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Recent Updates in the Formulation Strategies to Enhance the Bioavailability of Drugs Administered via Intranasal Route

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Abstract

Targeting drugs to the brain or Cerebrospinal fluid (CSF) is limited because of the physiological barriers like blood-brain barrier and blood-CSF barriers. Alternative non-invasive, patient compliant delivery routes like intranasal route was investigated by several research groups to target both small and large molecules. Several barriers that limit the bioavailability and research formulation strategies adopted by various research groups are discussed in brief in this review article.

Keywords: Brain; Cerebrospinal fluid; Intranasal; Formulation; Non-invasive

Introduction

Targeting drugs to the central nervous system via oral or IV route is a challenge because of the physiological barriers like Blood Brain and Blood cerebrospinal fluid (CSF) barrier. Intranasal (IN) route is devoid of the various barriers for delivery of drugs to CNS [1-16]. This route facilitates patent compliance, ease of administration, low dose requirement and minimal side effects [9,11-15,17-19]. The overall objective of the review is to provide the recent advances in the intranasal delivery of therapeutic agents to the brain and the CSF.

Intranasal delivery of drugs to the CNS will be delivered to the olfactory bulb and the brain via the olfactory and trigeminal components respectively. The transport of drugs will be further carried out across epithelial membrane barriers or to brain entry sites from nasal mucosa or from brain entry sites to other sites following a transcellular, paracellular or neuronal transport pathways.

Low membrane permeability across nasal mucosa is considered to be a major limiting factor for the absorption of polar drugs and peptides. The absorption of the drugs across the nasal epithelium is influenced by the physicochemical properties of the drug. Lipophilic drugs have a higher rate of absorption whereas various factors like molecular weight, membrane permeability, mucociliary clearance and enzymatic degradation influence the absorption of hydrophilic drugs.

In addition rapid mucociliary clearance also serves as a road block and confines the residence time of the drugs which in turn reduces the half-life of the intranasal formulations (liquid and powder dosage forms) to an order of 15-20 min [19,20]. Site of deposition either anterior or posterior area of the nasal region also influences the clearance of drugs. Drugs targeted to the anterior part of the nasal cavity may be subjected to minimal nasal clearance and promote absorption compared to the deposition in further back region. Various enzymes present in the mucosal region may also limit the bioavailability of the drugs. In the current various formulation strategies to enhance the bioavailability of drugs administered via intranasal route is discussed.

Formulation Strategies to Enhance Intranasal Drug Delivery

To overcome the barriers that limit the bioavailability of drugs administered via intranasal route, various formulation approaches such as enhancing the drug permeability across the nasal epithelium, minimizing clearance from the nasal passage and protecting drugs from degradation may enhance the capabilities of intranasal drug delivery to CNS.

Alteration of Membrane Permeability Using Permeation Enhancers

The poor permeability of the nasal mucosa limits the permeability of the drugs across nasal mucosa and it could be enhanced by improving permeability of drugs across the mucosal epithelium. This enhancement in permeation aids in the enhancement of extracellular transport to the CNS along olfactory and trigeminal nerve. Tight junctions present in the epithelia also limit the permeability to a certain extent and limits the bioavailability of the drug molecules. The use of permeation enhancers like surfactants, tight junction modifiers, bile salts, lipids and polymers may modify the permeability of the drugs across the nasal mucosa.

Cationic polymers like chitosan when co-administered may enhance the absorption across the nasal mucosa. Vaka et al. investigated the efficacy of chitosan to facilitate brain bioavailability of intranasally administered nerve growth factor (NGF) and reported that use of chitosan enhanced the permeation of NGF across the olfactory epithelium by 5 fold compared to the control during the *in vitro* permeation studies [21,22]. A comparative evaluation of the intranasal administration of NGF with chitosan and without chitosan was also evaluated in Sprague Dawley rats and it is very clearly evident form the PK results that C_{max} of NGF in brain was enhanced by ~14 fold upon use of chitosan compared to its control.

Manda et al., investigated the ability of the chitosan to enhance the permeation of Cefotaxime and reported that 0.25% w/v chitosan across the olfactory epithelium was enhanced about ~2 fold in the 2 hours of

time compared to control [9,23]. *In vivo* studies were carried out in Sprague Dawley rats by intravenous and intranasal administration of cefotaxime. The MIC levels were attained within a short time span and were maintained for a considerable period of time. The time required to attain maximum concentration in case of intranasal (t_{max}=30 min) was rapid compared to intravenous (t_{max}=180 min) and the absolute bioavailability following intranasal administration was about 86%.

Vaka et al. investigated the ability of peppermint oil to enhance the permeation of NGF across the olfactory mucosa and reported that peppermint oil at concentrations of 0.05, 0.1 and 0.5% v/v enhanced the *in vitro* transport of NGF by 5, 7 and 8 fold, respectively. *In vivo* studies employing brain microdialysis in rats demonstrated that intranasal administration of NGF formulation with 0.5% peppermint oil enhanced the bioavailability by ~8 fold compared to rats administered with NGF alone [24-26]. The bioavailability of NGF in the brain could be enhanced by intranasal administration of peppermint oil.

The change in osmolarity of the formulation may enhance the intercellular or extracellular transport mechanism to the CNS region. A change in the amount of vasoactive intestinal peptide with a change in osmolarity of the formulation was reported [27]. Ionization state of the drug and pH of the formulation may also affect the permeability of the drugs when administered intranasally. Sulphonamides with different fractions of ionization when administered intranasally were found to have differences in permeability to the CSF [28].

Nanoparticular Delivery System

Mucociliary clearance reduces the contact time of drugs with the nasal epithelia and rapidly removes drugs from the delivery site. Use of nanoparticles, mucoadhesive agents, absorption enhancers, surfactants, lipid emulsions, vasoconstrictors and efflux transporter inhibitors are some of the potential approaches to reduce the clearance and enhance the residence time [29-37].

Nanoparticulate drug delivery systems have the capability to enhance the bioavailability of drugs upon intranasal administration compared to drug solutions [38-43]. These formulations were reported to increase the residence time in the nasal cavity and prevent the effect of enzymatic degradation on these drugs [41]. Insulin nanoparticles were also reported to reduce the plasma glucose levels when compared to the insulin solution [38,44,45]. The better efficacy of the nanoparticulate formulation was due to the strengthened contact of the nanoparticles with the epithelium.

Nanoparticle with modified surface properties may be used for mucosal binding, reduce clearance and enhance delivery to CNS. In a study by Kravtzoff et al. it was reported that the mean residence half-life was extended to 2.3 h in the human nasal cavity when compared to that of the residence half-life (15-30 min) of solution upon the use of cationic Biovector™ nanoparticle system [46,47]. The levels of fluorescent markers in various regions of brain was enhanced when Ulex europeus agglutinin I and wheat germ agglutinin conjugated horseradish peroxidase upon conjugation with PEG-PLA nanoparticles compared to unmodified nanoparticles. Use of vasoconstrictors to reduce the clearance in to the blood and treatment with inhibitors of the efflux transporters reduces the clearance in to the blood and enhances the drug to the CNS. Vaka et al. investigated the capabilities of carnosic acid nanaoparticular systems to enhance the *in vivo* efficacy of carnosic acid and enhance the neurotropin expression in the brain [48-50]. It was reported that intranasal administration of carnosic acid nanoparticles resulted in comparable levels of endogenous

neurotrophins level in the brain that was equivalent to the four, once a day intranasal administration of solution in rats and demonstrated the fact that nanoparticulate drug delivery system for intranasal administration of carnosic acid reduces the number of administrations to elicit the required pharmacological activity.

Polymeric Delivery Systems

Polymers with high molecular weight and flexible chains are used as bioadhesives, they have the capability to interact with mucin by forming hydrogen, electrostatic, hydrophobic or van der waals interactions. Thermoreversible polymers have the capability to exist in both sol and gel form at low and high temperatures respectively, and are referred as *in situ* gels. Because of its dual nature, it can be used as drug carrier for intranasal delivery where the therapeutics will be administered in the solution form at low temperatures and turns to semi-solid gels with change in physiological temperature. Polymeric vehicles like Kolliphor P 407 are reported to deliver the drugs at therapeutic concentrations, prolong the release of therapeutic agents and protect the therapeutic agents from enzymatic degradation. Perez et al. successfully delivered naked siRNA and poloxamer polymers, as *in situ* mucoadhesive gels to brain via olfactory epithelium [51]. Chen et al. could successfully enhance effect of radix bulperi and retain its effect for a longer time in CSF following administration of temperature sensitive *in situ* gels [52]. Manda et al. investigated the ability of delivering ziconotide via intranasal route. Ziconotide when delivered using poloxomer as a vehicle could not only attain therapeutic concentration rapidly but also prolong the release of ziconotide, maintain therapeutic levels in CSF for a longer period of time compared to solution and reduce the frequency of administration [53].

Conclusion

Intranasal delivery appears to be a promising route for targeting drugs either to brain and CSF. This route will be very effective in treating various CNS disorders and various formulation strategies have already demonstrated the potential to enhance and prolong the release of therapeutic agents. It will be of great interest to the research community to explore further advances in targeting drugs to CNS via non-invasive patient compatible intranasal route for disease conditions that need a rapid onset of action.

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