory. Among these, the respiratory region is the most important for systemic drug delivery [20].



The respiratory epithelium consists of four types of cells-basal, mucus-containing goblet, ciliated columnar and nonciliated columnar cell [20,21]. The cilia move in a wave like fashion to transport particles to the pharynx area for ingestion [20,22]. Additionally, the cells in this region are covered by nearly 300 microvilli which provide a large surface area for absorption [20]. Below the epithelium is the lamina propria, where blood vessels, nerves, serous glands, and mucus secretory glands may be found [21]. The lamina propria possess a dense network of capillaries, through which drug absorption takes place. The nasal epithelium is covered by a mucus layer that is renewed every 10 to 15 minutes [23]. The pH of the mucosal secretions ranges from 5.5 to 6.5 in adults [24]. The mucus layer entraps particles, which are consequently cleared from the nasal cavity by the cilia. The mucus moves through the nose at a rate of 5 to 6 mm/ min (approximately) resulting in particle clearance every 20 minutes [19].

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM

1. Provides rapid absorption and fast onset of action of drug due to relatively large surface of absorption and high vascularization.
2. Avoidance of hepatic first pass metabolism and thus reduce the dose significantly as compared to oral delivery.
3. Penetration of lipophilic, low molecular weight drugs through the nasal mucosa is good.
4. Direct delivery of drug to the CNS via the olfactory region, thus, by-pass the blood brain barrier [25].
5. Direct delivery of vaccine to lymphatic tissue and induction of a secretory immune response at distant mucosal site [26].
6. Easy accessibility, non invasive drug delivery and do not require trained personnel; this facilitates self medication, thus patient compliance is improved as compared to parenteral routes [27].

DISADVANTAGES OF NASAL DRUG DELIVERY SYSTEM

1. All drugs cannot be given by this route..
2. Some drugs can cause nasal irritation.
3. Few drugs undergo enzymatic degradation in nasal cavity.

One of the major limitations of nasal route is the Mucociliary clearance. The function of mucociliary clearance system is to remove foreign substances and particles from the nasal cavity, consequently preventing them from reaching the lower airways. The normal mucociliary transit time in humans has been reported to be 12-15 min, which limits the time available for absorption [28,29]. Rapid mucociliary clearance of drug formulations that are administered in the nasal cavity is thought to be an important factor underlying the low bioavailability of intranasally administered drugs.

Microspheres can be used as carriers to encapsulate an active drug and can be designed to be mucoadhesive to increase the retention time and facilitate sustained release.

MUCOADHESIVE MICROSPHERES

Microspheres are small spherical particles (typically 1 μm to 1000 μm), sometimes referred to as microparticles. The microspheres can be

made up of either natural or synthetic polymers [30].

Generally microspheres possess potential to be employed for targeted and controlled release of drug, but incorporating mucoadhesive properties to microspheres will furthermore improve absorption and bioavailability of the drugs [31-34]. Tailored mucoadhesive microspheres offers the possibilities of localized as well as controlled release of drugs by adherence to any mucosal tissue present in eye, nasal cavity, urinary, and GI tract.

Advantages of Mucoadhesive Microspheres [30]:

1.Provide sustained therapeutic effect.
2.Reduces the frequency of drug administration and thus improve patient compliance.
3.Improve the bioavailability of drug by improving absorption..
4. As drug dose is reduced, the chance of adverse effects also decreased.

Limitation of Mucoadhesive Microspheres [30]:

1.The release rate may alter by a variety of factors like food and the rate of transit though gut, mucin turnover rate etc.
2.Differences in the release rate may occur from one dose to another.
3.Any loss of integrity of formulation alters the release pattern of the dosage form may lead to potential toxicity.
4.These dosage forms cannot be crushed or chewed.

Table 1: Some of Mucocoadhesive Polymers Used Are [35]

Synthetic polymers	Natural polymers
Hydroxy propyl methyl cellulose (HPMC)	Chitosan
Poly acrylic acid polymers(carbomers, polycarbophil)	Sodium alginate
Poly vinyl pyrrolidone (PVP)	Pectin
Poly vinyl alcohol (PVA)	Locust bean gum
Poly hydroxyethyl methylacrylate	Guar gum
Poly ethylene oxide	Xanthan gum
Sodium carboxy methyl cellulose (Na CMC)	Karaya gum
Hydroxyl ethyl cellulose (HEC)	Gelatin
Hydroxy propyl cellulose (HPC)	Tragacanth
Ethyl cellulose (EC)	Soluble starch

POLYMER –MUCUS INTERACTION

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. The series of events occurring during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive polymer, leading to the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently, weak chemical bonds can become operative [36,37].

Hydration of the polymer plays a very important role in bioadhesion. A critical degree of hydration is required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not entirely liberated and available for interaction. On the other hand, an excessive hydration leads to weakening due to over extension of the hydrogen bonds. During hydration, dissociation of hydrogen bonds of the polymer chains takes place. The polymer–water interaction becomes more than the polymer–polymer interaction, thereby making the polymer chains available for mucus penetration [38].

THEORIES OF MUCOADHESION

1. Electronic theory:

According to this theory, electron transfer occurs upon contact of adhesive polymer with a mucus glycoprotein network because of difference in their electronic structures which results in the formation of electrical double layer at the interface. For example, Interaction between positively charged polymer- chitosan and negatively charged mucosal surface [39,40].

2. Adsorption theory:

According to this theory, after an initial contact between two surfaces, the material adheres because of the presence of the surface force between the atoms of two surfaces. The adsorption theory of bioadhesion states that adhesion of a polymer to a biological tissue results due to: (1) primary chemical bonds that are somewhat strong and permanent and therefore undesirable in bioadhesion, (2) Vander Waals, hydrogen, hydrophobic and electrostatic forces form secondary chemical bonds [41-43].

3. Diffusion theory:

According to this theory, a semi-permanent

adhesive bond is created between the polymer chains and the mucus when they mix to a sufficient depth. The depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact [44,45].

4. Wetting theory:

The wetting theory postulates that if the contact angle of liquids on the substrate surface is less, then there is a high affinity for the liquid to the substrate surface and it spreads easily. When two substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive between the two substrate surface [46-48].

5. Fracture Theory of Adhesion:

This theory states that the force required for the separation of two surfaces after adhesion is equal to adhesive strength through the following equation:

$$\sigma = (E \times \varepsilon/L)1/2$$

where; σ is the fracture strength, ε fracture energy, E young modulus of elasticity, and L the critical crack length. This theory is useful for the study of bioadhesion by tensile apparatus [49].

METHOD OF PREPARATION

Mucoadhesive microspheres can be prepared by using different techniques like:

1. Complex coacervation
2. Hot melt microencapsulation
3. Single emulsion technique
4. Double emulsion method
5. Solvent extraction method
6. Solvent evaporation method
6. Ionotropic gelation
8. Spray drying

Complex Coacervation:

In this method the coating material phase is prepared by dissolving immiscible polymer in a suitable vehicle and the core material is dispersed in a solution of the coating polymer under constant stirring. Microencapsulation is achieved by utilizing one of the methods of phase separation:

- by altering the temperature of the polymer solution
- by changing the pH of the medium
- by adding a salt or an incompatible polymer or a non-solvent to the polymer solution
- by inducing a polymer polymer interaction.

The microspheres thus formed are filtered and washed and dried [50.51].

Hot Melt Microencapsulation:

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. After the emulsion is stabilized, it is cooled until the polymer particles solidify. The obtained microspheres are then washed by decantation with petroleum ether [52].

Single Emulsion Technique:

The microspheres of natural polymers are prepared by single emulsion technique. The polymers and drug are dissolved or dispersed in aqueous medium followed by dispersion in organic medium e.g. oil, results in formation of globules, and then the dispersed globules are cross linked by either using heat or by using the chemical cross-linkers. The chemical cross-linkers used are formaldehyde, glutaraldehyde, diacid chloride etc. [53]

Double Emulsion Method:

In this method an aqueous solution of drug and polymer is added to the organic phase with vigorous stirring to get primary water-in-oil emulsion. This emulsion is then poured to a large volume of water containing an emulsifier like polyvinyl alcohol or polyvinylpyrrolidone, under stirring, to get the multiple emulsions (w/o/w). The stirring is continued until most of the organic solvent evaporates, leaving solid microspheres. The microspheres are then washed and dried [54].

Solvent Extraction:

This method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process involves direct addition of the drug or protein to polymer organic solution which is then added to the aqueous continuous phase. The organic water miscible solvent on coming in contact with water is extracted and solid microspheres are eventually obtained [55].

Solvent Evaporation:

In this technique the drug is dissolved in polymer which was previously dissolved in water immiscible volatile organic phase and the resulting solution is added to aqueous phase containing emulsifying agent. The above mixture is stirred till the drug and polymer transformed into fine droplet which solidified into rigid

microspheres by solvent evaporation .The microspheres are then collected by filtration and washed with demineralised water and dried [55,56].

Ionotropic Gelation Method:
In this method, microspheres are formed by dissolving the gel type polymers (alginate, chitosan etc.) in an aqueous solution followed by suspending the drug in the polymer solution and extruding the solution through needle to produce micro droplets which fall into a polyionic hardening solution under stirring at low speed [57].

Spray Drying:
In Spray Drying the polymer is dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug is then dispersed in the polymer solution under high-speed homogenization. After this dispersion is atomized in a stream of hot air leading to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying [58].

EVALUATION OF MUCOADHESIVE MICROSPHERES

The microspheres are evaluated for the following parameters.

1. **Particle Size and Shape:**
   Light microscopy (LM) and scanning electron microscopy (SEM) both can be used to determine the size, shape and outer structure of microspheres [53].

2. **Surface Characterization of The Mucoadhesive Microspheres:**
   Data from the scanning electron microscopy, scanning tunneling microscopy and the electron microscopy provides insight to the surface morphology of microspheres and the morphological changes produced through degradation of polymer. Changes in the surface morphology occurring through degradation of polymer can be studied by incubating the microspheres in the phosphate buffer saline at different intervals of time. It was found that microspheres with the coarser surface improve the adhesion through stronger mechanical interactions, while smooth surface of the microspheres leads to weak mucoadhesive properties [32,46].

3. **Surface Charge Study:**From photon correlation spectroscopy data the surface charge (zeta potential) of the mucoadhesive microspheres can be determined. The surface charge can be determined by relating measured electrophoretic mobility into zeta potential with in-built software based on the Helmholtz– Smoluchowski equation. Zeta potential is an indicator of particle surface charge, which is used to predict and control the adhesive strength, stability, and the mechanisms of mucoadhesion [59].

4. **Entrapment Efficiency:**
   The entrapment efficiency of the microspheres or the percent entrapment can be determined by keeping the microspheres into the buffer solution and allowing lysing. The lysate obtained is filtered or centrifuged and then subjected for determination of active constituents as per monograph requirement. The percent entrapment efficiency is calculated using following equation [53]:
   % Entrapment = Actual content/Theoretical content x 100

5. **Swelling Index:**
   Swelling index illustrate the ability of the mucoadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption ,which is a primary requirement for initiation of mucoadhesion. The percent swelling value can be determined using following equation [60]:

   Percent swelling = DT - D0 / D0 × 100

   Where; D0 = weight of dried microspheres
   DT = weight of swelled microspheres.

6. ***In- Vitro* Diffusion Study:**
   In Vitro diffusion studies can be performed using *in vitro* nasal diffusion cell. The receptor chamber is filled with buffer maintained at 37 ± 2°C. Accurately weighed microspheres equivalent to 10 mg are spread on sheep nasal mucosa. At selected time intervals, 0.5 ml of diffusion samples are withdrawn through a hypodermic syringe and replaced with the same volume of pre-warmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples are analyzed spectrophotometrically [61].

7. ***Ex-Vivo* Mucoadhesion Study**:
   A strip of sheep nasal mucosa is mounted on a glass slide and 50 mg of accurately weighed microspheres are sprinkled on the nasal mucosa. This glass slide is incubated for 15 min in a desiccator at 90% relative humidity to

allow the polymer to interact with the membrane and finally placed on the stand at an angle of 45º. Phosphate buffered saline of pH 6.4 previously warmed to 37 ± 0.5 ºC is allowed to flow over the microspheres and membrane at the rate of 1 ml/min for 5 min with the help of a peristaltic pump. At the end of the process, the detached particles are collected and weighed [62].

$$\% \text{ Mucoadhesion} = (W_a - W_1) / W_a \times 100$$

Where; W_a is the weight of microspheres sprinkled, W_1 is the weight of microspheres detached.

8. **Stability studies of Microsphere:**
Stability studies are carried out at 5 ºC ± 3º C, 25 ºC ± 2 ºC /60% ± 5% RH and 40 ºC ± 2º C / 75% ± 5% RH. The selected formulations are packed in amber coloured glass containers and closed with air tight closures and stored for 90 days. Samples are analyzed at the end of 30, 60 and 90 days for % Drug entrapment efficiency, *in vitro* mucoadhesion test and *in vitro* drug diffusion studies [63].
9. **Drug polymer interaction (FTIR) study:**
The FTIR studies reveal the interactions between the drug and the polymer used.

RESEARCH DONE ON INTRANASAL MICROSPHERES

Various researches have been done using different mucoadhesive polymers. Chitosan has been widely used in researches. In 2014, Kashikar V *et al.,* formulated and evaluated nasal mucoadhesive microsphere of Pirfenidone by spray drying and cross-linking method using chitosan and HPMC K4M. They concluded that drug release from microspheres followed non-Fickian diffusion kinetics and the histopathological study indicated nonirritant nature of microsphere [64].

A successful attempt was made by Dave K *et al.,* in 2013 to deliver Lamotrigine via intranasal route as mucoadhesive microspheres, developed by emulsion-solvent evaporation using chitosan as polymer, cross linked by Gluteraldehyde. And similar work was done by Pilicheva B *et al.,* in the same year using same polymer. They formulated and evaluated betahistine-loaded chitosan microspheres intended for nasal delivery using W/O emulsion solvent evaporation technique. Both the studies confirmed that chitosan based microspheres are suitable for the intranasal delivery of respective drugs [65.66].

Chitosan was also used by Nagda CD *et al*., 2012 for delivery of Ketorolac [67]. In 2011, Deshpande T. *et al.* and Ibezim EC. *et al*., for Sumatriptan and Pyrimethamine [68,69], respectively. Chitosan has been found compatible with many drugs namely, Promethazine HCL (Iliger SR. & Demappa T. 2011), Carvedilol (Patil S *et al.,* 2010), Resveratrol (Peng H. *et al*., 2010), Clonazepam (Shaji J. *et al.,* 2009), Amlodipine besylate (Patil SB & Murthy RS. 2006), Propranolol HCl (Harikarnpakdee S. et al., 2006).

Egg albumin and Pectin were also used as a mucoadhesive polymer. In 2012, Jain BK prepared mucoadhesive norethisterone-egg albumin microspheres by multiple emulsion method by the gluteraldehyde cross linking and thermal denaturation technique for nasal administration. In same year Mahajan HA *et al.,* prepared Odansetron microspheres by the spray–drying technique using pectin as polymer The results obtained showed that microspheres had sufficient mucoadhesive strength [67,68].

Gelatin, HPMC, Carbopol, PVA are other few polymers on which researches hav been done. In 2011, Iliger SR *et al*.,formulated mucoadhesive microspheres of Promethazine hydrochloride in the blend of gelatin and chitosan for intranasal systemic by emulsion crosslinking method using Glutaradehyde as a crosslinking agent. Results showed good mucoadhesivity and drug release profile.

In 2011, Nanjwade BK *et al*., worked on HPMC and Carbopol for intranasal delivery of Neostigmine bromide. Both *in-vitro* and *in-vivo* studies concluded that Carbopol based microspheres are better than HPMC based microspheres for the delivery of Neostigmine Bromide. In 2011, Prajapati RK. *et al.* and Swamy NGN & Abbas Z used PGLA and PVA respectively for intranasal delivery of respective drugs, Carvedilol and Amlodipine besylate.

Different grades of HPMC were studied by Jain SA. *et al*., in 2009.They developed mucoadhesive microspheres of sumatriptan succinate (SS) using hydroxypropyl methylcellulose (HPMC) K4M and K15M by spray-drying technique. The particle size, swelling ability and incorporation efficiency of microspheres was found to increase

with increasing drug-to-polymer ratio.

Alginate was studied by Patil SB *et al.*, in 2009. They aimed at development and optimization of alginate mucoadhesive microspheres of carvedilol for nasal delivery. The microspheres were prepared by water -in-oil (w/o) emulsification technique. *In vitro* mucoadhesion was observed in a range from 69.25-85.28.

Starch was also studied for its mucoadhesive properties. In 2008, Yadav AV *et al.*, formulated Domperidone microspheres for intranasal administration by emulsification crosslinking technique using starch a biodegradable polymer and epichlorhydrine as cross-linking agent. Bioadhesive strength was in range from 8.51 g to 9.67 g.

Table 2: List of researches done till date on mucoadhesive microspheres for nasal delivery

S. No	Compound	Polymer	Researcher, Year
1	Pirfenidone	Chitosan, HPMC K4M	Kashikar V. et al.,2014
2	Lamotrigine	Chitosan	Dave K & Purohit S. 2013
3	Betahistine dihydrochloride	Chitosan	Pilicheva B *et al.*, 2013
4	Norethisterone	Egg albumin	Jain BK, 2012
5	Odansetron	Pectin	Mahajan HA. *et al.*, 2012
6	Ketorolac	Chitosan, Carbophil and Carbopol	Nagda CD *et al*., 2012
7	Sumatriptan	Chitosan	Deshpande T. *et al.*, 2011
8	Pyrimethamine	Chitosan	Ibezim EC. *et al*., 2011
9	Sumatriptan	Chitosan	Khalandar DKS. *et al.*, 2011
10	Neostigmine bromide	HPMC,Carbopol	Nanjwade BK. *et al*., 2011
11	Carvedilol	PGLA	Prajapati RK. *et al.* 2011
12	Amlodipine besylate	PVA	Swamy NGN & Abbas Z. 2011
13	Promethazine HCl	Gelatin A, Chitosan	Iliger SR. & Demappa T. 2011
14	Midazolam	Carbopol 934P	Desai S. *et al*., 2010
15	Carvedilol	Chitosan	Patil S *et al.*, 2010
16	Resveratrol	Chitosan	Peng H. *et al*., 2010
17	Sildenafil	Gellan gum	Shah V *et al.*, 2010
18	Sumatriptan succinate	HPMC K4M, HPMC K15M	Jain SA. *et al*., 2009
19	Carvedilol	Alginate	Patil SB & Sawant KK. 2009
20	Clonazepam	Gelatin -Chitosan	Shaji J. *et al.*, 2009
21	Domeperidome	Starch	Yadav AV. *et al.*, 2008
22	Propranolol HCl	Gelatin	Dandagi P. *et al*., 2007
23	Amlodipine besylate	Chitosan	Patil SB & Murthy RS. 2006
24	Propranolol HCl	HPMC, Chitosan, Carbopol934P	Harikarnpakdee S. et al., 2006

APPLICATION OF NASAL DRUG DELIVERY SYSTEM

Local delivery [94,95]:

Antihistamines and corticosteroids for rhinosinusitis and nasal decongestants for cold symptoms are common examples for the local delivery of drugs via nasal route.

Systemic delivery [94,96-98]:

The intranasal administration of drugs is an effective way for systemic availability of drugs as compared to oral and intravascular routes as it is facilitates fast and extended drug absorption. Examples include analgesics (morphine), cardiovascular drugs as propranolol and carvedilol, hormones such as levonorgestrel, progesterone and insulin, anti-inflammatory agents as indomethacin and ketorolac, and antiviral drugs (acyclovir). Some examples which are available in the market include zolmitriptan and sumatriptan for the treatment of migraine and cluster headaches.

Nasal vaccines [99-101]:

Nasal mucosa is the first site of contact with inhaled antigens and therefore, it is used for vaccination, especially against respiratory infections. Examples of the human efficacy of intranasal vaccines include those against influenza A and B virus, proteosoma-influenza, adenovirus-vectored influenza, group B meningococcal native, attenuated respiratory syncytial virus and para-influenza 3 virus.

CNS delivery through nasal route [95]**:**

The delivery of drugs to the CNS from the nasal route may occur via olfactory neuro-epithelium and also via trigeminal nerve system. Drug delivery through nasal route into CNS has been reported for Alzheimer's disease, brain tumors, epilepsy, pain and sleep disorder.

CONCLUSION

A Conclusion which can be drawn from the review is that, mucoadhesive microspheres thus offer versatile and promising drug delivery system which enhances bioavailability and specific needs by utilizing multiple modification steps, polymer, methods and number of process parameters of dosage form and it symbolize adaptability, compatibility and versatility of mucoadhesive microsphere for nasal cavity.

REFERENCES

1. Lawrence MJ, Warisnoicharoen W. Recent Advances in Microemulsions as Drug Delivery Vehicles. In: Vladimir PT, editor. Nanoparticulates As Drug Carriers. London: Imperial College Press; 2006.p. 124-171.
2. Chein YW, Su KS, Chang SF. Nasal system delivery. In: Chein YW, editor. Novel Drug Delivery Systems. 2nd ed. New York: Dekker; 1989.p. 229-266.
3. Turker S, Onur E, Ozer Y. Nasal route and drug delivery systems. Pharm world Sci 2004; 26: 137-142.
4. Beht *et al*. Optimization of systemic nasal drug delivery with pharmaceutical excipients. Adv Drug Del Rev 1998; 29: 117-133.
5. Luessen HL, Verhoef JC, Boer AG, Junginger HE, De Leeuw BJ, Borchard G, *et al*. Multifunctional polymers for the peroral delivery of peptide drugs. In: E. Mathiowitz. D.E. Chickering III. C.-M. Lehr, editors. Bioadhesive Drug Delivery Systems. Fundamentals. Novel Approaches and Development. New York: Marcel Dekker; 1999.p. 299– 339.
6. Dodane V, Amin KM, Merwin JR. Effect of chitosan on epithelial permeability and structure. Int J Pharm 1999; 182: 21– 32.
7. Kotze AF, Luessen HL, Thanou M, Verhoef JC, De Boer AG, Junginger HE, et al. Chitosan and chitosan derivatives as absorption enhancers for peptide drugs across mucosal epithelia. In: E. Mathiowitz. D.E. Chickering III. C.-M. Lehr editors. Bioadhesive Drug Delivery Systems. Fundamentals. Novel Approaches and Development. New York: Marcel Dekker; 1999.p. 341–386.
8. Bernkop-Schnurch A, Kast CE, Richter MF. Improvement in the mucoadhesive properties of alginate by the covalent attachment of cysteine. J Control Release 2001; 71: 277– 285.
9. Wang J, Sakai S, Deguchi Y, Bi D, Tabata Y, Morimoto K. Aminated gelatin as a nasal absorption enhancer for peptide drugs: evaluation of absorption enhancing effect and nasal mucosa perturbation in rats. J Pharm Pharmacol 2002; 54:181–188.
10. Mygind N. Scanning electron microscopy of the human nasal mucosa. Rhinology 1975; 13: 57-75.
11. Watanabe K, Watanabe I, Saito Y, Mizuhira V. Characteristics of capillary permeability in nasal mucosa. Ann Otol Rhinol Laryngol 1980; 89: 377-382.
12. Geurkink N. Nasal anatomy, physiology, and function. J Allergy Clin Immunol 1983; 72: 123-128.
13. Brofeldt S, Secher C, Mygind N. Biophysical characteristics of nasal secretions: A preliminary report. Eur J Respir Dis 1983; 64: 436-440.
14. Bende M. Studies of blood flow in the human nasal mucosa. Eur J Respir Dis 1983; 64: 400-402.
15. Bisgaard H, Krogsgaard O, Mygind N. Measurement of secretion in nasal lavage. Clin Sci 1987; 73: 217-222.
16. Dawes JDK, Prichard M. Studies of the vascular arrangement of the nose. J Anat 1953; 87: 311-322.
17. Cauna N, Hinderer KH. Fine structure of blood vessels of the human nasal respiratory mucosa. Ann Otol Rhinol Laryngol 1969; 78: 865-885.
18. Pomponi M, Giacobini E, Brufani M. Present state and future development of the therapy of Alzheimer's disease. Aging 1990; 2: 125-153.
19. Mygind N, Anggard A. Anatomy and physiology of the nose pathophysiology alterations in allergic rhinitis. Clin Rev Allergy 1984; 2: 173-188.
20. Illum L. Transport of drugs from the nasal cavity to the central nervous system. Eur J Pharm Sci 2000; 11: 1-18.

21. Schipper NG, Verhoef JC, Merkus FW. The nasal mucocilliary clearance: relevance to nasal drug delivery. Pharm Res 1991; 8: 807-814.
22. Mathison S, Nagilla R, Kompella UB. Nasal route for direct delivery of solutes to the central nervous system: fact or fiction. J Drug Target 1998; 5: 415-441.
23. Chien YW, Chang SF. Intranasal drug delivery for systemic medication. Crit Rev Ther Drug Carrier Syst 1987; 4: 67-194.
24. Hehar SS, Mason JD, Stephen AB, Washington N, Jones NS, Jackson SJ, *et al*. Twenty four hour ambulatory nasal pH monitoring. Clin Otolaryngol Allied Sci 1999; 24: 24-25.
25. Talegaonkar S, Mishra PR. Intranasal delivery: An approach tobypass the blood brain barrier. Ind J Pharmacol 2004; 36 Suppl 3:140-147.
26. Davis SS. Nasal vaccines. Adv Drug Deliv Rev 2001; 51: 21-42.
27. Pontiroli A, Albertto M, Calderara A, Pajetta E, Pozza G. Absolute bioavailability of nicotine applied to different Nasal administrationof glucagon and human calcitonin to nasal regions. Eur J Clin Pharmacol 1991; 41: 585-588.
28. Schipper NGM, Verhoef JC, Merkus HM. The nasal mucociliary clearance: relevance to nasal drug delivery. Pharm Res 1991; 8: 807.14.
29. Liote H, Zahm JM, Pierrot D, Puchelle E. Role of mucus and cilia in nasal mucociliary clearance in healthy subjects. Am Rev Respir Dis 1989; 140: 132-136.
30. Kataria S, Middha A, Sandhu P, Bilandi A, Kapoor B. Microsphere: A Review. Int J Res Pharm Chem 2011; 1 Suppl 4: 1185-1198.
31. Kunisawa J, Okudaira A, Tsutusmi Y, Takahashi I, Nakanishi T, Kiyono H, *et al*. Characterization of mucoadhesive microspheres for the induction of mucosal and systemic immune responses .Vaccine 2000; 19 Suppl 4: 589-594.
32. Chowdary KPR, Rao YS. Mucoadhesive microspheres for controlled drug delivery. Biol Pharm Bull 2004; 27 Suppl 11:1717-1724.
33. Belgamwar V, Shah V, Surana SJ. Formulation and evaluation of oral mucoadhesive multiparticulate system containing metoprolol tartarate: an *in vitro, ex vivo* characterization. Curr Drug Deliv 2009; 6 Suppl 1:113-121.
34. Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of furosemide: *in vitro* and *in vivo* evaluations of bilayer tablet formulations. Drug Dev Ind Pharm. 2000; 26 Suppl 8: 857-866.
35. Punitha S, Girish Y. Polymers in mucoadhesive buccal drug delivery system: A review. Int J Res Pharm Sci 2010; 1 Suppl 2: 170-186.
36. Jimenez-Castellanos MR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm 1993; 19: 143– 194.
37. Duchene D, Touchard F, Peppas NA. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Dev Ind Pharm, 1988; 14: 283– 318.
38. Chang HS, Park H, Kelly P, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery: II. Synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers. J Pharm Sci 1985; 74: 399– 405.
39. Derjaguin BV, Toporov YP, Muller VM, Aleinkova IN. On the relationship between the molecular component of the adhesion of elastic particles to a solid surface. J Colloid Interface Sci 1966; 58: 528-533.
40. Lee JW, Park JH, Robinson JR, bioadhesive based dosage forms: the next generation, J Pharm Sci 2000; 89: 850-86.
41. Longer MA, Robinson JR. Fundamental aspects of bioadhesion. Pharm Int 1986; 5:114– 117.
42. Good RJ. Surface energy of solids and liquids. Thermodynamics, molecular forces, and structure. J Colloid Interface Sci 1977; 59: 398-419.
43. Tabor D. surface forces and surface interactions. J Colloid Interface Sci 1977; 58: 2-13.
44. Voyutskii SS. Autoadhesion and adhesion of high Polymers. In: H.F. Mark, E.H. Immergut, editors. Polymer Reviews. 1st ed. New York: John Wiley & Sons; 1963.p. 272.
45. Mikos AG, Peppas NA. Systems for controlled release of drugs- Bioadhesive systems. S T P Pharmacol 1986; 2: 705-716.
46. Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer

bioadhesion on soft tissue. J Controlled Release 1985; 2: 257-275.
47. Mikos AG, Peppas NA. Measurement of the surface tension of mucin solutions. Int J Pharm 1989; 53: 1-5.
48. Baszkin A, Proust JE, Monsengo P, Boissonnade MM. Wettability of polymers by mucin aqueous solutions. Bio rheology 1990; 27:503-514.
49. Kammer HW. Adhesion between polymers. Acta Polym 1983; 34: 112.
50. Zhang L, Liu Y, Wu Z and Chen H. Preparation and characterization of coacervate microcapsules for the delivery of antimicrobial oyster peptides. Drug Dev Ind Pharm. 2009; 35 Suppl 3: 369-278.
51. Mathiowitz E, Kreitz MR and Peppas LB. Microencapsulation. In: Mathiowitz E, editor. Encyclopedia of Controlled Drug Delivery. New York: John Willey & Sons; 1999; 9: 493-504.
52. Mathiowitz E and Langer R. Polyanhydride microspheres as drug carriers I. Hot-melt microencapsulation. J Control Release 1987; 5 Suppl 1: 13-22.
53. Alagusundaram M, Chetty MS, Umashankari K, Badarinath AV, Lavanya C, Ramkanth S. Microspheres as a novel drug delivery system: A review. Int J Chem Tech Res 2009; 1 Suppl 3: 526-534.
54. Bogataj M, Mrhar A, Korosec L. Influence of physicochemical and biological parameters on drug release from microspheres adhered on vesical and intestinal mucosa. Int J Pharm1999; 177 Suppl 2: 211-220.
55. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery: Novel Carrier System. 1st ed. New Delhi: CBS publication and distributors; 2002.p. 81-121.
56. Patel NR, Patel DA, Bharadia PD, PandyaV, Modi V. Microsphere as a novel drug delivery. Int J of Pharm & Life Sci 2011; 2 Suppl 8:992-997.
57. Lim F, Moss RD. Microencapsulation of living cells and tissues. J Pharm Sci 1981; 70 Suppl 4: 351-354.
58. U.S. Koff (1963). Patent, March 2, 1963, *3*, 080, 292.
59. Bogataj M, Vovk T, Kerec M, Dimnik A, Grabnar I, Mrhar A. The correlation between zeta potential and mucoadhesion strength on pig vesical mucosa. Biol Pharm Bull. 2003; 26 Suppl 5: 743 746.
60. Rajput G, Majmudar F, Patel J, Thakor R, Rajgor NB. Stomach-specific mucoadhesive microsphere as a controlled drug delivery system. Sys Rev Pharm 2010; 1 Suppl 1:70-78.
61. Patel JK, Patel RP, Amin AF, Patel MM. Formulation and evaluation of mucoadhesive glipizide microspheres. AAPS Pharm Sci Tech 2005; 6:49-55.
62. Pisal S, Shelke V, Mahadik K, Kadam S. Effect of Organogel components on *in vitro* nasal delivery of Propranolol hydrochloride. AAPS Pharm Sci Tech 2004; 4: 1-9.
63. Tamizharasi S, Rathi JC, Rathi V. Formulation and evaluation of Pentoxifylline-loaded poly (-caprolactone) microspheres. Ind J Pharm Sci 2008; 70 Suppl 3: 333-7.
64. Kashikar V, Dhole S, Kandekar U, Khose P. Study of mucoadhesive microsphere of pirfenidone for nasal drug delivery .Asian J Pharm 2014;8:43-50.
65. Dave K, Purohit S. Formulation and *in vitro* characterization of intranasal mucoadhesive microspheres of Lamotrigine using chitosan by gluteraldehyde cross linking. Int J Pharm Bio Sci 2013; 4 Suppl 3:402 – 415.
66. Pilicheva B, Zagorchev P, Uzunova Y, Kassarova M. Development and *in vitro* evaluation of mucoadhesive microsphere carriers for intranasal delivery of Betahistine dihydrochloride. Int J Drug Delivery 2013; 5: 389-401.
67. Jain BK. Preparation and *in vitro* characterization of mucoadhesive Norethisterone-egg albumin microspheres for nasal aministration. Asian J Biomed Pharm Sci 2012; 2 Suppl 15:49-57.
68. Mahajan HA, Tatiya BV, Nerkar PP. Ondansetron loaded pectin based microspheres for nasal administration: *In vitro* and *in vivo* studies. Powder Tech 2012; 221:168-176.
69. Nagda CD, Chotai NP, Nagda DC, Patel SB, Patel UL. Preparation and characterization of spray dried mucoadhesive microspheres of Ketorolac for nasal administration.Curr Drug Deliv 2012; 9 Suppl 2:205-218.

70. Rastogi B, Chaudhary A, Nagaich U. Formulation development and evaluation of Aceclofenac Chitosan Microspheres. J Adv Pharm Edu & Res 2012; 2 Suppl 4:215-220.
71. Deshpande T, Masareddy R, Bolmal U. Development of mucoadhesive microspheres for nasal delivery of Sumatriptan. Int J Pharm Sci Rev Res 2011; 7 Suppl 2:193-197.
72. Ibezim EC, Andrade CT, Marcia C, Barretto B, Odimegwu DC. Lima FD**.** Ionically cross-linked Chitosan/Tripolyphosphate microparticles for the Controlled Delivery of Pyrimethamine. Ibnosina J Med Biomed Sci 2011; 77-88.
73. Iliger SR, Demappa T. Formulation and characterization of mucoadhesive microspheres of Promethazine hydrochloride for nasal delivery. J Pharm Res 2011; 4 Suppl 1:276-279.
74. Khalandar DKS, Yajaman S, Jayaveera KN. Chitosan based nasal microspheres of Sumatriptan: Formulation and *in vitro* evaluation. Res J Pharm Biol Chem Sci 2011; 2 Suppl 3:489-498.
75. Nanjwade BK, Parikh KA, Deshmukh RV, Nanjwade VK, Gaikwad KR, Thakare SA, *et al*. Development and evaluation of intranasal mucoadhesive microspheres of Neostigmine bromide. Pharm Anal Acta 2011; 2 Suppl 2:1-6.
76. Prajapati RK, Mahajan HS, Surana SJ. PLGA based mucoadhesive microspheres for nasal delivery: *in vitro / ex vivo* studies. Indian J Novel Drug delivery 2011; 3 Suppl 1:9-16.
77. Swamy NGN, Abbas Z. Preparation and in vitro characterization of mucoadhesive polyvinyl alcohol microspheres containing Amlodipine besylate for nasal administration. Ind J Pharm Sci 2011; 73 Suppl 6:608-614.
78. Wang G, Li P, Peng Z, Huang M, Kong L. Formulation of vanillin cross-linked chitosan nanoparticles and its Characterization**.** Adv Mat Res 2011; 335-336:474-477.
79. Desai S, Vidyasagar G, Desai D, Brain targeted nasal Midazolam microspheres. Int J Pharm Biomed Sci 2010; 1 Suppl 2:27-30.
80. Patil S , Babbar A, Mathur R, Mishra A, Sawant K. Mucoadhesive chitosan microspheres of Carvedilol for nasal administration. J Drug Target. 2010; 18 Suppl 4:321-331**.**
81. Peng H, Xiong H, Li J, Liu Y, Bai C, Chen L. Vanillin cross-linked chitosan microspheres for controlled release of Resveratrol. Food Chem 2010; 121:23–28.
82. Shah V, Sharma M, Parmar V, Upadhyay U. Formulation of Sildenafil citrate loaded nasal microsphers: An *in vitro*, *ex vivo* characterization. Int J Drug Delivery 2010; 2:213-220.
83. Jain SA, Chauk DS, Mahajan HS, Tekade AR, Gattani SG. Formulation and evaluation of nasal mucoadhesive microspheres of Sumatriptan succinate. J of Microencapsul 2009; 26 Suppl 8:711-721.
84. Nasti A, Zaki NM, Leonardis PD, Ungphaiboon S, Sansongsak P, Rimoli MG, et al. Chitosan/TPP and Chitosan/TPP-Hyaluronic acid nanoparticles: systematic optimization of the preparative process and preliminary biological evaluation. Pharm Res 2009; 26 Suppl 8:1918-1930.
85. Patil SB, Sawant KK. Development, optimization and *in-vitro* evaluation of alginate mucoadhesive microspheres of Carvedilol for nasal delivery. J Microencapsul 2009; 26 Suppl 5:432-443.
86. Shaji J, Podder A, Iyer S. Brain-Targeted Nasal Clonazepam Microspheres**.** Ind J Pharm Sci 2009; 71 Suppl 6:175-178.
87. Yadav AV, Mote HH. Development of biodegradable starch microspheres for intranasal delivery. Ind J Pharm Sci 2008; 70 Suppl 2:170-174.
88. Dandagi PM, Mastiholimath VS, Gadad AP, Iliger SR. Mucoadhesive microspheres of Propranolol hydrochloride for nasal delivery. Ind J Pharm Sci 2007; 69 Suppl 3:402-407.
89. Ramanand M, Kumar DS, Shirwaikar A, Kumar R, Sampath KD, Prasad RS. Preparation of mucoadhesive microspheres for nasal delivery by spray drying. Ind J Pharm Sci 2007; 69:651-657.
90. Patil SB, Murthy RS. Preparation and in vitro evaluation of mucoadhesive chitosan microspheres of Amlodipine besylate for

nasal administration. Ind J Pharm Sci 2006; 68:64-67.

91. Harikarnpakdee S, Lipipun V, Sutanthavibul N, Ritthidej GC. Spray dried mucoadhesive microspheres: Preparation and transport through nasal cell. AAPS Pharm Sci Tech 2006; 7 Suppl 1:79-88.
92. Hameed MD, Kellaway IW. Preparation and *in vitro* characterisation of mucoadhesive polymeric microspheres as intranasal delivery systems. Eur J Pharm Biopharm1997; 44 Suppl 1:53-60.
93. Illum L, Jorgenson H, Bisgaard H, Krogsgaard O, Rossing N. Bioadhesive microspheres as a potential nasal drug delivery system. Int J Pharm 1987; 39:189-199.
94. Sharma PK, Chaudhari P, Kolsure P, Ajab A, Varia N. Recent trends in nasal drug delivery system - an overview. Int J Pharm Pharm Sci 2011; 3 Suppl 2: 6-11.
95. Pires A, Fortuna A, Alves G, and Falcão A. Intranasal Drug Delivery: How, Why and What for? J Pharm Pharm Sci (www.cspsCanada.org) 2009; 12 Suppl 3:288 - 311.
96. Heidari A, Sadrai H, Varshosaz J. Nasal delivery of insulin using bioadhesive chitosan gels. Drug Deliv 2006; 13: 31-38.
97. Stoke DG, Reber KR, Waltzman LS, Erns C, Hamilton D, Gawareck D, *et al*. Analgesic efficacy and safety of morphine-chitosan nasal solution in patients with moderate to severe pain following orthopedic surgery. Pain Med 2008; 9: 3-12.
98. Shao Z, Park GB, Krishnamoorthy R, Mitra AK. The physicochemical properties, plasma enzymatic hydrolysis, and nasal absorption of acyclovir and its 2'-ester prodrugs. Pharm Res 1994; 11: 237-242.
99. Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: Physicochemical and therapeutic aspects. Int J Pharm 2007; 337: 1-24.
100. Huang J, Garmise RJ, Crowder TM, Mar K, Hwang CR, Hickey AJ, et al. A novel dry powder influenza vaccine and intranasal delivery technology: induction of systemic and mucosal immune responses in rats. Vaccine 2004; 23: 794-801.
101. Greenberg DP, Walker RE, Min-Shi L, Reisinger KS. A bovine para-influenza virus type 3 vaccine is safe and immunogenic I early infancy. J Infect Dis 2005; 191: 1116-1122.