Review Article

POTENTIAL OF CHITOSAN FOR NOSE TO BRAIN DRUG DELIVERY

Sharma Sumit*[1], Lohan Shikha[1], Murthy R.S.R.[1]
[1] Nanomedicine Research Centre, ISF College of Pharmacy, Moga, Punjab, India.
***Corresponding author's E-mail:** sumit.ssharma17@gmail.com

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ABSTRACT

Owing to ease of administration and the improved bioavailability offered by the nasal system this delivery system has been potentially exploited for the delivery of drugs. Targeting brain via this route has been very promising and has shown to be effective in treatment of variety of disorders associated with the brain dysfunction. Chitosan owing to its property of biodegradability and mucoadhesive behavior offers huge potential for the delivery of such delivery systems and this polymer can be modified to form nanoparticles, microspheres. Chitosan in the form of hydrogels have also been successfully used for the effective treatment of diseases and has added advantage of controlled drug delivery, prolong the residence time of the active moiety on the mucosal surface thereby aiding in enhanced availability through this route. Thus this route offers promising results for treatment of brain disorders.

Keywords: Chitosan, olfactory, trigeminal, nanoparticles, microspheres, hydrogels.

INTRODUCTION

Recent studies have shown that nasal route has been a potential route for the delivery of proteins and peptides such as vaccines, small molecular weight drugs and biomolecules which are susceptible to degradation by acidic, enzyme or first pass hepatic metabolism. Studies have also indicated that nasal route can be used as an alternative to intravenous route in certain cases such as insulin in rat nasal[1], vaccines using chitosan microspheres[2]. Recent developments have proved the possibility of exploiting the nasal route for direct transport of drugs from nose to brain in man. Hence, Frey declared that by nasally administering insulin-like growth factor (IGF-1) the drug could bypass the blood brain barrier and reach the central nervous system (CNS) directly from the nasal cavity. Therefore nasal cavity can be exploited for systemically acting drugs and for centrally acting drugs. The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability. Drugs can cross the epithelial cell membrane either by the transcellular route, exploiting simple concentration gradients, receptor mediated transport, vesicular transport mechanisms or by the paracellular route through the tight junctions between the cells. The drug can be transported through the olfactory neuron cells by intracellular axonal transport primarily by the olfactory bulb and/or via the trigeminal nerves directly to the CNS[3] .But due to rapid clearance of administered formulation from nasal cavity by mucociliary clearance mechanism, drugs are not easily absorbed across the nasal membrane[4].

EARLY NOSE-TO-BRAIN THERAPEUTICS

Through the time memorial intranasal administration of medicines and recreational therapeutics has been recorded. Chinese traditional system has been well known for intranasal administration. As early as the Han Dynasty (150 AD), Zhongjing Zhang used the method of dripping the ground juice of *Allium chinense G. Don* into the nasal cavity to revive a patient from unconsciousness in an emergency. In addition to this *Chinese Pharmacopeia* contains evidence of administering Tong Guan San, consisting of three herbs including Manchurian Wild ginger, for relieving palsy and faint via nasal administration[5]. Tibetans have also been known to follow a similar pattern wherein Rinpoche & Kunzang have given evidence that ancient Tibetans used extracts of sandalwood and aloewood given nasally as anti-emetics [6]. For recreational purposes also this route has been potentially exploited; cocaine, a highly addictive central nervous system stimulant extracted from the leaves of the coca plant (*Erythroxylon coca*) is administered intranasal[7]. Earliest evidences showing the existence of direct pathway from nasal passages to brain has been demonstrated by Balin *et al.,* 1986 who have convincingly demonstrated the extracellular pathway between nasal passages and brain using horseradish peroxidase (HRP), a 40 kDa protein tracer[8]. They have also used lectin conjugate wheat germ agglutinin-HRP and following intranasal application it has been shown to undergo adsorptive endocytosis into olfactory sensory neurons and subsequent transcytosis to olfactory bulb glomeruli thereby showing anterograde axoplasmic transport within olfactory sensory neurons i.e. intracellular pathway from nasal cavity to the brain[9, 10]. However, a clear and detailed understanding of the transport pathways of drugs directly from nose to brain has only become available in recent times.

POTENTIAL OF NASAL ROUTE

Nasal route is nowadays potentially exploited for the delivery of drugs. This route offers vital advantages which can be utilized for the efficient drug delivery[11].

1. Nasal mucosa underlines a very rich vasculature and as such can significantly enhance systemic absorption of drugs.
2. It can comparably reduce the enzymatic degradation of drugs.
3. This system successfully bypasses the first pass metabolism and as such can improve bioavailability of poorly bioavailable drugs.
4. Olfactory area in the nasal cavity can be exploited for direct delivery to the brain with enhanced efficacy[12].
5. The drug via the olfactory neurons is transported via the extracellular transport route and as such the drug reaches the brain within minutes[13].
6. This route can be used for potent drug delivery.
7. Illum has reported that the lipophilic drugs are well absorbed from the nasal cavity with pharmacokinetic profiles identical to those obtained after an intravenous injection with a bioavailability approaching 100% [4].
8. Illum has confirmed that the nasal drug delivery is a safe and acceptable route for brain targeting generally for drugs with biological effects on the central nerves system (CNS) and limited blood–brain permeability (BBB) [14] and
9. Last but very important consideration is the patient compliance as this process of drug delivery is non-invasive, rapid and efficient.

But in spite of these advantages they are prone to some serious disadvantages which limit their use and efficiency in designing drug delivery systems.

1. Sakane *et al.,* has shown by various studies that only the low molecular weight lipophylic, unionized drugs are favorably absorbed through this route of delivery[15].
2. Mygind *et al.,* have hypnotized and proved that during the nasal congestion of the nasal cavity due to the allergy or infection the drug delivery in such conditions may not be possible which may hamper the treatment regimen and significantly alter the drug therapy [16].
3. Targeting via the olfactory epithelium may prove to be difficult as this area lies at the roof of the nasal cavity in man which is not an easily accessible site and the drug targeting to this route may prove to be time consuming and challenging [17] and
4. The relative toxicity offered to the olfactory area and the trigeminal nerve has not been significantly proved and identified.

The advantages overweigh the disadvantages that come with the nasal delivery and as such these systems have been extensively studied in light of the effective drug delivery systems and the potential usage has been explained below.

NASAL PHYSIOLOGY AND THE ANATOMY

The area that are the main target sites for the drug delivery via the nasal route include the olfactory area and has been successfully exploited for this drug delivery system and the knowledge of such system become immensely important for successfully delivery of drugs to brain via such systems. Nasal cavity is divided into three regions:

1. Nasal vestibule
2. Olfactory region
3. Respiratory region

The region that needs to be understood in details is the olfactory region and the trigeminal nerve areas as these are responsible for the direct delivery of drugs from the nose to the brain.

Olfactory region

The olfactory area is located in the upper portion of the nasal cavity partially overlying the cribriform plate which is a bony structure that contains pores to allow the passage of neuronal bundles from the olfactory epithelium to the CNS [3].

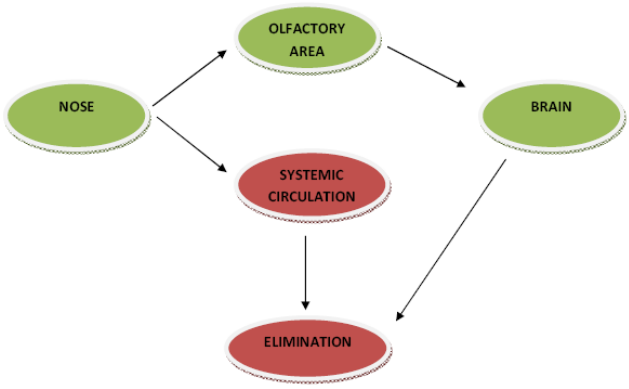

Figure 1: Pathway indicating nose to brain drug delivery

The olfactory mucosa is located in the upper nasal cavity, just below the cribriform plate of the skull. It contains olfactory cells which traverse the cribriform plate and extend up into the cranial cavity hence drug molecules when come in contact with this region they are directly absorbed into brain bypassing blood brain barrier [18]. It has been observed that the olfactory epithelium only comprises about 10-20 cm^2 (8%) of the nasal surface epithelium in humans which in contrast to animals is relatively very small as olfactory area is about 50% of the nasal cavity in rats[17]. The olfactory epithelial layer predominantly contains three types of cell each with their specific function:

1. The olfactory neural cells: these cell types are unmylinated axons interspread within the sustentacular cells which originate at the olfactory bulb in the CNS and terminate at the apical surface of the olfactory epithelium.
2. The sustentacular (also known as supporting) cells: columnar cells with microvillus and are similar to glial cells; helpful in producing mucus.
3. The basal cells: these provide mechanical support to the sustentacular cells.

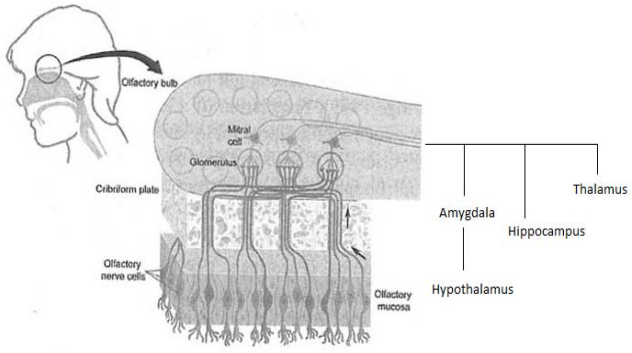

Figure 2: Anatomy of Olfactory region in humans showing the network of bundle of neurons exposed directly to external environment.[19]

The olfactory knob (or vesicle) is one of the most important components of this nasal delivery system and protrudes out from and above the apical surface of the olfactory epithelium. The average diameter of olfactory axons, as determined by electron microscopy, in 2-month-old rabbits is ~200 nm, however, many of the axons have diameters of <100 nm[20] thus Oberdörster *et al.,* concluded that nanoparticles of sufficiently small size could potentially be transported via axons through the olfactory bulb into the olfactory cortex to the caudal pole of the cerebral hemisphere and finally into the cerebrum and the cerebellum[21]. Olfactory axonal diameters for some other species have also been evaluated, for the African Clawed frog diameters of 198±93nm has been found[22], various bird species have 210-260nm diameter and for humans 100-700nm is considered[23]. Below the olfactory epithelium lies lamina propria containing the blood supply, mucus secreting acinar glands (Bowman's glands), nasal lymphatics, and a neuronal supply that consists of olfactory axon bundles, autonomic nerve fibres and the maxillary branch of the trigeminal nerve[24, 25].

Trigeminal nerve

The trigeminal nerve is thought to be the largest of the cranial nerves has three major branches namely:

1. The ophthalmic nerve: Sensory function
2. Maxillary nerve : Sensory function
3. Mandibular nerve: Sensory and motor functions

Neurones from the ophthalmic and maxillary branches of the trigeminal nerve pass directly through the nasal mucosa and are thus important for nose-to-brain drug delivery. Thorne et al have successfully shown that these neurons could effectively deliver the neurotrophic factor, IGF-1(MW7.65 kDa), to the brain stem and spinal cord areas in the *in vivo* rat model.[26] Hence, in contrast to rostral entry of drug via the olfactory pathway, the trigeminal nerve was shown to enhance nose-to-brain delivery to caudal brain areas.

FACTORS INFLUENCING DRUG ABSORPTION FROM NOSE TO BRAIN

Physicochemical properties

The ability, rate and extent of absorption of molecules from nose to brain depend on its physicochemical properties like lipophilicity, relative molecular weight and degree of ionization (pKa). It has been found that like other biological membranes, nasal mucosa also enables lipophilic drugs to penetrate through it. Hence these drug molecules are absorbed across nasal membrane by means of transcellular mechanism[27], but it has also been shown that very high lipophilic moieties show diminished permeation and penetration as the drug does not dissolve easily in the aqueous environment of nasal cavity thereby increasing the mucociliary clearance and at the same time decreasing contact time with the membrane[28]. Drug absorption is not only influenced by lipophilicity of drug molecule but also depends upon degree of ionization. According to pH partition theory, the non-ionized fraction of a drug is more permeable than the ionized fraction. Zaki *et al.,* in their study on metoclopramide hydrochloride have indicated that the nasal absorption of weak electrolytes depends on their ionization degree and the largest absorption occurs for the nonionized species[29]. Sakane *et al.,* have also studied the effect of ionization on the drug absorption and concluded that the nasal clearance increases with the elevation in the un-ionized fraction of the drug, and the ratio of the drug concentration in CSF to that in the nasal perfusion fluid changes in accordance with the un-ionized fraction of the drug, showing that both the nasal absorption and the drug transport conforms to the pH partition theory [30]. Molecules less than 400 Daltons can easily cross nose to brain barrier and on increasing the molecular weight penetration decreased with almost minimal penetration for molecules beyond 1000 Daltons. This has been proved by Sakane *et al.,* in their experiments using Dalton fluorescent-labeled dextrans of different molecular weights and subsequently determining their concentration in cerebrospinal fluid (CSF) after both nasal and i.v administration and successfully proved that concentration of dextrans in CSF decreased with increasing molecular weight[31].

Mucociliary Clearance

It is perhaps most important consideration for the nasal drug delivery as it limits the time allowed for drug absorption. The normal half-time of clearance in humans is about 20 min[32] and it varies due to physiological conditions like common cold, sinus rhinitis, some drugs

and pharmaceutical excipients may also influence mucociliary clearance. Mucociliary clearance is slower in anterior part of nose as compared to posterior part of nose where there is increased density of cilia therefore drugs delivered in posterior part are cleared rapidly[33]. On the other hand Charlton *et al.,* have demonstrated that numerous microvilli on the ciliated nasal epithelium provide more surface area on the membrane which enhances drug absorption as compared with non-ciliated epithelium. Therefore in order to promote drug transport to the brain, retention of the drug at the absorption site must be prolonged to weaken the clearance effect of nasal mucous membrane, especially to increase the deposition of drug on the olfactory mucosa[34].

Nasal Enzymes

Nasal mucosa is a host for broad range of metabolic enzymes which hampers nose to brain drug availability. Among them are present proteolytic enzymes such as proteases and amino peptidases, they are believed to be major barrier for peptide drugs such as insulin and calcitonin[35], [36]. Oxidative phase I enzymes such as cytochrome P-450 enzymes are also present in nasal mucosa which are capable of metabolizing drugs like nicotine, cocaine and progesterone. Moreover Carboxyl esterases, aldehyde dehydrogenases, epoxide hydrolases and gluthatione S-transferases have been found in nasal epithelial cells and are responsible for the degradation of drugs in nasal mucosa[37]. Zhou *et al.,* have investigated the level of activity of these nasal enzymes and concluded that the level of activity for nasal enzymes seems to be lower than those in gastrointestinal tract or liver on the basis of the amount of tissue involved [38].

Efflux Transport Systems

Apical region of ciliated epithelial cells and the sub mucosal vessels of the human olfactory region contain P-gp as efflux transport systems. Graff *et al.,* performed experiments to assess the brain distribution of 3H-verapamil, the anatomic location of P-glycoprotein (P-gp) on the nose-brain barrier and found that P-gp is localized to both the olfactory epithelium and the endothelial cells that surround the olfactory bulb. Efflux transporters such as P-gp represent significant barriers to effective delivery of pharmacologic agents to the brain [39].

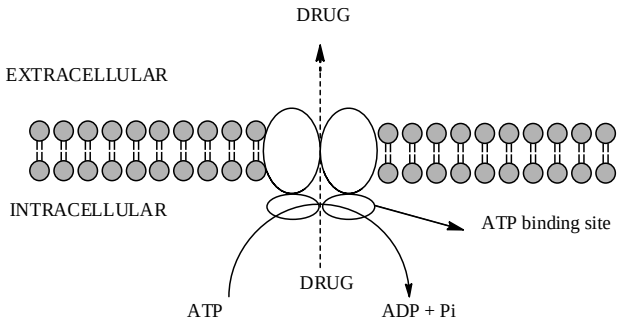

Figure 3: ATP dependent P-glycoprotein efflux pump preventing entry of drug (D) from nose to brain.

CHITOSAN AS A POLYMER

Chitosan is the most important derivative obtained from chitin. Chitin is the second most abundant natural polysaccharide after cellulose in nature, and it is primarily present in the exoskeletons of marine zooplankton spp., like corals and jellyfishes ,crustaceans (such as krimp, crab, shrimp, lobster etc.) and various insects such as butterflies and ladybugs, worms, fungi and mushrooms in varying amount. Chitin makes up to 45% of the cell wall of *Aspergillus Niger* and *Mucor rouxii* and 20% of the cell wall of *Penicillium notatum* [40]. Despite the widespread occurrence of chitin in nature, presently crab and shrimp shells remain the primary commercial sources. The chemical structure of chitin poly-β-(1 → 4)-N-acetyl-D-glucosamine is similar to cellulose, with a difference that in chitosan one hydroxyl group on each monomer has substituted with an acetyl amine group. Chitosan is a linear polysaccharide consisting of (1-4)-linked 2-amino-2-deoxy-b-D-glucopyranose. Chitosan is a modified, natural carbohydrate polymer derived by deacetylation of chitin under alkaline conditions with the average molecular weight 1.0 to 5×105Da [41]

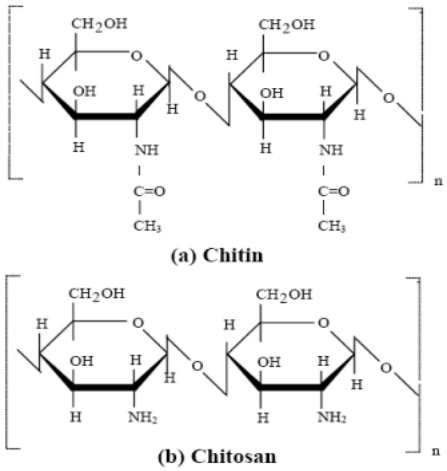

Figure 4: Chemical structure of chitin (a) and chitosan (b)

Industrial-scale Chitosan production involves five steps:

a) Demineralization (DM)/Decalcification-Raw material are treated with dilute aqueous HCl solution (3%-5% Hcl w/v Hcl at room temperature).

b) Deproteinization (DP)-Treated with dilute aqueous NaOH solution (3%-5% w/v NaOH) is given.

c) Decoloration (DC)-Using 0.5% KMnO4 aqueous or oxalic acid aqueous or exposing to sunshine. At this step chitin is obtained.

d) Deacetylation (DA) 1, 2.-Chitin is treated with hot conc. NaOH solution (40%-50% NaOH).

e) Isolation of chitosan wherein the crude chitosan is dissolved in aqueous 2% acetic acid solution. The insoluble material is removed giving a clear supernatant solution, which is neutralized with NaOH solution resulting in a purified sample of chitosan as a white precipitate.[42], [43]

Chitosan displays interesting properties such as pH sensitivity, biocompatibility, biodegradability[44]. Chitosan is metabolized by certain human enzymes, especially lysozyme, and is thus considered as biodegradable and the degradation products obtained are non-toxic, non-immunogenic and non-carcinogenic[45]. Chitosan has the special feature of adhering to mucosal surfaces which makes it a useful polymer for mucosal drug delivery. It also has mucoadhesive properties due to its positive charges at neutral pH that enable an ionic interaction with the negative charges of sialic acid residues of the mucus. Transient opening of tight junctions in nasal epithelial cells is due to interaction with protein kinase C signaling pathway and ultimately not only increase the residence time of formulation but also promote the absorption of drugs into CNS when administered directly to the olfactory region[34], [46]. Chitosan exhibits a myriad of biological actions, namely hypocholesterolemic, antimicrobial, and wound-healing properties. Nano and micro-particles of chitosan are suitable for controlled drug release. Association of vaccines to these particulate systems has also shown to enhance the antigen uptake by mucosal lymphoid tissues, thereby inducing strong systemic and mucosal immune responses against the antigens. Chitosan, however, suffers from low solubility at a physiological pH of 7.4, limiting its use as absorption enhancer. Chitosan is only soluble in few dilute acid solutions. Another limitation of chitosan for the preparation of sustained release systems arises from its rapidly adsorbing water and higher swelling degree in aqueous environments leading to faster drug release. In order to overcome these problems, a number of chemically modified chitosan derivatives have been synthesized and tested. Chemical modification of chitosan improves its solubility and widens its applications Chemically modified chitosan has great utility in controlled release and targeting. Therefore, chitosan has prospective applications in many fields such as biomedicine, waste water treatment, functional membranes, flocculation and its some recent applications involve periodontal drug delivery, vaginal drug delivery, gene delivery, vaccine delivery, imaging techniques, wound healing and nasal drug delivery etc.

Chitosan Nanoparticles

Chitosan nanoparticles have proven to be a good carrier system for nasal drug absorption due to its bioadhesion and absorption promoting effect through paracellular pathway. Moreover size and surface charge also play a great role. In addition to these, it avoids the use of hazardous organic solvents while fabricating particles as it is soluble in aqueous acidic solution, The readily available free amino groups of this linear polyamine polymer provides cationic nature as well as allows ionic cross linking with multivalent anions, it has mucoadhesive character, which increases residual time at the site of absorption. LD50 of chitosan in laboratory mice is 16 g kg^{-1} body weight, which is close to sugar or salt. Chitosan is proven to be safe in rats upto 10% in the diet [47]. Estradiol by encapsulating in chitosan nanoparticles has been successfully delivered to cerebrospinal fluid by intranasal route. X. Wang et al has shown that in CSF, estradiol had a Cmax of (76.4 ± 14.0) ng ml^{-1} at 28 min after intranasal delivery, but delayed to 60 min (29.5 ± 7.4 ng ml^{-1}) by intravenous administration, which illustrated that Estradiol could arrive at the brain tissue earlier following intranasal administration and it has been found that CSF concentrations achieved after intranasal administration (76.4 ± 14.0 ng ml^{-1}; tmax 28 ± 17.9 min) were significantly higher than those after intravenous administration (29.5 ± 7.4 ng ml^{-1} tmax 60 min). The reason for this enhanced absorption has been proposed for two reasons i.e. due to improved adhesion between the formulation and the nasal tissues by chitosan and the transient effect of chitosan on paracellular transport processes which has been successfully proved by various investigations on cell culture specifically CaCo-2 cells as well as in animal models [48]. Chitosan can open the tight junctions between cells through an effect upon F actin filaments and it is proved by immune histological studies. Unlike other absorption promoters chitosan is proved to be safe and non toxic in human subjects. This combination of bioadhesion and paracellular transport effects has led to a consideration of the use of chitosan for the delivery of Estradiol via the nasal cavity. For nose to brain drug delivery the ophthalmic and maxillary branches of the trigeminal nerve are important because neurons from these areas are directly exposed to external environment through nasal mucosa. It has been proven that neurotrophic factor IGF-1 has been successfully delivered to multiple areas of brain via nose to brain along olfactory and trigeminal pathway [26]. Experiments have shown that rapid entry of most of the drugs into the CNS through intranasal administrations mainly occurred by two routes i.e. one associated with the peripheral olfactory system connecting the nasal passages with the olfactory bulbs and rostral brain regions (e.g. anterior olfactory nucleus and frontal cortex) and the other associated with the peripheral trigeminal system connecting the nasal passages with brain stem and spinal cord regions.

Microspheres as a tool in nasal delivery of drugs to the brain

Microspheres are drug carrier systems which act as vectors for the delivery of drugs to the specific organ of interest by their capacity of increasing the residence time of drugs in nasal mucosa compared to solutions and hence exert a direct effect on the nasal mucosa which result in the opening of tight junctions between the epithelial cells [49] and increased uptake by the nasal surface leading to increased administration of drug in the brain.[50]. The microsphere as delivery systems offer huge potential and importance due to the fact that these protect the drug from enzymatic metabolism and sustain drug release hence prolonging its effect [51]. Various natural polymers such as alginate, chitosan have been widely used in the development of delivery systems and

chitosan microspheres have been widely used and characterized for nasal drug delivery. Chitosan is most commonly employed for preparing these microspheres due to ease of production, wide availability of chitosan and its additional properties of biocompatibility, biodegradability, great potential for biomedical and pharmaceutical applications due to its high charge density, and non-toxicity. It enables increased retention time and it is a good absorption enhancer. Furthermore chitosan as an excipient is able to enhance the dissolution rate of low water soluble drugs[52], [53]. Also it has shown to have adjuvant activity in the mucosal immune response thereby increasing its popularity as an aid for the nasal drug delivery in the form of microspheres. Nasal route is generally selected owing to the property that many drugs have better bioavailability by nasal route than the oral route. Various drugs have been delivered using this novel delivery route for the treatment of several brain disorders like epilepsy, nausea, brain tumors, Alzheimer's disease, Parkinson's etc. Good results have been obtained which are demonstrated below:

Table 1: Various drugs in chitosan microspheres for nose to brain drug delivery.

Polymer system	Drug	Use	Result	Reference
alginate/chitosan	carbamazepine	Epilepsy	Open tight junctions in the epithelium were observed and these spray-dried microspheres are promising as mucoadhesive nasal carriers.	[54]
Gelatin-chitosan	Clonazepam	Epilepsy	Intranasal administered clonazepam microspheres resulted in higher brain levels with drug targeting.	[55]
Chitosan Glutamate (CG)-based mucoadhesive microspheres	Rokitamycin	Macrolide antibiotic	Drug successfully goes to the CSF and the bloodstream only after nasal administration	[56]
Chitosan glutamate	Carbamazepine	epilepsy	*In vivo* administration of drug-loaded glutamate microspheres (CG-CBZ) remarkably increased the CBZ concentration found in the serum, enhancement of the drug bioavailability in general was observed.	[54]
Chitosan microspheres	Methotrexate	Brain Tumor	Significant improvement in bioavailability and fraction of Methotrexate could be transported directly from nose to brain.	[57]

Chitosan as hydrogel systems for nose to brain delivery of potent drugs

Even though nasal route has overcome many barriers for the drug delivery into the brain by bypassing the BBB but there are several other challenges that are faced when this route is realistically employed for the drug delivery and nasal residence is one the most hindering obstacle for such a delivery design as it is determined by mucus turnover time which is limited to approximately 15–20 min therefore insufficient time for drug/nanoparticles to be taken up by the nasal epithelial membrane, in addition to this ciliary beat frequency also obstructs the drug transfer into the nasal lobe. Therefore the need to incorporate mucoadhesive viscoelastic hydrogels in nasal drug delivery in order to prolong the residence time of the active moiety on the mucosal surface thereby aiding in enhanced availability through this route. These mucoadhesive hydrogels have a unique property of undergoing sol-gel transition wherein the solution transforms to viscous hydrogel because of the lifted temperature (37°C) in the nasal cavity, which can potentially reduce the mucociliary clearance rate from the nasal cavity and releases the drug slowly. Illum *et al.,* by means of various experiments have suggested that the combination of bioadhesive polymers with specific brain targeting ligands provide the desired targeting, retains the formulation for an extended time period and enhances both receptor mediated as well as paracellular transport. Chitosan, a natural polymer possessing biodegradability, biocompatibility properties seems to be the best option for formulating such systems. Chitosan has been proved to be mucoadhesive in the nasal cavity by Soane *et al.,*[34] they have shown that the increase in half-life of nasal retention was increased to 40 min as compared to 15 min for a non bioadhesive system when administered in solution to human volunteers. Smith etal have proved that the Chitosan interacts with Protein Kinase C pathway[58] and is thus capable of opening tight junctions in nasal epithelial cells thus considered to be a very effective absorption enhancer.[59]

Chitosan/glycerophosphate gels

Chenite *et al.,*[60] first developed the thermosensitive chitosan/glycerophosphate gels for the delivery of sensitive biological materials such as proteins and gene-based therapeutics.

N-trimethyl chitosan chloride gels

Sieval *et al.,* prepared and characterized a positively charged derivative of chitosan i.e. N-trimethyl chitosan chloride (TMC) which showed improved solubility profile, enhanced mucoadhesive properties, significant absorption enhancing effect over a wide pH range [61] as well as enhancing the properties of the thermo sensitive

formulations. Nazar et al. studied various rheological and mucoadhesive properties of the gel in reference to nasal drug delivery, this gel for the nasal delivery was Co-formulated of poly (ethylene glycol) and glycerophosphate with N-trimethyl chitosan of medium average molecular weight and low degree of quaternisation. The results were encouraging as it yielded an aqueous formulation that exhibits a sol–gel transition at 32.5°C and within 7 min. The same hydrogel formed rheologically synergistic mixtures with mucus and also exhibited good affinity for mucosal surfaces. Therefore this chitosan gel can be further investigated for the active delivery of drugs via the nasal route[62].

Quaternized chitosan gels

Owing to non-toxicity, mucoadhesivity and capacity to open the tight junctions between epithelial cells of quaternized chitosan, Wu *et al.,* developed a new thermosensitive hydrogel by simply mixing N-(2-hydroxy-3-trimethylammonium) propyl chitosan chloride (HTCC) and poly (ethylene glycol) (PEG) with a small amount of a-b-glycerophosphate (a-b-GP). Owing to its low viscosity at room temperature, it can be dropped or sprayed easily into nasal cavity and can spread widely on the nasal mucosa in the solution state. They entrapped insulin in the gel system to treat diabetes and in animal experiments, the hydrogel formulation was found to decrease the blood glucose concentration apparently (40–50% of initial blood glucose concentration) for at least 4–5 h after administration, and no apparent cytoxicity was found after application [1].

Chitosan/b-glycerophosphate thermo-sensitive gel

Kim *et al.,* prepared a chitosan/b-glycerophosphate thermo-sensitive gel for the delivery of ellagic acid for the treatment of brain cancer. When disodium b-GP is added into chitosan solution the pH tends to increase which reduces the electrostatic repulsion between chitosan chains thereby an increase in chitosan interchain hydrogen bonding which further raises the temperature and releases hydrogen bonds between water molecules and chitosan chains, which allow increased hydrophobic interactions between chitosan chains 32–34, 38. They studied the anti tumour activity and showed that the DCh/b-GP gel loaded with ellagic acid could inhibit the growth of cancer cells in an ellagic acid concentration dependent manner. Therefore they positively concluded that the injectable chitosan gel can deliver the anti-cancer activity of ellagic acid via a simple injection and be considered as a promising delivery method for a local chemotherapy[63]. Vaka *et al.,* administered neurotrophic factor via nasal route using chitosan gel and found that the brain bioavailability of rats administered intranasally with BDNF solution containing *chitosan was significantly enhanced* ~13-fold compared to rats administered with same concentration of BDNF solution without chitosan therefore they concluded that the intranasal formulations containing chitosan as barrier-modulating agent significantly enhanced brain bioavailability of BDNF [64].

Manda etal performed similar experiments where they delivered cefotaxime in chitosan gel and found that the amount of cefotaxime that permeated across the olfactory mucosa when 0.25% w/v of chitosan was used as a permeation enhancer was ~1.5- and ~2-fold higher at the end of the first hour and second hour, respectively, over control (29.56 ± 6.18 µg/cm(2)). These results suggested that intranasal administration of cefotaxime was a potential method of delivering various antibacterial agents to the brain [65].

Further studies were carried out and various chitosan combination in form of thermoreversible gels were employed to study their efficacy in case of nasal delivery. To enhance permeation and solubility of an intranasal delivery system of fexofenadine hydrochloride (FXD HCl), a new formulation using poloxamer 407/hydroxypropyl-beta-cyclodextrin (HP-beta-CD)-based thermoreversible gels with chitosan, was developed. The results showed that the bioavailability of the optimized thermoreversible gel containing 0.3% chitosan was about 18-fold higher than that of the solution type. Medium viscosity chitosan more efficiently enhanced permeation of FD 40Â K across olfactory mucosa as compared to other grades. Brain bioavailability of rats administered intranasal with brain-derived neurotrophic factor (BDNF) solution containing chitosan was significantly enhanced ~13-fold compared to rats administered with same concentration of BDNF solution without chitosan. Intranasal formulations containing chitosan as barrier-modulating agent significantly enhanced brain bioavailability of BDNF. Delivery of BDNF was found to counteract stress-induced depression in rats. Hence we can say that if such formulations are directly delivered to the olfactory area it would increase the retention of the formulation at this site and at the same time promote the transport of drugs from the olfactory region to the CNS and the hydrogel chitosan systems offer unique properties which potentially increase the use of this system in nasal drug delivery of potent drugs and release modification can also be achieved easily with slight modifications in the formulation parameters.

CONCLUSION

In summary, the evidences shown by above literature have revealed that chitosan has desired properties for brain targeting through nose to brain delivery. Chitosan as nanoparticles has shown the ability to enter into brain through transient effect on tight junctions and promoting absorption effect through paracellular route. Moreover due to its small size it is absorbed through bundle of neurons from olfactory bulb and trigeminal nerve. Therefore a large number of drugs can be effectively delivered by this route.

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