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Nasal Microspheres as a Potential Carrier in Nasal drug delivery

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ABSTRACT

Micro-particulate systems have already shown their potential as a carrier in delivery of many therapeutic molecules. Due to this potential, such systems are now most preferred over other conventional systems of drug delivery. Micro-carriers (Microspheres) shows features like controlled release, improvement in the residence time and thus enhancing bioavailability of administered drug. Nasal microspheres are now a day's becoming more popular for delivery of many therapeutic moieties. For building of microparticulate systems polymers from natural and synthetic origins are generally used. Drugs which are not suitable for oral administration due to high first pass effect (i:e presystemic metabolism), instability in gastrointestinal tract can be successfully delivered via nasal route. Systems like mucoadhesive microspheres provide sufficient time for drug to remain in contact with mucosal membrane so as to increase their absorption. This is the basic underlined reason suggests why most of the polar drugs have shown improvement in the bioavaibility when compared with their conventional intranasal formulations. This review mainly focuses on the basic aspects of microspheres as a potential carrier in the drug delivery.

Keywords: Microspheres, Nasal Drug Delivery, Mucoadhesive.

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INTRODUCTION

Microspheres are the carrier systems of free flowing powders prepared using different Polymers. Microspheres are having size range from 1–1000 µm. Mucoadhesive microspheres are found to improve bioavailability of therapeutic moiety as it provide longer residence for absorption.[1]

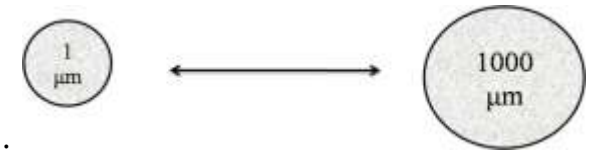

Figure 1: Size range for Microspheres.

Microspheres are of two types microcapsules and micro-matrices. Microcapsules are the systems in which entrapped substance is surrounded by distinct capsule wall and Micro-matrices are the one in which entrapped substance is dispersed throughout the microspheres matrix. [2,3]

Figure 2: Micro-matrix.

Merits and Demerits of Nasal Drug Delivery

Merits

1. Nasal route offers a way for systemic delivery by ease of administration.
2. Avoidance of first pass hepatic metabolism through direct absorption to the systemic circulation.
3. Presence of larger surface area and porous endothelial basement membrane provides better absorption of drug.[5]
4. Nasal route is considered as potential site to elicit both mucosal and systemic immune response.[6]
5. Nasal route is used for CNS targeting through olfactory region for treatment Alzheimer's Disease, Depression, Migraine, Schizophrenia.[7]

Demerits

1. Major problem associated with nasal drug delivery is presence of Mucociliary clearance.[8]
2. This route is associated with low membrane permeability and thus poor bioavailability for proteins and peptides.[9]
3. Formulation excipients like surfactant and permeation enhancers can cause nasal irritation and mucosal damage respectively.[10]
4. Pathological conditions like rhinitis can obstruct nasal drug delivery.

5. Nasal route is well suited only for drug with low dose.[11]
6. Polar drugs are considered as poor candidate for nasal delivery.[12]
7. Nasal delivery is a non-invasive in nature.[13]

Categories of Drug Entrapped Through Micro-Particulate System

1. Antiasthamatic

Farid et al formulated mucoadhesive sodium alginate microspheres loaded with salbutamol sulphate by emulsion cross-linking method for nasal administration. The study aimed to by-pass pre-systemic metabolism. Obtained microsphere were characterized for Particle size, Drug Content, Swelling ability, and mucoadhesiveness. From overall study researchers were concluded that microspheres are suitable carrier systems for nasal delivery of the model drug Salbutamol sulphate. This study shows that approach like microspheres not only carries drug but also exhibit sustained release profile[14].

2. Antibiotics

Nasal route was found to be an obstacle for administration of polar drugs due to their poor absorption profile. Permeability across the nasal mucosal membrane is the limiting factor for absorption of high molecular weight polar drugs like gentamicin sulfate. Gonul et al were designed microsphere formulation for a highly polar aminoglycosidal antibiotic, gentamicin sulfate. The microspheres were prepared by spray drying technique. They were tried to combat issues like poor permeability and nasal mucociliary clearance by co-administration of permeation enhancer (Sodium cholate) and mucoadhesive polymer (Hydroxypropyl methylcellulose) respectively along with polar antibiotic i: e gentamicin sulfate. Prepared microsphere system is then subjected for in vitro drug release studies in Franz diffusion cell by using dialysis membrane. In vitro drug release profiles showed that gentamicin sulfate microsphere formulations with drug/polymer ratio 4:1 had highest drug release than drug / polymer ratio 1:2.[15]

Brown et al also developed biodegradable micro-particles of Gentamicin sulfate. In present study, Chitosan hydroglutamate (CH), Hyaluronic acid (HA) and a combination of both polymers were employed for preparation of microsphere systems. Water in oil (w/o) emulsification solvent evaporation technique was used to prepare microsphere formulations. Further in-vivo studies showed that bioavailability of gentamicin was poor for nasal solution i: e 1.1% and for dry powder it is 2.1%. Bioavailability profile for microparticulate systems composed of polymer chitosan hydroglutamate was 31.4%, for Hyaluronic acid it was 23.3% and 42.9% for combination of both polymers, respectively. Results clearly suggested that

combination of both polymer (Hyaluronic acid and Chitosan hydroglutamate) showed better bioavailability than when used alone.[16]

Manjunatha and other co-researchers also exploited same drug i:e gentamicin sulfate for microparticulate system. In this study Chitosan and HPMC were used as mucoadhesive polymers. All the prepared formulations were evaluated for particle size, encapsulation efficiency, shape and surface properties, drug polymer interaction, mucoadhesive property, stability and in vitro drug release. Microsphere formulation were prepared by maintaining drug polymer ratio 1:1, 1:2, 1:3 for batch number 1,2,3 respectively. Microspheres obtained from Chitosan were found to be more uniform in size than HPMC. β-cyclodextrin was used as permeation enhancer.[17] Researchers also prepared ciprofloxacin-hydrochloride loaded microspheres using copolymers synthesized from acrylic and meth-acrylic acid esters as a retardant material for nasal administration. Ciprofloxacin belongs to broad-spectrum antibiotic active against gram positive and gram negative bacteria. The basic objective this study was to formulate sustained release nasal microspheres of ciprofloxacin HCl to avoid the first pass metabolism and to maintain the optimum therapeutic drug level for prolonged period.[18] Antibiotics incorporated in microspheres are listed in table 1

Table 1. List of antibiotics formulated in micro-particulate system.

Sr No	Drug	Polymer	Reason
1	Gentamicin Sulfate	Hydroxypropyl methylcellulose.	To provide a platform for absorption of polar antibiotic.
2	Gentamicin Sulfate	Chitosan hydroglutamate, Hyaluronic acid & combination of both polymer.	To study combination effect of polymer on absorption of polar antibiotic.
3	Gentamicin Sulfate	Chitosan and Hydroxypropyl methylcellulose.	To provide a platform for absorption of polar antibiotic.
4	Ciprofloxacin Hydrochloride	Eudragit S 100.	To obtain sustained release of drug.

3.Anti-Emetics

Giunchedi et al prepared Spray-dried microspheres of metoclopramide by using methylpyrrolidinone chitosan as new carrier for nasal administration. Chitosan has showed its potential use in the preparation of microsphere formulations containing therapeutic moiety. When amino groups of glucosamine units present in the backbone structure of Chitosan are partially substituted by methylpyrrolidinone at position 5, leads to formation of new derivative of Chitosan known as 5-Methylpyrrolidinone Chitosan (MPC). This derivative offers both biocompatibility and hydrophilicity. The microspheres were prepared by using aqueous solutions containing different concentration of polymer 5-Methylpyrrolidinone Chitosan. Chitosan micro

particles containing only drug were treated as reference by dissolving Chitosan and drug in acetic acid solution. For comparison, blank microspheres were prepared from Chitosan or 5-Methylpyrrolidinone Chitosan. Obtained microspheres were characterized for encapsulation efficiency, morphology, size and drug release behavior. Metoclopramide concentration in the obtained microspheres was determined by HPLC analysis. Encapsulation efficiency was calculated from the ratio between the real drug content and the theoretical amount. In drug release study, dissolution of plain drug was found rapid and whole drug was recovered in 5 min. when the same drug was encapsulated inside the mucoadhesive polymer, slower release rate was obtained. Drug release profile was found to be polymer dependent. As the concentration of polymer was increased a slower release rate was observed and 100% of drug was recovered in phosphate buffer after about 1 h.[19] In another study, Galgatte et al prepared microspheres of same drug Metoclopramide hydrochloride by using HPMC E4M and Corbopol 934P along with combination of both HPMC E4M and Corbopol 934P. In Vitro Drug release study shown that with increasing concentration of HPMC E4M and Corbopol 934P the drug release from microspheres was decreased. From Scanning Electron Microscopy it was observed that all micro-particles were spherical and smooth in surface. From Transmission Electron Microscopy it was observed that batch of optimized microspheres are in the range of 500nm to 1µm.[20] Mahajan et al prepared spray dried mucoadhesive microspheres of ondansetron HCl by using Chitosan for nasal administration. The o/w emulsion and simple dispersion is spray dried to obtain microspheres. Microspheres were then characterized for various parameters like particle size, entrapment efficiency, swelling index, mucoadhesive strength and in vitro drug release study. The particle size was found to be in range 7- 9µm. Encapsulation efficiency was found to be in range 89-98%. Mucoadhesion time of 120 min was observed for all the microspheres.[21] All above mentioned studies revealed that micro-particle system can serve as potential carrier for delivery of therapeutic moieties. Antiemetic drugs incorporated in microspheres listed in table 2

Table 2. List of Antiemetics formulated in micro-particulate system.

Sr No	Drug	Polymer	Reason
1	Metoclopramide Hydrochloride	Methylpyrrolidinone Chitosan	Study on the feasibility of nasal route for administration of antiemetic drug.
2	Metoclopramide Hydrochloride	Hydroxypropyl methylcellulose(E4M) and carbopol 934P.	Study on the feasibility of nasal route for administration of antiemetic drug.
3	Ondansetron	Chitosan	Study on the feasibility of nasal route for administration of antiemetic drug.

4. Antihistaminics

Kim et al prepared, intranasal spray-dried microspheres of Fexofenadine·HCl hydrochloride by using Hyaluronic acid polymer. Due to high solubility and low permeability, Fexofenadine· hydrochloride comes under class III of the Biopharmaceutical Classification System (BCS). Fexofenadine·hydrochloride is a second-generation non-sedating histamine (H1) receptor antagonist. It is widely used in seasonal allergic rhinitis. Solutions of Fexofenadine·HCl and Hyaluronic acid were prepared separately in 100 ml of ethanol and distilled water, respectively. After this, both solutions are mixed and added with varying weight ratios of (Fexofenadine·HCl: PEG 6000: Sodium taurocholate). The newly formed mixture of Hyaluronic acid–Fexofenadine·HCl–PEG–Sodium taurocholate was then spray dried to obtain microspheres. Obtained microspheres were then evaluated for various parameters like drug contents, encapsulation efficiency and particle size. The shape and surface morphology along with size of microspheres were observed by Scanning Electron Microscopy. High performance liquid chromatography (HPLC) analysis was carried out to find out drug content in each microsphere. From this study authors concluded that PEG was responsible for improvement in drug release rate and sodium taurocholate increased the permeation of Fexofenadine·HCl across the mucosal membrane.[22] In another work bioadhesive microspheres of loratadine were developed for nasal administration. Loratadine is second-generation lipophilic antihistaminic drug. It undergoes extensive first-pass metabolism in the liver and for this reason authors were decided to formulate it in a microspheres for nasal administration. Researchers were also aimed to reduce the chances of interaction of loratadine with other therapeutic moieties if administered orally. For this study Chitosan (CM) and Ethyl cellulose (EC) were selected as polymer. Microspheres were prepared from spray-drying of simple dispersion, oil-in-water (O/W) emulsion and suspension.[23]

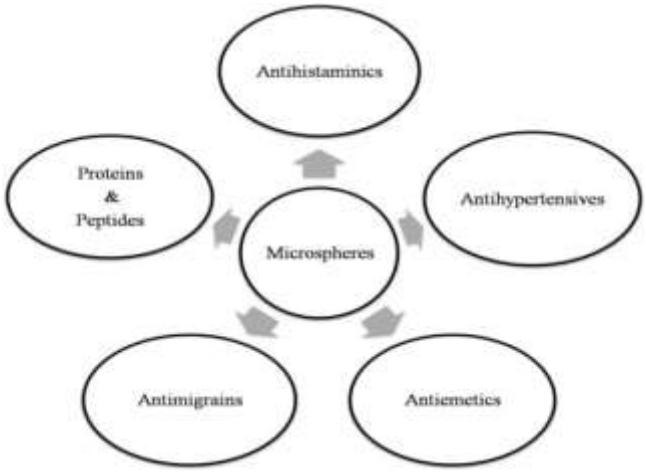

Figure 3. Categories of Drug Entrapped into Micro-Particulate System.

5. Antihypertensives

N. Swamy and Z. Abbas fabricated Amlodipine Besylate microspheres for intranasal administration with an aim to avoid first-pass metabolism, and to achieve controlled blood level profiles. Study consist of evaluation of prepared microspheres for various parameters like particle size, particle shape and surface morphology by Scanning Electron Microscopy, percentage yield, drug entrapment efficiency, in vitro mucoadhesion test, degree of swelling and in vitro drug diffusion through sheep nasal mucosa. Amlodipine Besylate is a calcium channel blocker, and drug of choice for hypertension and angina pectoris. Amlodipine Besylate undergoes hepatic first-pass metabolism when administered orally and exhibits 60-65% bioavailability. Researchers were used Phase separation emulsification technique for preparation of Mucoadhesive Poly Vinyl Alcohol microspheres containing Amlodipine Besylate. [24] Sahi and co-workers, formulated mucoadhesive microspheres of atenelol for nasal administration. The objectives behind this study were to avoid first pass metabolism of drug and to get maximum efficacy. The polymer used for this study was of HPMC K4M grade and method employed was spray drying.[25] In another work researcher developed Carvedilol loaded PLGA microspheres by spray drying technique. Poly (lactide-co-glycolic acid) (PLGA), is a biodegradable copolymer of poly (lactic acid) and poly (glycolic Acid). Carvedilol (CV) is used to treat cases of moderate hypertension, angina pectoris and congestive heart failure. Carvedilol also shows significant pre-systemic metabolism. In characterization, microspheres were evaluated for various parameters like swelling property, in vitro mucoadhesion, in vitro drug diffusion, ex-vivo permeation study, histopathological examination and stability study. The histopathological evaluation of tissue incubated in phosphate buffer (pH 6.6) for 6 h. after collection, it was compared with tissue incubated in diffusion chamber with formulation. Histopathological evaluation showed that, mucosal structure remained unaffected even after incubation with microsphere formulation up to 6hr.[26] Sivanarayana studied effect of cross-linking agents and polymers on the characteristics of Diltiazem hydrochloride loaded mucoadhesive microspheres. Diltiazem hydrochloride, a calcium channel blocker, is widely used for the treatment of angina pectoris, hypertension and arrhythmias. The method adopted by researchers for preparation of Diltiazem hydrochloride loaded mucoadhesive microspheres was emulsification-internal gelation. Polymer selected was composed of alginate alone and combination with Hydroxy Propyl Methyl Cellulose (HPMC) or Sodium Carboxy Methyl Cellulose (NaCMC). Aluminum chloride or Barium chloride or Calcium chloride were selected as cross linking agent. From results it was observed that higher release rate was observed for Microspheres of Sodium alginate in combination with other

mucoadhesive polymers like HPMC than Sodium alginate+ NaCMC and Sodium alginate alone. Release rate was also affected by various cross linking agents and it was observed that maximum release rate was observed for microspheres cross linked by Calcium chloride than Barium chloride and Aluminum chloride.[27] Antihypertensive drugs incorporated in microspheres are listed in table 3

Table 3. List of Antihypertensive formulated in micro-particulate system.

Sr No	Drug	Polymer	Reason
1	Amlodipine Besylate	Polyvinyl Alcohol	To avoid first pass effect of drug.
2	Atenolol	Hydroxypropyl methylcellulose(E4M) and carbopol 934P.	To avoid first pass effect of drug, maintenance of constant drug plasma level for extended period of time.
3	Carvedilol	Poly(lactide-co-glycolic acid)	To avoid first pass effect of drug.

6. Antimigrain

Velaga et al developed Chitosan micro-particles containing Zolmitriptan by spray drying technique. Chitosan is a biodegradable polymer with sufficient mucoadhesiveness. Chitosan have ability to open the tight junctions in the epithelial membrane. Structure of Chitosan consist of linear β (1→4) linked monosaccharide unit. The biocompatibility, biodegradability, low toxicity and low immunogenicity are the extra qualities owned by of Chitosan. Zolmitriptan is a second-generation triptan derivative used in the management of migraine attacks. Present study aimed to enhance bioavailability of Zolmitriptan by increasing its residence time in nasal cavity. Investigators concluded that drug release from the microspheres is affected by both proportion and the molecular weight of the Chitosan.[28] In another study, microparticulate formulation same drug was prepared by emulsions Crosslinking technique. This study concluded that Emulsification-cross linking is a suitable technique for preparation of Zolmitriptan micro particles with high drug loading (95-103%).[29] Other triptan derivative like rizatriptan was also been exploited in the preparation of microparticulate formulations. The technique employed was spray drying. Outcome of this study was polymer like chitosan is capable of minimizing the Mucociliary clearance and therefore increases residence time of drug in nasal cavity. [30] Antimigrain drugs incorporated in microspheres are listed in table 4

Table 4. List of Antimigrain formulated in micro-particulate system.

Sr No	Drug	Polymer	Reason
1	Zolmitriptan	Chitosan	To improve bioavailability of drug.
2	Rizatriptan Benzoate	Chitosan	To improve bioavailability of drug.

7. Proteins and Peptides

Morath et prepared Dextran microspheres containing insulin for nasal drug delivery. The suspensions of drug and microspheres(dextran) were lyophilized to load insulin into the Dextran microspheres. The amount of immune-reactive insulin in the micro-spheres was determined by Radio immuno assay. From results it was concluded that micro-spheres with insulin on the surface were more effective in promoting insulin absorption than those with insulin distributed within the dextran matrix.[31] Some researchers evaluated the use of Hyaluronic acid ester microspheres for the nasal delivery of insulin. Suspension containing drug and Hyaluronic acid ester was freeze dried to load insulin inside microsphere. The in-vivo studies are performed on sheep. Plasma glucose level was determined by glucose oxidase method while plasma insulin level was determined by radioimmunoassay. From results it was concluded that mean relative bioavailability obtained in sheep was 11% for microspheres which was better than nasal solution (1.2%).[32]

Illum et studied The effect of bioadhesive starch microspheres on absorption enhancers on the transport of the insulin across the nasal membrane. Enhancers studied were Lysophosphatidylcholine (LPC), Glycodeoxycholate (GDS) and Sodium taurodihydroxyfusidate (STDHF). A bile salt derivative and it was found that bioadhesive starch microspheres were enhanced synergistically the effect of the absorption enhancers on the transport of the insulin across the nasal membrane.[33] Morimoto et al exploited use of Aminated gelatin microspheres for intranasal delivery of insulin. From the study, Aminated gelatin microspheres were found to improve the nasal absorption of insulin when administered in dry powder forms. The researchers concluded that enhanced absorption for microsphere formulation could be due to absorption of water from the nasal mucosa, thus resulted in a temporary dehydration of the epithelium and opening of the tight junctions. Such type of effect allowed drug to follow paracellular pathway and thus improved nasal absorption. Dry powder formulations (Aminated gelatin microspheres) showed significant hypoglycemic effect but no such type of effect was observed, when administered as in suspensions forms.[34] Some researchers utilized thiolated Chitosan derivatives for fabrication of micro-particles. Chitosan derivative like with thiolated Chitosan have better mucoadhesiveness and permeation enhancing properties compared to chitosan. Absolute bioavailability for nasally administered chitosan–TBA–insulin micro particles, chitosan–insulin micro particles, and mannitol–insulin microparticles was found to be 7.24±0.76, 2.04±1.33, and 1.04±0.27 respectively. These results showed that thiolated derivatives of Chitosan are the better option for deliver peptide formulations.[35]

8. Hypnotics and Sedatives

S. Jose et al, formulated thermo-sensitive gel containing lorazepam microspheres for brain targeting through intranasal administration. Chemically lorazepam is a benzodiazepine derivative and drug of choice for status epileptics. They selected Pluronics (PF-127 and PF-68) as thermo-reversible polymers. Solution of this polymer has ability to form gel at body temperature (37^{o}c). Mucoadhesive microspheres in the gel will provide prolonged drug release and enhanced bioavailability. Researchers were studied effect of polymer concentration (Chitosan), emulsifier concentration (Span 80) and cross-linking agent (Glutaraldehyde) on the mean particle size of microspheres. Microspheres of Chitosan were prepared by emulsion Crosslinking method. Aqueous phase is made up of drug and Chitosan solution prepared in 4% aqueous glacial acetic acid. Light liquid paraffin was used as Oil phase containing Span 80 as emulsifying agent. Emulsion was then obtained by the addition of aqueous phase into oil phase through needle with stirring at 1500 rpm by mechanical stirring. Glutaraldehyde was used as Crosslinking agent. Researchers suggested that microspheres incorporated in pluronics hydrogel is use as a carrier for the sustained release of hydrophobic drugs.[36]

In another work. Microspheres of midazolam were developed for nose to brain delivery. For this purpose HPMC was used as a mucoadhesive polymer. Researcher attempted to prepare nasal microspheres of midazolam for combating its first pass effect when administered orally, also to improve the patient compliance, and to improve the therapeutic efficacy of same drug. Emulsion cross linking method was adopted for preparation of microspheres. The aqueous phase was prepared by using 4% HPMC in phosphate buffer (pH 5.5) and drug. Liquid paraffin (heavy and light 1:1 mixture) was used as oil phase containing 0.5% Tween 80. Emulsion was obtained by the addition of aqueous phase into oil phase through syringe with continuous stirring at 2000 rpm. Obtained emulsion was then cross-linked by using Gluteraldehyde.[37] Microspheres of the same drug were also developed by using same method but different polymer i: e corbopol.[38]

Dave et al were prepared intranasal mucoadhesive microspheres of lamotrigine by using Chitosan polymer. Lamotrigine is an anticonvulsant drug and used in the treatment of epilepsy and bipolar disorder. Intranasal Lamotrigine microspheres were prepared by Emulsion Solvent Evaporation method. For emulsion preparation Liquid paraffin was used as oil phase which act as external phase. While mixture of drug and polymer solution was used as aqueous phase which is internal phase. Obtained emulsion was then cross-linked by using gluteraldehyde. [39]

9. Anticoagulant

Yildiz ozsoy et al fabricated heparin-loaded nasal microspheres based on poly (lactic acid).

Heparin is the drug of choice for condition like deep vein thrombosis. In this study, heparin-loaded microspheres were prepared with PLA using solvent evaporation method. The prepared microspheres were characterised for various basis like shape and surface properties, particle size, production yield, encapsulation efficiency and in vitro drug release. In-vivo studies were also performed on female Wistar albino rats. In-vivo studies suggested that heparin-loaded microspheres would be functional via nasal route.[40]

10. Analgesic

Jiang et al, Prepared and characterized a-cobrotoxin-loaded poly(lactide-co-glycolide)/polyanhydride microspheres for nasal delivery. A-Cobrotoxin is neurotoxin protein consisting of single polypeptide chain of 60~70 amino acids residues and cross-linked by four disulfide bonds . due to its nerve blocking effect it can be exploited for analgesic effect. A-Cobrotoxin microspheres were prepared by a modified w/o/o emulsion solvent evaporation method. The obtained microspheres showed enhanced mucoadhesion and exhibited mild, reversible toxicity to nasal mucosa. From this work authors concluded that microspheres containing a-cobrotoxin can be utilized for nasal drug delivery [41].

11. Vaccines

Mortazavi et al made an attempt to formulate microspheres containing Diphtheria Toxoid, as a potential system for nasal vaccination. In present study, Chitosan with high, medium and low molecular weight was used as a carrier for intranasal immunization. Diphtheria Toxoid (DT) was exploited as a model antigen. For synthesizing microparticulate system of Diphtheria Toxoid, emulsion-solidification Technique was adopted. Outcomes of the study was microspheres prepared by high Molecular Weight Chitosan and Glutaraldehyde (cross-linking agent) had the highest loading efficiency (95.61±3.57 percent). This outcomes showed that the loading efficiency of Chitosan microspheres depends on the Molecular weight and the type of cross-linker used.[42]

12. Others

Gangadi and co-researcher were formulated mucoadhesive microspheres for intra -nasal delivery by using neostigmine bromide as a model drug. Neostigmine bromide – a cholinesterase inhibitor and is widely used for treatment of myasthenia gravis. Cholinesterases are the set of enzymes responsible for hydrolysis of acetylcholine. Due to poor oral absorption profile there is need of providing this drug by other route. The aim of the present study was to overcome the drawbacks of the Conventional dosage forms (tablet) by formulating intranasal microspheres of Neostigmine Bromide with Corbopol 974P NF and HPMC K15 M along with film forming

polymer ethyl cellulose by emulsion-solvent evaporation method[43].

CONCLUSION

Nasal Microspheres are considered as a novel carrier for many therapeutic drugs. Use of mucoadhesive polymer in the fabrication of microspheres may lead to improvement in the bioavailability of given therapeutic moiety by increasing its residence time in nasal cavity. Present review mainly emphasizes on various points that suggests why microspheres are considered as potential carrier in the drug delivery.

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