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REVIEW ARTICLE

Nanoparticles: Nasal Delivery of Drugs

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ABSTRACT

Diseases of the Central Nervous System (CNS) such as schizophrenia, meningitis, migraine, parkinson's disease and alzheimer's disease require delivery of the drug to the brain for treatment. Treatment of CNS diseases are difficult because of presence of blood – brain barrier (BBB). This review highlights about the nanoparticles which represent, one of the possibilities to overcome this barrier. NPs and other colloidal drug-delivery systems modify the kinetics, body distribution and drug release of an associated drug. Intranasal administration of drug offers an alternative to the oral and parenteral drug delivery. In recent years, Nasal delivery has been explored as an alternative administration route to target drugs directly to the brain via the olfactory neurons. Intranasal administration circumvents first-pass elimination and drug absorption is rapid due to the existence of a rich vasculature and a highly permeable structure within the nasal membranes which provide faster onset of action as compared to peroral administration. The purpose of this review, to provide complete information about nasal drug delivery system such as advantage, limitations, mechanism of drug absorption, absorption improvement aspects and novel drug formulations.

KEYWORDS

Brain, Nanoparticles (NPs), Nasal delivery, Microemulsion

INTRODUCTION

Drug delivery can be defined as the process of releasing a bioactive agent at a specific rate and at a specific site. Most of the drugs are limited by their poor solubility, high toxicity, high dosage, aggregation due to poor solubility, nonspecific delivery, in vivo degradation and short circulating half-lives. Targeted drug-delivery systems can convey drugs more effectively and conveniently than those of the past, increase patient compliance, extend the product life cycle, provide product differentiation and reduce healthcare costs.[1]

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In addition, novel drug-delivery systems would offer protection and improve the pharmacokinetics of easily degradable peptides and proteins that often have short half-lives in vivo. Therefore, the development of techniques that could selectively deliver drugs to the pathological sites is currently one of the most important areas of drug research.[1,2] Nanoparticles as one of the most recent novel drug delivery carriers have been shown to improve drug efficiency via targeting the delivery of drugs. The main features of nanoparticles, making them ideal candidates for drug delivery, are small size and use of biodegradable materials in their preparation. Indeed the nano-sized character of these particles causes their extravagation through the endothelium in inflammatory sites, epithelium, tumors, or penetrate microcapillaries and

consequently allows for efficient uptake by a variety of cell types.[3] Nanocarriers, on account of their higher ratio of surface area to volume, show improved pharmacokinetics and biodistribution of therapeutic agents and thus minimize toxicity by their preferential accumulation at the target site.[4] They improve the solubility of hydrophobic compounds and render them suitable for parenteral administration. Furthermore, they increase the stability of a variety of therapeutic agents, like peptides, oligonucleotides, and so forth.[5]

They can be used to deliver the drug to the central nervous system owing to their smaller size and higher barrier permeability. Use of biodegradable materials minimizes the possibilities of hypersensitivity reactions and affords good tissue compatibility.[6] Ideally, a nanocarrier should be capable of providing extended blood circulation, delivering the active moiety at the targeted site and bypassing the endosome-lysosome processing.[7] Selection of bioactive for nanoparticulate approach is crucial to the success of the technology. In general, molecules that are difficult to be delivered by conventional means due to poor biopharmaceutic and pharmacokinetic properties which include poor solubility and permeability, narrow therapeutic index, high toxicity, high target specificity, P-glycoprotein efflux, etc., are some of the parameters that need to be considered for nanoparticulate delivery along with intellectual property rights. Another important point to bear in mind is that high dose drugs cannot be delivered by nanoparticles.[8] Nanoparticles (NPs) act as potential carries for several classes of drugs such as anticancer agents, antihypertensive agents, immunomodulators, hormones and macromolecules such as nucleic acids, proteins, peptides and antibodies.[9]

Polymeric Nanocarriers

Nanoparticles for the purpose of drug delivery are defined as submicron (1-1000nm) colloidal particles. This definition includes monolithic nanoparticles (nanospheres) in which the drug is adsorbed, dissolved, or dispersed throughout the matrix and nanocapsules in which the drug is confined to an aqueous or oily core surrounded by a shell-like wall. Alternatively, the drug can be covalently attached to the surface or into the matrix.[10] A large panel of biodegradable polymers is available to form nanoparticles. They can be either natural or synthetic.[11] Natural materials used for oral delivered nanoparticles include chitosan, dextran, gelatine, alginate, agar among which chitosan is the most popular.[12,13] Nanoparticles are made from biocompatible and biodegradable materials such as polymers, either natural (e.g., gelatin, albumin) or synthetic (e.g., polylactides, polyalkylcyanoacrylates), or solid lipids. In the body, the drug loaded in nanoparticles is usually released from the matrix by diffusion, swelling, erosion, or degradation. The following are among the important technological advantages of nanoparticles as drug carriers: high stability (i.e., long shelf life); high carrier capacity (i.e., many drug molecules can be incorporated in the particle matrix); feasibility of incorporation of both hydrophilic and hydrophobic substances; and feasibility of variable routes of administration, including oral administration and inhalation. These carriers can also be designed to enable controlled (sustained) drug release from the matrix.[14]

Advantages of NPs as Drug Delivery Systems[2]

- Increase the aqueous solubility of the drug
- Protect the drug from degradation
- Produce a prolonged release of the drug
- Improve the bioavailability of the drug
- Provide a targeted delivery of the drug
- Decrease the toxic side effects of the drug
- Offer appropriate form for all routes of administration
- Allow rapid-formulation development

NPs due to their small size can efficiently penetrate across barriers through small capillaries into individual cells, thus allowing efficient drug accumulation at the target site.

Therefore, the unwanted side effects and the toxicity of the therapeutic agent is reduced and the therapeutic efficacy is enhanced.[15] Another characteristic function of NPs is their ability to deliver drugs to the target sites across biological barriers such as the blood-brain barrier (BBB).[16,17] The most promising application of nanomaterials is the promise of targeted, site-specific drug delivery. The potential of eliminating a tumorous outgrowth without any collateral damage through nanomaterial-based drug delivery has created significant interest and nanoparticles form the basis for bio-nano-materials and major efforts in designing drug delivery systems are based on functionalized nanoparticles.[18] Modifying or functionalizing nanoparticles to deliver drugs through the blood brain barrier for targeting brain tumors can be regarded as a brilliant outcome of this technology.[19] For example, doxorubicin does not cross the blood–brain barrier, but its integration with polysorbate 80 modified polybutylcyanoacrylate nanoparticles can increase its delivery to the brain to a significant extent.[20,21] Polymer-based coatings may be functionalized onto other types of nanoparticles to change and improve their biodistribution properties. The biologically inert polymer poly (ethylene glycol) (PEG) has been covalently linked onto the surface of nanoparticles.[22] This polymeric coating is thought to reduce immunogenicity, and limit the phagocytosis of nanoparticles by the reticuloendothelial system, resulting in increased blood levels of drug in organs such as the brain, intestines, and kidneys.[23,24]

Nose-to-Brain Transport of Nano-Sized Vectors

In recent years the nasal route has received a great deal of attention as a convenient and reliable method for the systemic administration of drugs.[25] However, polar drugs and some macromolecules are not absorbed in sufficient concentration due to poor membrane permeability, rapid clearance and enzymatic degradation into the nasal cavity.[26] Earlier studies have demonstrated that intranasal administration offers a practical, non-invasive, and an alternative route of administration for rapid drug delivery to brain.[27,28,29,30] The large surface area of the nasal cavity and the relatively high blood flow, thereby achieving a rapid absorption and avoidance of hepatic first-pass elimination are attractive features of nasal drug administration.[31,32] It also offers the advantages of being administered simply, cost effectively and conveniently. Additionally, direct transport of drugs to brain, circumventing the brain barriers following intranasal administration provides a unique feature and better option for targeting drugs to brain.[33,34,35] However, few formulation factors should be considered while designing the drug delivery system for intranasal administration. The formulation should be designed so as to provide a rapid transport of drug across nasal mucosa and a longer residence time in nasal cavity to overcome the nasal mucociliary clearance.[36] Nasal mucociliary clearance is one of the most important limiting factors for nasal drug delivery. It severely limits the time allowed for drug absorption to occur and effectively rules out sustained nasal drug administration. However, bioadhesive polymers can be used to increase the nasal residence time, thus allowing longer absorption times, and to achieve a more intimate contact with the nasal mucosa, which results in a higher concentration gradient and subsequent increased absorption.[18] Mucoadhesive polymers have been introduced to construct microparticle type formulations which could overcome problems of poor bioavailability by increasing the residenc time in the applied site. Mucoadhesive polymers that have been used for drug delivery include polyacrylic acids, cellulose derivatives, chitosan, gelatin and hyaluronic acid.[37,38,39] Among these, hyaluronic acid (HA) is especially beginning to be recognized as an effective component of nasal delivery.[40] Chitosan, a polycationic polymer, has been widely used to deliver various therapeutics including nerve growth factors, insulin, and drugs to the brain via intranasal route of delivery.[41,42] Chitosan is known to be a mucoadhesive agent; the amines in chitosan react with sialic residues present on the mucosal

layer that helps reduce clearance rate from nasal cavity.[43] Due to its mucoadhesive property, it has been used for intranasal delivery of various formulations for ocular and pulmonary diseases.[44,45,46,47] Another important limiting factor in the nasal application is the low permeability of the nasal mucosa for the drugs. It seems to be necessary to consider an absorption enhancement mechanism for co-administration of drugs with either mucoadhesive polymers or penetration enhancers or combination of the two. The mechanism of action of absorption enhancers is not well known but, generally, they change the permeability of epithelial cell layer by modifying the phospholipidic bilayer, increasing membrane fluidity or opening tight junctions between epithelial cells and, thus, increasing paracellular transport. In fact, surfactants, bile salts, fatty acids, phospholipids and lyso-phospholipids modify cell structures, leaching out proteins or even stripping off the outer layer of the mucosa.[48] From a drug delivery perspective, application of nanoparticles composed of polymers (which are typically used in drug delivery) have shown statistically greater ability, than a simple formulation of the drug, to deliver model drugs such as nimodipine to the olfactory bulb or to enhance the pharmacological activity of morphine, when these small molecules were applied intranasally in combination with nanoparticles.[49] A mucoadhesive *in situ* gel was developedin order to improve the bioavailability of the antiemetic drug, metoclopramide hydrochloride (MCP HCl). The bioavailability study in rabbits revealed that the absolute bioavailability of MCP HClwas significantly increased from 51.7% in case of the oral drug solution to 69.1% in case of the nasal *in situ* gel.[50] Surface modification of the nanoparticles could achieve targeted CNS delivery of a number of different drugs. Recently, several studies in rodents have shownthat direct nose to- brain transport of small molecular weight drugs is enhanced by application in a nanoemulsion, and surface modified nanoemulsion formulation. For example, risperidone has a greater efficacy for direct nose-to-brain drug delivery when applied as a chitosan coated nanoemulsion formulation compared to nanoemulsion alone and to a simple solution formulation.[51,52]

Transport Pathways from Nose to Brain

Diseases of the Central Nervous System (CNS) such as schizophrenia, meningitis, migraine, Parkinson's disease and Alzheimer's disease require delivery of the drug to the brain for treatment. However such transport remains problematic, especially for hydrophilic drugs and large molecular weight drugs, due to the impervious nature of the endothelial membrane separating the systemic circulation and central interstitial fluid, the Blood–Brain Barrier (BBB).[53] Systemic administration of various neuropeptides and hydrophilic therapeutic agents, such as antibiotics and anticancer agents, has failed to cross the BBB. The CNS only allows small, lipophilic compounds (<400–500Da) to permeate and cross the BBB. Current clinical strategies include surgical interventions, which are invasive and can later pose postsurgical complications with fatal side effects. Some of the currently employed invasive approaches (mechanically breaching the BBB) include (a) interstitial delivery, intracerebroventricular delivery, intracerebral delivery, and convection enhanced delivery.[54] It has been shown in the literature from animal and human investigations, that transport of exogenous materials directly from nose-to-brain is a potential route for by-passing the BBB.[55] This route, involves the olfactory or trigeminal nerve systems which initiate in the brain and terminate in the nasal cavity at the olfactory neuroepithelium or respiratory epithelium, respectively. They are the only externally exposed portions of the CNS and therefore represent the most direct method of non-invasive entry into the brain. However, the quantities of drug administered nasally that have been shown to be transported directly from nose-to-brain are very low, normally less than 0.1%, and hence the system is not currently used therapeutically and no product is licensed specifically via this route.[56] The ophthalmic and maxillary branches of the trigeminal nerve are important for nose-to-brain drug delivery since

neurones from the branches pass directly through the nasal mucosa. In fact, these neurones have been proven to deliver the neurotrophic factor, IGF-1 (MW 7.65 kDa), to the brain stem and spinal cord areas in the *in vivo* rat model.[57] 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. It has been found in animal models that increasing the drug hydrophilicity, molecular weight (above 20 kDa) and degree of ionisation can reduce drug transport into the CNS after *i.n.* administration.[58,59,60] In addition, small molecular weight drugs are also affected by the active efflux transporter pumps at the apical membrane surface (P-gp) or enzymatic degradation in the olfactory epithelium.[61,62] Therefore, transport of a drug directly into the CSF, as a measure for CNS delivery, is determined by a combination of molecular and biological properties of the drug which are at this stage difficult to predict. Finally, a number of studies have shown that CNS bioavailability of small molecular weight drugs after *i.n.* instillation is very low (typically less than 0.12% of administered dose for sulphonamides, dopamine and morphine.[63] Many drugs such as insulin, analogues of luteinizing hormone releasing hormone, growth hormone releasing factor and calcitonin show much lower absorption efficiencies when administered intranasally.[64,65,66] Various approaches have been order to increase the absorption attempted in and thus the bioavailability of drugs administered intranasally. Substances such as bile salts (e.g. sodium glycocholate) and surfactants (e.g. polyoxyethylene-9-lauryl ether) in combination with the drug will modify the properties of the nasal mucosa, thereby enhancing absorption efficiency. The absorption promoting effect of these enhancers has been shown generally to be due to their ability to increase membrane fluidity for example by extracting proteins from the nasal membrane. For bile salts there is also the ability of these materials to inhibit enzyme activity in the membrane and to reduce the viscosity of the mucus and thereby allow for an easier diffusion of the drug through this layer.[67,68] It has been shown that in most cases absorption enhancers can increase the absorption efficiency of drugs. Thus, using a surfactant absorption enhancer, it was showed that a two-fold increase in the area under the blood level curve for the intranasal administration of salmon calcitonin as compared to the administration of the drug alone. The nasal route could be important for drugs that are used in crisis treatments, such as for pain, and for centrally acting drugs where the putative pathway from nose to brain) might provide a faster and more specific therapeutic effect.[69,70]

Advantages of Nasal Drug Delivery[71,72]

1) Drug degradation that is observed in the gastrointestinal track is absent.

2) Hepatic first pass metabolism is avoided.

3) The nasal bioavailability for smaller drug molecule is good.

4) Studies so far indicates that the nasal route is an alternative to parenteral route, especially for protein's and peptide drug.

5) Convenient for the patient especially for those on long term therapy, when compared with parenteral medication.

6) Polar compound exhibiting poor oral absorption may be particularly studies for this route of delivery.

7) Large nasal mucosa surface area for dose absorption.

8) Ease of administration, non-invasive.

9) Lower dose reduced side effects.

10) Self-administration.

Limitations:[72,73,74]

1) Delivery is expected to decreases with increasing molecular weight of drug.

2) Mucosal damages may occurs due to frequently use of intra nasal route.

3) Very specific amount i.e. 25-200µl can be delivered throw intra nasal route.

4) Ciliary movement after the drug permeability.

5) Difficult to administered drug in pathological condition such as nasal congestion due to cold or allergic reaction.
6) Some drug cannot administered throw this route because they causes nasal irritation.
7) There could be mechanical loss of dosages form into the other part of respiratory track like lungs because of the improper technique of administration.
8) The histological toxicity of different type of penetration enhancer used is not clearly known

Cellular Mechanisms for Transmucosal Drug Delivery

Nanoparticles (when larger than about 20 nm) are thought to pass transcellularly (apical to basolateral transport through epithelial cell) in nose-to-brain drug delivery. The transcellular route of cell transport is less well characterized than the paracellular route.[75] Novel spectroscopy and microscopy techniques such as electron energy loss spectroscopy and energy filtering transmission electron microscopy have recently provided new insights into endocytosis and the cellular mechanism responsible for the transcellular transport of particles.[76] Endocytosis has been categorised by a number of different molecular mechanisms including macropinocytosis, clathrinmediated, clathrin-independent, caveolin-mediated, caveolin independent and phagocytosis.[77] Macropinocytosis is an endocytic mechanism where the action of actin filaments gives rise to curved 'ruffles' on the cell surface. Sealing of the aperture into discrete vacuoles forms the macropinosome (0.5–5μm diameter) which efficiently takes up extracellular fluid into the cell. Considerable volumes of dissolved molecules and suspended particles can be taken up in this way. Macropinocytosis is generally thought of as a constitutive process by which the cell can sample the extracellular environment and is not believed to be initiated by receptor activation at the cell surface.[78] Phagocytosis is a clathrin-independent receptor-mediated uptake of exogenous materials by specialised phagocytic cells such as macrophages. Relatively large (>1μm) patches of membrane are internalized.[79] One fundamental study has shown that basic parameters such as particle size strongly influence the initiation of certain endocytic mechanisms over others. Another factor that influences the internalisation pathway of particles is their surface charge. Anionic 90nm diameter PEG–PLA nanoparticles were produced and a cationic version which incorporated the cationic lipid stearylamine. They incubated these particles separately with MDCK (Canine Kidney Epithelial) cells and used confocal microscopy, immunofluorescence and Western blotting to determine that both types of particles entered the cell via the clathrin-mediated endocytic pathway.[80,81]

Formulation Strategies for Enhancing Direct Nose-to-Brain Drug Transport

Microemulsions offer an interesting and potentially quite powerful alternative carrier system for drug delivery because of their high solubilization capacity, transparency, thermodynamic stability, ease of preparation, and high diffusion and absorption rates when compared to solvent without the surfactant system. A microemulsion is defined as a thermodynamically stable, isotropic dispersion of two relatively immiscible liquids that consists of microdomains of one or both liquids stabilized by an interfacial film or surface-active molecules. Microemulsions, by virtue of their lipophilic nature and having low globule size, are widely explored as a delivery system for enhancing uptake across mucosa.[82] Microemulsion based delivery system have many characteristics which make them suitable for intranasal drug delivery. These include ease of preparation (due to spontaneous formation),thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability, and less inter and intra-individual variability in drug pharmacokinetics.[83] In a recent study microemulsions/mucoadhesive microemulsions of Diazepam (D), Lorazepam (L) and

Alprazolam (A), were prepared and their pharmacodynamic performances were evaluated by performing comparative sleep induction studies in male albino rats. Onset of sleep and duration of sleep were observed in the following order: Lorazepam > Alprazolam>Diazepam. Faster onset of sleep following intranasal administration of microemulsions (<20 min) compared to oral administration (29-33 min) and control group (>45 min) for all three drugs suggested selective nose-to-brain transport of drug(s). Intranasal administration of microemulsion based formulations resulted in even faster onset of sleep (<12 min) with intranasal mucoadhesive microemulsion(s) resulting in fastest onset of sleep (<9 min). Duration of sleep was longest with the intranasal mucoadhesive microemulsions. These results are suggestive of larger extent of distribution of drug(s) to brain after intranasal administration of mucoadhesive microemulsion(s).[84]

CONCLUSION

Nanocarriers are designed to improve the pharmacological and therapeutic properties of conventional drugs. Due to small dimensions, nanocarriers are able to cross the blood-brain-barrier (BBB) and operate on cellular level. There is evidence to suggest that direct nose-to-brain transport using synthetic nanoparticles is possible, even to therapeutic levels in animal models and in humans.

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