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Nanoparticle-Mediated Nose-to-Brain Drug Delivery Systems: A Promising Approach for CNS Therapeutics

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Abstract

The nose-to-brain delivery of drugs by nanoparticles has developed as an attractive non-invasive drug delivery methodology in order to circumvent the constraints of traditional central nervous system (CNS) therapeutics, especially the constraining quality of the blood-brain barrier (BBB). Nasal delivery allows direct delivery of the drugs to the brain through the olfactory-trigeminal neural pathway and improves drug bioavailability and decreases systemic exposure. Combining the intranasal delivery systems with nanotechnology has several benefits, such as increased solubility of drugs, resistance to enzyme degradation, controlled drug release, and delivery to the selected parts of the brain. Nanoparticulate carriers including polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and nanoemulsions have been widely studied towards this effect. These systems allow an increase in the permeation of the nasal mucosa and increase the residence time, leading to an increase in the efficacy of the therapy in the treatment of neurological disorders like Alzheimer disease, Parkinson disease, epilepsy, and brain tumors. Although encouraging results have been seen in preclinical studies, various issues, such as mucociliary clearance, formulation stability, scalability, and regulatory factors are still a challenge. Recent developments on the surface modification and ligand-mediated targeting have further improved brain uptake and specificity. This review brings out the mechanisms, types of nanoparticles, formulation strategies, and recent advances in the nanoparticle-mediated nose-to-brain drug delivery systems and their potential in enhancing CNS therapeutics. In general, it is a revolutionize platform that has a great potential in future clinical application.

Introduction

Management of central nervous system (CNS) diseases is among the most complicated fields in contemporary therapeutics because of the existence of extremely selective biological barriers, especially the blood-brain barrier (BBB). The BBB is a highly controlled portal that is created by the endothelial cells, astrocytes and pericytes, limiting the access of most therapeutic substances to the brain. Although this barrier is important to ensure the homeostasis of the brain, it is a major hindrance to the usefulness of the traditional drug delivery systems in treating neurological conditions like Alzheimer disease, Parkinson disease, epilepsy, brain tumors and other neurodegenerative diseases. Consequently, attainment of a satisfactory drug concentration at the target site in the brain still remains a significant challenge of CNS pharmacotherapy. Conventional methods of drug administration such as oral and parenteral administration do not provide adequate amounts of drugs to the brain because of the low permeability of the BBB, enzyme breakdown and side effects in the system. The invasive techniques like intracerebral injections and implants, though effective in bypassing the BBB have been known to be accompanied with high risks, such as infection, patient discomfort, and expensive treatment costs. Thus, non-invasive, effective and selective drug delivery approaches that can address these shortcomings are urgently required(1).

The intranasal route has been of recent interest as one of the promising methods of direct delivery of drugs to the brain. Nares provides a distinctive anatomical and physiological route that provides direct access of the external world to the CNS through olfactory and trigeminal nerves. This is a direct nose-to-brain route, which enables the therapeutic agents to circumvent the BBB and a quicker action and better drug bioavailability in the brain. Moreover, intranasal delivery is non-invasive, convenient, and enhances compliance with patients in comparison to traditional and invasive routes. Nevertheless, intranasal drug delivery is experiencing a number of challenges such as low drug absorption, high mucociliary clearance, enzyme breakdown in the nose, and inability of some drug molecules to penetrate the nasal lining. These constraints have led to the creation of improved drug delivery methods which may result in higher drug stability levels, increases residence time and efficiency in the transportation of drugs through the nasal mucosa(2).

Nanotechnology has come to tackle these issues, and improve the efficacy of nose-to-brain drug delivery systems. Nanoparticles are particles that are commonly used to deliver drugs because they are 1 to 1000 nanometers in size and therefore have special physicochemical properties that enable their easy utilization as drug carriers. These are a high surface area-volume ratio, the capacity to entrap both hydrophilic and lipophilic drugs, to prevent drug degradation and the possibility of surface modification to obtain directed delivery(3).

Nanoparticles of different types have been considered as intranasal delivery to the brain, among them polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, dendrimers, and nanoemulsions. Such nanocarriers may increase the drug permeation across the nasal mucosa via transcellular and paracellular transport events. Also, the bioadhesive property of nanoparticles can be enhanced by surface modification with bioadhesive polymers like chitosan and hence the residence time of the nanoparticle increases in the nasal cavity resulting in an increase in drug absorption. The other notable advantage of the nanoparticle-mediated delivery systems is that, it offers a controlled and sustained release of drugs, which are mainly useful in the treatment of chronic CNS disorders. Moreover, targeting ligands on the surface of nanoparticles allow receptor-mediated transportation, enhancing specificity and minimizing off-target(4). These innovations have created possibilities in developing efficient and specific CNS drug delivery systems.

Recent studies have shown the possibility of nanoparticle-based intranasal preparations to enhance the treatment outcomes of different neurological disorders. As an example, nanoparticles containing drugs have been demonstrated to have better pharmacokinetic profiles and increased brain absorption of drugs in contrast to traditional preparations. In addition, nanoparticle systems have been effectively applied in the delivery of numerous therapeutic agents, such as small molecules, peptides, proteins, and nucleic acids. Although these have been positive developments, there are a number of challenges that need to be overcome before this can be used clinically on a large scale. Problems with formulation stability, mass-manufacturing, regulatory acceptance as well as long-term safety are still the problems. Also, the difference in the physiology of the nose in various people can influence the drug absorption and the effectiveness of delivery. Thus, additional research and development is necessary to streamline nanoparticle formulations and make them safe and effective in clinical practice(5).

In summary, the nasal to brain drug delivery systems employing nanoparticles is a novel and inspiring concept to overcome the drawbacks of the traditional methods of CNS drug delivery. This approach

presents a non-invasive, effective and targeted method of nanocarrier delivery of therapeutics to the brain by integrating the benefits of intranasal administration with the special characteristics of nanocarriers. With ongoing research in this area, these systems are predicted to be very instrumental in the future of CNS drug delivery and therapies of neurological diseases(6).

Nose-to-Brain Transport (Mechanism)

The nose-to-brain drug delivery is a special and non-invasive route, which directly conveys therapeutic agents between the nasal cavity and the central nervous system (CNS) and bypassing the blood-brain barrier (BBB). This is mediated by the anatomical and physiological relationships between the nasal mucosa and the brain, which is mainly through the olfactory and trigeminal neural pathways(7).

Olfactory Pathway

The olfactory system is considered to be the most important and direct way of nose-brain drug delivery. The olfactory receptor neurons are located on the olfactory epithelium (the upper part of nasal cavity) and their axons run through the cribriform plate and directly to the olfactory bulb of the brain. The two main pathways through which drugs used by the intranasal route can reach the brain are: by passing through the olfactory epithelium and the brain. Drug molecules are endocytosed into the olfactory neurons in the intracellular or neuronal transport pathway and then transported by the axons to the olfactory bulb. Conversely, the extracellular or paracellular route entails diffusion of drug molecules between intercellular spaces or perineural channels into the cerebrospinal fluid. This dual mode of transport allows rapid and efficient delivery of drugs to the forebrain and other parts of the central nervous system bypassing the body and reducing enzyme destruction(8).

Trigeminal Nerve Pathway

The nasal cavity has both the respiratory and olfactory parts that are innervated by the trigeminal nerve. It offers a different pathway to transport drugs, particularly to the brainstem and spinal cord. Drugs have the ability to interact with the trigeminal nerve endings and can be carried by intracellular or extracellular diffusion routes. This route plays a special role in conveying medications to deeper brain regions and is a supplement to the olfactory route(9).

Systemic Circulation Pathway

The drugs in this indirect route are absorbed into the systemic circulation through the highly vascularized nasal mucosa and then by the BBB they enter the brain. Nonetheless, such a route is less effective because of the BBB limitations and has systemic side effects(10).

Lymphatic and Glymphatic Transport.

Recent research indicates that intranasally administered drugs could reach the brain through lymphatic drainage and the glymphatic system as well. The routes assist in the transportation of molecules to the CSF and the interstitial fluid of the brain, increasing the distribution of drugs(11).

Role of Nanoparticles in Transport

Nanoparticles can augment these transport systems, promoting receptor-mediated endocytosis, enhanced mucoadhesion and retention of time in the nasal cavity, and controlled and targeted delivery of drugs. Moreover, nanoparticles with surface modifications have the potential to specifically interact with receptors on the nasal epithelium, facilitating an effective cellular uptake and subsequent delivery of therapeutic agents into the central nervous system. Nose-to-Brain Drug delivery Nanoparticles(12).

Polymeric Nanoparticles

Nanocarriers Nanoparticles Nose-to-brain drug delivery Polymeric nanoparticles are the most widely-researched nanocarriers because of their versatility, biocompatibility and control over drug delivery. Such systems are generally produced with biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), chitosan, alginate, and polyethylene glycol (PEG). Polymeric nanoparticles may be divided into nanospheres (matrix systems) and nanocapsules (core-shell systems), depending on their structure, which allows effective encapsulation of drugs and prevents their destruction by enzymes in the nasal cavity.The potential to increase mucoadhesion when using polymeric nanoparticles is one of the most significant opportunities, which is observed in the example of chitosan-based systems. The cationic polymer, chitosan, has an electrostatic interaction with negatively charged mucosal surfaces, enhancing residence time and drug absorption. Further, the surface of polymeric nanoparticles may be modified by addition of ligands to enable receptor-mediated uptake and delivery into a particular region of the brain(13).

Sustained and controlled release of drugs is also promoted by these nanoparticles and this is advantageous in chronic neurological diseases treatment. In addition, their capability to absorb both hydrophilic and hydrophobic drugs makes them very versatile in a variety of therapeutic agents. Nevertheless, issues like possible cytotoxicity,

products of degradation of polymers, and scalability need to be prudently considered. On the whole, polymeric nanoparticles are a very promising vehicle of efficient and specific CNS drug delivery through the intranasal route(14).

Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are nanocarriers made of physiologically compatible solid lipids that are stabilized by surfactants and are made of lipid. They have also acquired much interest in nose-to-brain drug delivery because of their high biocompatibility, low toxicity, and capacity to increase the stability of drugs. SLNs have a solid lipid core that forms a rigid skeleton, which is used to preserve encapsulated drugs against enzymatic breakdown and chemical instability, especially in the nasal environment.SLNs would be particularly effective in the delivery of lipophilic drugs, which can be readily integrated into the lipid matrix. When administered intranasally, SLNs are in contact with the nasal mucosa whereby they assist in drug absorption via transcellular and paracellular routes. Also, they have a small particle size and high surface area, which increases their drug permeation and bioavailability into the brain(15).

A second significant benefit of SLNs is that they offer controlled drug release which assists in maintaining therapeutic drug concentrations long-term. Besides, bioadhesive polymers or targeting ligands can be surface-modified to SLNs to improve the mucoadhesion and brain targeting efficacy. Although such benefits exist, SLNs possess some disadvantages, such as low drug loading capacity and drug expulsion occurrence during storage as a result of lipid crystallization. Yet, SLNs have been a popular and efficient nanocarrier system in the nose-to-brain administration of CNS drugs(16).

Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs) are regarded as a second-generation lipid-based nanoparticle system that has been developed to address the shortcomings of solid lipid nanoparticles (SLNs). NLCs consist of a mixture of solid and liquid lipids, thus forming a less ordered lipid matrix which increases drug loading capacity and reduces drug expulsion during storage. The special structure forms defects in the lipid matrix, which enables more drug incorporation and stability.NLCs have a number of benefits in the context of nose-to-brain drug delivery, such as a higher permeability of the nasal mucosa and increased bioavailability of the drug in the central nervous system. Their lipid structure is very similar to biological membranes and allows them to interact with nasal epithelial cells more easily and allows them to be transported to the cell through transcellular channels. Also, NLCs have long-term release patterns, which are advantageous in achieving long-lasting therapeutic effects in CNS diseases. Surface coating of NLCs with mucoadhesive polymers e.g. chitosan or polyethylene glycol also leads to increased retention time in the nasal cavity leading to decreased mucociliary clearance and increased drug absorption. NLCs have already been used successfully to deliver a diverse collection of therapeutic agents, such as antipsychotics, anti-Alzheimer drugs, and anticancer drugs(17).Regardless of their potential, some of the challenges include complexity of formulation, stability concerns, and mass production must also be tackled. All in all, the NLCs provide a very effective and sophisticated system of nanocarriers to target the brain intranasally(18).

Liposomes

Liposomes are vesicular nanocarriers which consist of a single or multiple phospholipid bilayers around a watery core. Liposomes are very biocompatible because they are structurally similar to the biological membranes and they can be used to encapsulate hydrophilic as well as lipophilic drugs. Their dual-loading system renders them especially appealing when it comes to the delivery of a broad spectrum of therapeutic agents to the brain by the intranasal route.During nose-to-brain delivery, liposomes are used to carry drugs by either fusing with cell membranes of the nasal epithelial tissue or undergoing endocytosis. This increases the permeation of drugs through the nasal mucosa and directs the drug to the central nervous system. Also, liposomes may be surface-modified with polyethylene glycol (PEGylation) to increase stability and prolong circulation and with targeting ligands to increase site-specific delivery(19).Another benefit of using liposomes is the ability to shield encapsulated drugs against destruction by enzymes in the nasal cavity and enhance drug stability and therapeutic efficacy. Their capability of transporting sensitive biomolecules like peptides, proteins and nucleic acids also increases their use in CNS diseases.Nevertheless, there are some weaknesses of liposomes such as physical instability, release of encapsulated drugs, and high cost of production. Nevertheless, advancement of liposomal technology is being made to overcome these challenges and make them a useful nanocarrier system to deliver drugs to the brain through nose-to-brain delivery(20).

Nanoemulsions

Nanoemulsions are thermodynamically stable, isotropic colloidal systems of oil, water, surfactants and co-surfactants, with a droplet size of 20 to 200 nm. They are common in intranasal drug delivery as they allow increasing the solubility and bioavailability of drugs with poor water solubility. Nanoemulsions are effective in improving the absorption of drugs in nose-to-brain delivery because they enhance the surface area of contact between the nasal mucosa and the drug. Their minute droplet size allows them to easily penetrate the epithelium of the nose by diffusing and permeating rapidly, and allows them to deliver drugs to the brain efficiently. Also, the nanoemulsions may be developed using mucoadhesive agents to increase residence time in the nasal cavity, and hence, increase drug uptake. The other benefit of nanoemulsions is that they are easy to prepare and to scale up and thus can be used in the industrial production. They also offer a constant environment to encapsulated drugs that is not degraded and enhances shelf life. Moreover, to obtain controlled drug release and targeted delivery, nanoemulsions can be customized using certain excipients or surface modifiers(21).

Although these are the benefits, nanoemulsions can lead to the irritation of the nasal mucosa because of the surfactants they contain and in addition their stability is influenced by environmental factors. Nevertheless, they still hold potential and versatility as a nanocarrier system to deliver CNS drugs through the intranasal route(22).

Dendrimers

Dendrimers are three-dimensional, highly branched nanostructures with a clearly defined architecture, comprising a central core, several layers of branches (generations) and many functional groups on the surface. This special and regulated framework enables a careful control of the size and shape of dendrimers as well as their surface chemistry thus dendrimers have become very appropriate in the targeted drug delivery system. Regarding nose-to-brain delivery, dendrimers are used to deliver drugs efficiently across the nasal mucosa by its size and surface functionality. Therapeutic agents may be entrapped in the internal cavities of the dendrimers or may be conjugated to the surface functional groups of the dendrimers, and a high drug loading capacity will be achieved. Moreover, dendrimers can be functionalized by targeting ligands, peptides, or antibodies to be incorporated to facilitate receptor-mediated absorption and targeting of brain tissues(23).

The ability to enhance the solubility and stability of drugs, especially those that are not soluble in aqueous solutions, is one of the greatest benefits of dendrimers. Moreover, they allow the controlled and sustained release of drugs, which is helpful in the long-term treatment of central nervous system disorders. They are also small and have surface properties that enable them to enter biological barriers more easily, such as the nasal epithelium. Nevertheless, some shortcomings have to be taken into account, such as possible toxicity of higher-generation dendrimers, and relatively high synthesis price. Nevertheless, dendrimers could be of great importance as sophisticated nanocarriers to the effective and targeted nose- to-brain drug delivery systems(24).

Polymeric Micelles

Polymeric micelles are nanosize colloidal carriers that are self-assembled by amphiphilic block copolymer in water. These nanostructures are generally a hydrophobic core and a hydrophilic shell, which enables easy encapsulation of poorly water-soluble drugs in the core and makes them stable in biological fluids. Polymeric micelles play a key role in intranasal drug delivery, as they enhance drug solubility, stability and permeability of the nasal mucosa. They can easily penetrate through biological membranes due to their small size, and transport drugs to the brain effectively through the olfactory and trigeminal pathways. The hydrophilic shell (which can be polyethylene glycol (PEG)) also sterically stabilizes, reduces aggregation, and increases circulation time. Surface-functionalization of polymeric micelles with targeting ligands can enhance specificity and uptake of the micelles by brain tissues. These properties of their being able to deliver controlled and sustained release of drugs further improve therapeutic efficacy especially in treating central nervous system diseases. Moreover, the systems have relatively low toxicity and biocompatibility, thus they can be applied in possible clinical practice(25).Nevertheless, polymeric micelles can have problems with stability during dilution in biological fluids, causing too early release of drugs. Even with this shortcoming, they are a very promising nanocarrier system in order to better nose-to-brain drug delivery and increase the levels of therapeutic outcomes of CNS treatments(26).

Evaluation Parameters

Nose-to-brain drug delivery systems involving nanoparticles are vital to the development process as the safety, efficacy, reproducibility, and regulatory acceptability of the technology in question are evaluated. Such delivery systems should be fully described to ensure that they have the desired physicochemical attributes, drug loading capacity, stability and biological performance to ensure effective targeting of the brain. Contrary to traditional

dosage delivery systems, intranasal nanoparticle systems are required to circumvent special physiological obstacles: mucociliary clearance, enzymatic degradation, and low absorption surface area. Thus, it is necessary to develop a comprehensive assessment plan to analyze their interaction with nasal mucosa, drug release kinetics, permeability, and in vivo functionality. Systematic evaluation consists of several steps, such as physicochemical characterization, in vitro studies, ex vivo permeation analysis, and in vivo studies. All these stages give important information on the formulation quality, performance and safety profile. Physicochemical characterization provides homogeneity and stability of nanoparticles whereas drug loading and release research establish therapeutic effectiveness. Mucoadhesion and permeation experiments evaluate the capability of the formulation to stay in the nasal cavity and deliver drugs back to the brain. Moreover, the in vivo and histopathological experiments support the efficiency and safety of the formulation when applied in the biological systems(27).

Together with these parameters, stability tests and pharmacokinetic analyses are crucial in stipulating the shelf life and brain targeting activity of nanoparticle systems. The efficiency of drug targeting (DTE%), and direct transport percentage (DTP%) are some of the key parameters that have been used to assess the efficiency of nose-to-brain delivery. Altogether, the successful development and clinical translation of nanoparticle-based intranasal drug delivery systems require a complex and well-organized evaluation system(28).

Physicochemical Characterization

Particle Size and Size Distribution

Some of the most important parameters that determine the performance of nose-to-brain drug delivery systems based on nanoparticles include particle size and size distribution. Nanoparticle size has a direct influence on its capacity to cross into the nasal mucosa, engage with epithelial cells and be transported to the brain through the olfactory and trigeminal pathways. Generally, nanoparticles used as intranasal delivery systems must be within the range of 10-200 nm in size to provide an ideal penetration and reduced elimination by cilia. The commonly used method to measure particle size, polydispersity index (PDI) is through dynamic light scattering (DLS), which informs about the stability and homogeneity of the nanoparticle system. A small PDI value is a good sign of a close size distribution, which is desirable to give reproducible performance and homogeneous drug delivery. Smaller particles have a greater surface area, which increases the dissolution and contact of the drug with the nasal epithelium. But very minute particles can be quickly cleared or absorbed into systemic circulation, decreasing targeting efficiency(29).Moreover, the size of the particles can affect cellular uptake processes with smaller nanoparticles having a higher probability of entering the cell through endocytosis. Also uniform size distribution provides predictable pharmacokinetics and reduces batch to batch variation. Hence, accurate measurement and assessment of the particle size and distribution are vital in maximizing the efficiency of nose-to-brain drug delivery systems(30).

Zeta Potential

Zeta potential is a significant parameter indicating the surface charge of nanoparticles and is important in determining its stability, mucoadhesive properties, and interaction with biological membranes. It is normally determined by the use of electrophoretic light scattering method and gives information on the electrostatic repulsion between suspended particles. The large positive or negative value of zeta potential is usually a good sign of stability, as it prevents aggregation. Compared to the negatively charged mucosal surfaces, positively charged nanoparticles are especially beneficial in the context of intranasal drug delivery, as they can interact more strongly. This electrostatic attraction enhances mucoadhesion, increases residence time in the nasal cavity, and increases drug absorption. They are usually achieved by the addition of polymers like chitosan to give the nanoparticles a positive surface charge. Zeta potential also has a role to play in cellular uptake and biodistribution because the charged particles do not interact with the cell membranes. Nevertheless, too high surface charge can result in nasal mucosa toxicity or irritation. As such, a balance has to be achieved to provide stability and biocompatibility. In general, the zeta potential is an important parameter that has to be taken into consideration in order to maximize the functioning of nanoparticle-based delivery systems(31).

Morphology

The morphological characterization of nanoparticles gives necessary data about the shape and surface structure of the nanoparticles and their physical integrity. High-resolution visualization of nanoparticles can usually be performed using techniques like scanning electron microscopy (SEM) and transmission electron microscopy (TEM). These imaging technologies enable scientists to ensure the size of particles, their shape uniformity, and surface smoothness, which play a significant role in determining drug delivery performance.

Nanoparticles shape may greatly influence their biosensing with biological membranes and cellular internalization. Nanoparticles with spherical shapes are usually favored because they can be easily spread evenly and transported across the biological barriers. Mucoadhesion and drug release behavior can also depend on surface features, like roughness or porosity. Morphological analysis assists to detect any structural defects, aggregation or irregularities that can influence the stability and efficacy of the formulation. It also offers an assurance of effective nanoparticles formation in the formulation procedure. Stable morphology guarantees predictability in biological systems and helps reproducibility in drug delivery performance. In general, morphological characterization is a significant step in the analysis of nanoparticle systems as it directly influences their functionality, stability, and interaction with nasal tissues(32).

Polymeric Micelles

Polymeric micelles are nanosized colloidal carriers that are self-assembled amphiphilic block copolymer in aqueous solutions. These nanostructures are usually designed with a hydrophobic core and a hydrophilic shell, enabling the convenient encapsulation of poorly water-soluble drugs to the core and stability in the biological fluids. Polymeric micelles also play an important role in improving the solubility, stability and permeability of drugs across the nasal mucosa in intranasal drug delivery. Their small size allows them to easily penetrate biological membranes, which makes them effectively transport drug to the brain via the olfactory and trigeminal pathways. The hydrophilic shell, typically consisting of polyethylene glycol (PEG), also ensures steric stabilization, reduces aggregation and increases circulation time. Surface-functionalization of polymeric micelles with targeting ligands can also enhance uptake and specificity by brain tissues. They can deliver controlled and sustained drug release, which further increases therapeutic efficacy especially in the treatment of the central nervous system disorders. Moreover, they are rather low-toxicity and biocompatible systems, and they can be used in clinical practice(33).

Nevertheless, polymeric micelles are likely to have stability problems when diluted in biological fluids, which can cause the early release of drugs. Notwithstanding this shortcoming, they still hold a great potential as a nanocarrier system to increase the delivery of drugs to the brain and improve the efficacy of CNS therapies(34).

Evaluation Parameters

The assessment of nose-to-brain drug delivery systems based on nanoparticles is a key stage in the development process to guarantee their safety, efficacy, reproducibility, and regulatory acceptability. These delivery systems should be well characterized to ensure that they have the desired physicochemical characteristics, drug loading capacity, stability and biological performance to be able to target the brain efficiently. In contrast to traditional dosage agents used, intranasal nanoparticle systems have to overcome some special physiological obstacles, including mucociliary clearance, enzymatic degradation, and low absorption surface area. Thus, an overall evaluation plan is needed to evaluate their interplay with nasal mucosa, drug release profile, permeation capacity, and in vivo functionality. Systematic analysis consists of several steps, such as physicochemical characterization, in vitro testing, ex vivo permeation testing, and in vivo tests. All these phases are essential in terms of the quality, performance, and safety profile of the formulation. Nanoparticles are characterized using physicochemical methods to guarantee uniformity and stability, and the effectiveness of drug loading and release studies to characterize therapeutic efficiency. Mucoadhesion and permeation tests are used to determine the capacity of the formulation to stay in the nose and deliver the drug to the brain. Moreover, in vivo and histopathology testing validate targeting effectiveness and safety of the formulation in life systems(35).

Along with these parameters, stability tests and pharmacokinetic analyses are crucial in establishing the shelf life and the efficiency of brain targeting pharmacokinetics of nanoparticle systems. Drug targeting efficiency (DTE%), direct transport percentage (DTP%), etc. are the parameters that are of interest especially in measuring the effectiveness of nose-to-brain delivery. In general, successful development and clinical translation of nanoparticle-based systems of intranasal drug delivery requires a well-developed and detailed evaluation structure(36).

Particle Size and Size Distribution.

One of the most important parameters that affect the performance of the nose-to-brain drug delivery systems using nanoparticles is particle size and size distribution. The dimensions of the nanoparticles have a direct influence on their penetration capability through the nasal mucosa, their interaction with the epithelial cells and on their transport to the brain via the olfactory and trigeminal pathways. Generally, nanoparticles to be used in the intranasal delivery system should be at the range of 10-200 nm in diameter to attain maximum permeation and minimal

mucociliary clearance.Both particle size and polydispersity index (PDI) are usually determined by dynamic light scattering (DLS), which offers details of the homogeneity and stability of the nanoparticle system. A small PDI value implies that the size distribution is narrow, which is desirable in terms of reproducible performance and a uniform delivery of drugs. Smaller particles have a greater surface area, which increases drug dissolution and contact with the nasal epithelium. Nevertheless, very fine particles can be easily swept out or taken into the bloodstream, lowering targeting(37).Moreover, the size of particles affects cellular uptake processes, because smaller nanoparticles have increased chances of being taken into the cell through endocytosis. Predictable pharmacokinetics and reduction of batch-to-batch variation are also guaranteed by uniform size distribution. Hence, accurate particle size and distribution control and assessment are key to the optimization of nose-to-brain drug delivery systems(38).

Zeta Potential

Zeta potential is a significant parameter used to identify the surface charge of nanoparticles and is an important parameter in appreciating their stability, mucoadhesive properties and interaction with biological membranes. It can be generally determined by electrophoretic light scattering methods and gives an idea of the electrostatic repulsion between suspended particles. When zeta potential is big in absolute value (negative or positive) then the stability is usually good as aggregation is not possible(39).

Positively charged nanoparticles are especially beneficial in the case of intranasal drug delivery as they interact more strongly with the negatively charged mucosal surfaces. This electrostatic attraction increases mucoadhesion, increases residence time in the nasal cavity and increases drug absorption. This is commonly done by adding polymers like chitosan so that nanoparticles have a positive surface charge. The cellular uptake and biodistribution is also affected by the zeta potential since the charged particles do not interact with cell membranes. But overly high surface charge can cause toxicity or irritation of the nasal mucosa. Thus, a good balance should be achieved to promote stability and biocompatibility. In general, zeta potential is an important parameter that needs to be considered to maximize the performance of nanoparticle-based delivery systems(40).

Morphology

Morphological analysis of nanoparticles also gives a critical information about the shape, surface structure and physical integrity of the nanoparticles. High-resolution visualization of nanoparticles is typically done using techniques like scanning electron microscopy (SEM) and transmission electron microscopy (TEM). These imaging techniques enable scientists to verify the size, shape consistency and smoothness of the surface of the particles, which are significant parameters that determine the performance of drug delivery. Nanoparticles shape can also greatly influence the interactions with biological membranes and cellular internalization. The preference of spherical nanoparticles is mainly because they are uniformly distributed and can be transported easily across biological barriers. Other surface properties including roughness or porosity may also affect drug release and the mucoadhesion. Morphological analysis would be used to identify any structural defects, aggregation, or irregularities that could interfere with the stability and efficacy of the formulation. Further, it offers an assurance of effective nanoparticle formation as part of the formulation process. Predictable behavior in biological systems is guaranteed by consistent morphology and can aid in reproducibility of drug delivery performance. Altogether, morphological characterization is an essential process in the assessment of nanoparticle systems, as it directly influences their functionality, stability, as well as interaction with nasal tissues(41).

Advanced Nanocarriers

Ligand-Targeted Nanoparticles

Ligand-targeted nanoparticles have been a breakthrough in nose-to-brain drug delivery systems because they provide the ability to target therapeutic agents to a site in the central nervous system. The ligands to these nanoparticles include peptides, antibodies, or small molecule that can selectively bind to receptors present on nasal epithelial cells or brain tissues. This type of targeting via this receptor increases cellular uptake and increases the effectiveness of drug delivery into the brain through the nasal mucosa. Ligand-targeted system decreases the off-target effect and increases the efficacy of the therapy since the drug is transported directly to the location of action. The ligands are also commonly used as transferrin, lactoferrin and cell-penetrating peptides that allow the receptor-mediated endocytosis. This localized therapy is especially useful in the management of neurological conditions where there is a need to have the drug localization. Moreover, ligand-targeted nanoparticles can be engineered in a manner that they penetrate biological barriers and enhance drug bioavailability. Dose reduction is also possible using these systems and this reduces the side effects that may occur. Nevertheless, issues of

stability of ligands, immunogenicity, and cost of production have to be considered. Nevertheless, the use of ligand-targeted nanoparticles remains a potential approach to improving the efficacy of nose-to-brain drug delivery systems despite these limitations(42).

Stimuli-Responsive Nanoparticles

Nanoparticles With stimuli-responsive nanoparticles, or smart nanoparticles, nanoparticles are engineered to release their drug cargo upon a particular physiological or external stimulus, including pH, temperature, enzymes or magnetic fields. These systems provide site-specific and controlled delivery of drugs, especially beneficial in the management of the central nervous system disorders. Nanoparticles that respond to stimulus can be designed in nose-to-brain delivery to react to the microenvironment of the nasal cavity or brain tissues, making sure that the drug is released at the target location. As an illustration, pH sensitive nanoparticles may be triggered to release drugs in the slightly acidic microenvironment of diseased tissues and enzyme sensitive systems may be triggered by particular enzymes that are found in the brain(43).These nanoparticles enhance the effectiveness of the therapy by lowering the premature leech age of the drug and limiting exposures to the whole body. Moreover, they increase patient compliance, as they allow sustained drug release and decreasing the dose frequency. Nonetheless, the optimization and design of stimuli-responsive systems should be carefully considered in terms of the triggering mechanism and the conditions of the environment. Irrespective of the complexity of their development, the stimuli-responsive nanoparticles are a new frontier technology in nanomedicine and have tremendous potential to enhance the accuracy and efficacy of nose-to-brain drug delivery systems(44).

Hybrid Nanocarriers

Hybrid nanocarrier Hybrid nanocarriers are the advanced carriers of delivery that incorporate the qualities of various kinds of nanoparticles to develop superior performance and multifunctionality. These systems can combine polymeric, lipid-based, and inorganic together to address the shortcomings of the nanocarriers on their own and deliver synergistic advantages.When it comes to nose-to-brain delivery, hybrid nanocarriers have an enhanced drug loading capacity, stability, and targeting efficiency. Indicatively, lipid-polymer hybrid nanoparticles have the structural integrity of polymeric systems and biocompatibility of lipid-based carriers, which lead to improved drug delivery performance. There is also the ability of the controlled release of drugs and better interaction with biological membranes through these systems. To improve specificity and responsiveness, hybrid nanocarriers may also be further functionalized with targeting ligands or stimuli-responsive elements. This multifunctional feature renders them very appropriate in elaborate therapeutic applications, such as administration of various drugs or combination therapies. Despite the important benefits of hybrid nanocarriers, their complicated design and production make them more difficult to scale and to be approved by the regulators. However, they are a potential future trend in the creation of next generation nanoparticle vehicles to CNS drug delivery(45).

Surface Modification Strategies

Nanoparticles surface modification is an important approach to improving the interaction of nanoparticles with biological systems and their efficacy in nose-to-brain drug delivery. In this method, functionalization of the surfaces of nanoparticles with different molecules including polymers, peptides, antibodies or ligands is done to attain desirable characteristics like enhanced stability, mucoadhesion, and targeting efficiency. Among the main goals of surface modification is to increase mucoadhesion, which increases the residence time of nanoparticles in the nasal cavity, and drug absorption. Nanoparticle surfaces are usually modified with polymers like chitosan and polyethylene glycol. Chitosan gives a positive surface charge to interact with the negatively charged mucosal surfaces whereas PEGylation gives the solution stability and reduces aggregation. Recent studies have shown that surface functionalization with targeting ligands can be used to induce receptor-mediated uptake, allowing nanoparticles to specifically target a particular receptor on nasal epithelial cells or brain tissues. This focused mechanism improves the systemic drug delivery efficiency and minimizes side effects. Furthermore, surface modification can be used to prevent enzyme degradation and immune recognition of nanoparticles, enhancing bioavailability. Altogether, surface modification strategies are crucial in maximizing the performance of nanoparticles and are critical in the effective evolution of the advanced nose-to-brain drug delivery system(46).

Uses in Neurological Disorders.

Alzheimer's Disease

The application of nanoparticles as nose-to-brain delivery has demonstrated great potential in enhancing the treatment of Alzheimer disease through the enhancement of delivery of therapeutic agents to the brain. Nanoparticles like donepezil and curcumin have been effectively integrated into nanoparticle

systems to enhance their bioreactivity and therapeutic action(47).

Parkinson's Disease
Nanoparticle systems have been used in Parkinson disease to improve the delivery of dopamine and neuroprotective agents and their stability and efficiency in targeting the brain(48).

Brain Tumors
Nanoparticles have also been highly explored in delivering chemotherapeutic agents to brain tumours with minimal systemic toxicity and enhanced treatment efficacy(49).

Gene and Protein Delivery.
Nanoparticle based systems have provided new opportunities in delivery of genetic materials and proteins in the treatment of neurological disorders. The systems facilitate the introduction of siRNA, DNA, and therapeutic peptides into the brain by the intranasal route(50).

Clinical Translation Challenges
Even though it promises to proceed with improvements, a number of obstacles impede the clinical implementation of the nose-to-brain delivery system based on nanoparticles, such as regulatory regulation, scalability, and long-term safety issues(51).

Future Perspectives
Future studies in this direction are directed at the creation of individual medicine solutions, AI-based drug delivery systems, and intelligent nanoparticles that can react to physiological states. Recent studies in this area are progressively oriented to the development of personalized medicine that will help to design therapeutic interventions in accordance with the specifics of each patient in order to achieve more positive results and fewer side effects. One of the major areas of concern is the incorporation of artificial intelligence (AI) in the optimization of drug delivery systems. AI-driven designs have the potential to process fairly intricate biological information to develop more controlled and specific drug delivery systems to enhance treatment results. Moreover, smart nanoparticles are also a promising frontier. These nanoparticles are dynamic, i.e. they can react to certain physiological factors, including pH, temperature, or enzymatic activity, to allow delivery of drugs to the target and reduce systemic exposure. This responsiveness increases the therapeutic index of drugs since they are likely to work at the desired location of action. Taken together, these advances have the potential to transform treatment paradigms by integrating the accuracy of AI with the versatility of nanotechnology, eventually leading to more effective and safer medical procedures(52).

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Not Applicable.

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Conflict of Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest among themselves. The authors alone are responsible for the content and writing of this article.

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Human and Animal Rights
NA

Ethics approval and consent to participate
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