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Review Article

# Intranasal nanoparticulate drug delivery systems for neurodegenerative disorders: an Overview

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Abstract

Intranasal nanoparticulate drug delivery systems have received increased attention in pharmaceutical research due to their ability to increase drug bioavailability, bypass the blood-brain barrier (BBB), and provide non-invasive, patient-friendly alternatives to drug administration, particularly for drugs intended for central nervous system (CNS) disorders. Drugs delivered via nasal route can enter the CNS via the olfactory pathway or the trigeminal nerve pathway, enabling access to deeper regions. Intranasal nanoparticulate systems have several pharmacological benefits, including increased bioavailability, a faster onset of action, higher patient compliance, and less systemic adverse effects. Intranasal nanoparticulate drug delivery has shown promise in a variety of therapeutic areas, including Alzheimer's disease, Parkinson's disease, depression, and anxiety. Intranasal vaccinations and antibacterial Nanoparticle are also utilized to treat respiratory and viral illnesses. This technique is thought to be useful in brain-targeted chemotherapeutic drugs for glioblastoma treatment. The authors of this review attempted to investigate the pharmacological features of nanoparticulate drug delivery systems, including their benefits, mechanisms, formulation methodologies, and clinical applications.

**Keywords:** Alzheimer's disease, Drug delivery, Nanoparticle, Nasal route, Neuro inflammation, Parkinson's disease,

## 1. Introduction:

Four decades ago (during 1980s) intranasal route was introduced to systemic deliver of some therapeutic agents as an alternative to conventional drug delivery systems.[1]In ancient Ayurvedic literature of Indian medicinal system, intranasal route was described as "Nasya Karma". [2] According to advancement of science and drug discovery, intranasal route is considered as a promising route by the researchers for delivery of different therapeutic agents targeted to lungs, brain etc. in the form of nanoparticulate drug delivery systems which possess several unique advantages over other conventional dosage forms that align well with the properties of nanoparticles and the physiological features of the nasal cavity. [3] The nasal cavity is in close proximity to the brain, and intranasal administration allows the therapeutic agents to bypass the blood-brain barrier (BBB), which is generally a major challenge in drug delivery for various CNS related disorders.[4]The major advantage to choose the intranasal route as it is structured with porous endothelial membrane and possess dense network of blood vessels which provides a quick and rapid absorption of therapeutic agents into the systemic circulation thereby enhance the solubility, stability, and bioavailability of drugs that can lead to a more effective therapeutic response.[5] Nanoparticulate delivery can facilitate the transport of various therapeutic agents directly to the brain through olfactory and trigeminal nerves, making the nasal route especially useful for different neurological disorders

such as Alzheimer's, Parkinson's, and brain tumors etc. [6] Intranasal drug delivery is non-invasive, pain-free, and easy to administer, which is a significant advantage over other parenteral routes like injection thereby improve patient compliance, especially in chronic treatments or pediatric and elderlypopulations.[7]Many challenges such as controlling the release of active drugs are observed during the development of a delivery system.[8] Nanoparticulate delivery system can be structured to control the release pattern of the drug, allowing it to exert sustained or prolonged drug action.[9] Additionally, nanoparticles can develop to be functionalized to target specific organs or proteinaceous macromolecules of tissues, rely on several strategies and principles that facilitate the targeted accumulation, penetration, and internalization of nanoparticles at the desired site thereby enhancing the therapeutic efficacy and reducing side effects(commonly observed with oral or intravenous administration).[10] In addition to systemic drug delivery, nanoparticles administered via intranasal route can also be used for localized treatment of diseases affecting the nasal and respiratory tract, such as infections, allergies, and inflammation.[11]Nanoparticle can protect sensitive drugs (like proteins, and nucleic acids) from degradation by enzymes in the nasal cavity. These contributions make the nasal route ideal for precision medicine. Nanoparticles can be structured in such a manner to enhance their ability to penetrate the nasal mucosa and reach systemic circulation or target tissues more efficiently. [12] The smaller size of nanoparticle allows them to pass through tight junctions between cells in the nasal epithelium, facilitating rapid absorption.[13]Another important mechanism for nanoparticulate drug delivery system is enhanced Permeability and retention (EPR) Effect, here, the mechanism exploits the leaky vasculature present in certain pathological tissues (like tumors) and the lymphatic system, allowing nanoparticles to accumulate more readily in these areas. This phenomenon is referred to as the EPR effect of nanoparticulate delivery system.[14] To exploit nanoparticulate EPR effect, the nanoparticles should be constructed with smaller sized particles (under 100 nm) and surface modifications such as PEGylation (coating with polyethylene glycol) etc. These properties of nanoparticles can enhance the circulation time and help to prevent premature clearance by the immune system.[15]

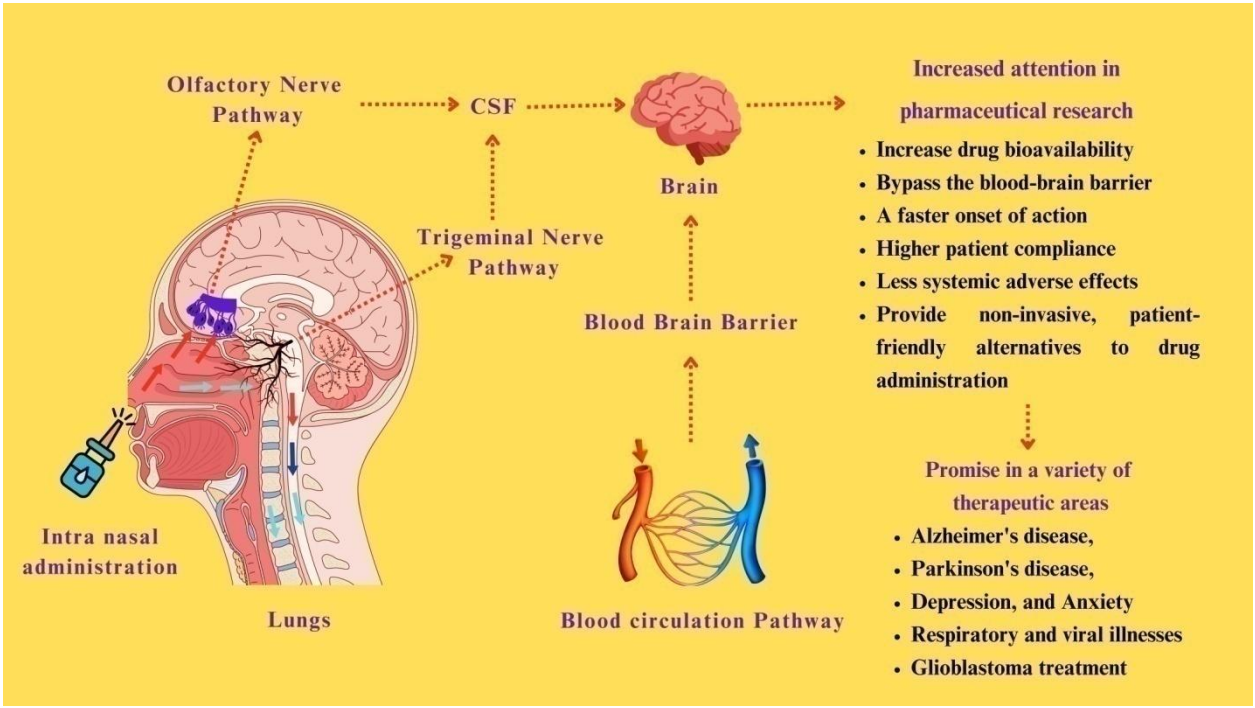


Figure 1: Graphical Abstract

## 2. Ideal Characteristics of intranasal nanoparticles:

**2.1 Particle size and surface architecture:** Intranasal nanoparticles are considered as an innovative drug delivery system because it offers a non-invasive route for drugs to bypass the gastrointestinal system and the blood-brain barrier (BBB).[16] For optimal performance, intranasal nanoparticles must have several ideal characteristics. The first and foremost characteristics particle size that should range between 100-500 nm in diameter. [17] Particle size above 500 nm may be trapped in the nasal mucosa.[18-19] Smaller sized particles may penetrate the mucus more easily and have a larger surface area for interaction. [20] Thus, an optimal size range is critical for prolonged retention. Similarly, surface architecture of nanoparticles is also of similar importance. The surface charge of nanoparticles can influence their interaction with the nasal mucosa.[21] Neutral to slightly positive charges are often preferred to ensure good mucoadhesion without causing irritation. [22] Cationic particles tend to interact more effectively with the negatively charged mucosal membranes but may also cause toxicity if used in high concentrations. Surface properties, such as roughness and hydrophobicity/hydrophilicity balance, also affect

mucoadhesion. [23] Hydrophilic particles are generally more mucoadhesive because they tend to form stronger interactions with the mucus compared to hydrophobic particles. [24]The surface of nanoparticles can be modified with ligand or coatings (e.g., PEGylation, chitosan, or surfactants) to enhance mucoadhesion, drug release, and targeting. [25]

**2.2 Mucoadhesion property of intranasal nanoparticles:** Mucoadhesion property of a nanoparticleis crucial for prolonging the residence time at the nasal mucosa and ensuring sustained drug release. [26] This can be achieved by incorporating biocompatible polymers like chitosan or poloxamers, which enhance adhesion to the mucosal surfaces and prevent rapid clearance. [27] Considering the anatomical architecture, the nasal mucosa consisting mucus layer which is negatively charged due to the presence of glycoproteins (such as mucins), while the polymeric nanoparticles often have a positive charge (when cationic polymers are used). [28]This situation creates attractive electrostatic interactions between the nanoparticles and the mucosal surface, facilitating adhesion. In some circumstances polymeric nanoparticles could form hydrogen bonds with the hydroxyl, carboxyl, and amino groups in the mucus layer. [29] This interaction helps improve the adhesion of the particles to the mucosal surface. Vander Waals Forces between the nanoparticles and mucus layer of nasal cavity are weaker but still significant forces that contribute to the adhesion between the nanoparticles and the mucosal layer.[30] Some specific polymer such as chitosan, are hydrophilic in nature and tend to swell when come in contact with the aqueous mucus layer.[31] This swelling property can increase the surface area of the nanoparticles, enhancing the contact time with the mucosal surface and enhances therapeutic effectiveness of a nanoparticle formulations.[32] The polymeric nanoparticles sometimes undergo interpenetration with the mucus gel layer, where the polymer chains present in the nanoparticles intertwine with the mucus, leading to form a stronger bond.[33] This entanglement improves the stability of the particles at the site of deposition. Sometimes Polymeric nanoparticles are modified by coating with specific bio-adhesive polymers, such as chitosan or thiolated polymers, thereby improve their interaction with the mucus and hence better mucoadhesion.[34]The viscosity of the nanoparticle formulation greatly influences how strongly the nanoparticles can interact with and penetrate the mucus.[35-36]Formulations that are too viscous may affect nanoparticle movement, while those that are too fluid may not stay in contact with the mucosa long enough for effective drug delivery.[37-38]Some environmental factors of nasal mucosa also affect the mucoadhesion of nanoparticle formulations. The pH of the nasal cavity and the ionic strength of the mucus also affect the degree of ionization of the polymers and the properties of the mucus. For example, pH changes may alter the charge on the nanoparticles and mucins, influencing their interaction.[39-40] In some specific circumstances, the ionic strength of the environment can also affect the viscosity of the mucus and influence the ability of nanoparticles to adhere to the mucosal surface.[41]

**2.3 Controlled Release characteristics of nanoparticle:** Controlled release of nanoparticles are considered as an essential factor to maintain therapeutic levels over an extended period of time as well as reducing the need for frequent dosing.[42-43] The drug is encapsulated in a nanoparticle matrix, and its release is governed by the diffusion of the drug molecules from the interior of the nanoparticles to the surrounding environment (nasal mucus).[44] In such circumstances, the drug molecules move from regions of high concentration (inside the nanoparticle) to regions of low concentration (the mucosal layer).[45]Smaller nanoparticles typically have a larger surface area to volume ratio, which can lead to faster initial drug release.[46-47] However, for controlled release, nanoparticles are often designed with a size that allows for a slower diffusion process.When the nanoparticles are made from biodegradable or bio-responsive polymers (e.g., PLGA, chitosan), the polymer matrix slowly degrades, allowing for a gradual release of the drug. Lipophilic drugs often require surfactants or encapsulation in specific polymer matrices to control their release, as their diffusion can be slower than hydrophilic drugs.[48-49] Some polymeric nanoparticles, such as hydrophilic polymers, absorb water from the mucus layer, causing them to swell. [50] The swelling process can lead to the gradual release of the encapsulated drug as the nanoparticle matrix becomes more porous, allowing the drug to diffuse out.[51-52] Hydrophilic polymers, like chitosan, are known to swell when they come into contact with water, which helps to release the encapsulated drug gradually. [53-54]The hydration and composition of the mucus also affect the swelling behavior of the nanoparticles, influencing the release rate. If the nanoparticles are made from biodegradable polymers (e.g., poly(lactic-co-glycolic acid) [PLGA], chitosan), the matrix can gradually degrade or erode over time.[55] As the polymer matrix breaks down, the encapsulated drug is released in a controlled manner. [56]The degradation rate of the polymer is critical to controlling the release rate. For instance, a slower degradation rate will result in a prolonged release of the drug. The degradation can occur through hydrolysis, enzymatic breakdown, or oxidation, depending on the type of polymer. [57]The nasal mucosal environment has a slightly acidic pH (around 5.5-6.5), and polymers can be designed to degrade in response to pH changes.[58]pH-sensitive polymers will degrade faster or slower depending on the local pH, allowing for site-specific drug release.[59]Polymers like poly(ethylene glycol) (PEG), polyacrylic acid, and other ionizable polymers can be used to design nanoparticles that release their contents in response to pH fluctuations.[60]The nasal mucosa has a slightly acidic pH, and pH-sensitive formulations can exploit this characteristic to trigger drug release only when they come into contact with the mucus. [61]Thermo sensitive polymers, such as poly(N-isopropylacrylamide) (PNIPAM), can be used in the formulation of nanoparticles that release the

encapsulated drug in response to temperature changes. [62] Upon exposure to the nasal mucosa, a slight temperature change can trigger a change in the nanoparticle structure (e.g., from a gel state to a sol state), leading to the release of the drug. [63-64] In some cases, nanoparticles are designed to release drugs through ion-exchange mechanisms or electrostatic interactions with the mucosal surface.[65] For example, anionic nanoparticles may release their drug payload through exchange reactions with the cations (e.g., calcium ions) in the mucus.[66] The electrostatic interaction between charged nanoparticles and the mucus can affect the release rate. [67] The drug may be tightly bound to the nanoparticles through ionic interactions, and the release is controlled by the strength of these interactions.[68] Changes in the ionic strength of the mucus (e.g., due to inflammation or infection) can influence the release rate by altering the electrostatic interactions between the nanoparticles and the mucosal layer.[69-70] Some nanoparticles are designed to be susceptible to enzymatic degradation. [71] Enzymes present in the nasal mucosa, such as mucosal or digestive enzymes, can break down the polymer matrix or degrade the drug itself, leading to a controlled release. [72] The nanoparticle matrix can be engineered to contain specific linkages (e.g., ester or peptide bonds) that are cleaved by enzymes.[73] The release rate is dependent on the concentration and activity of the enzymes in the nasal mucosa.[74]

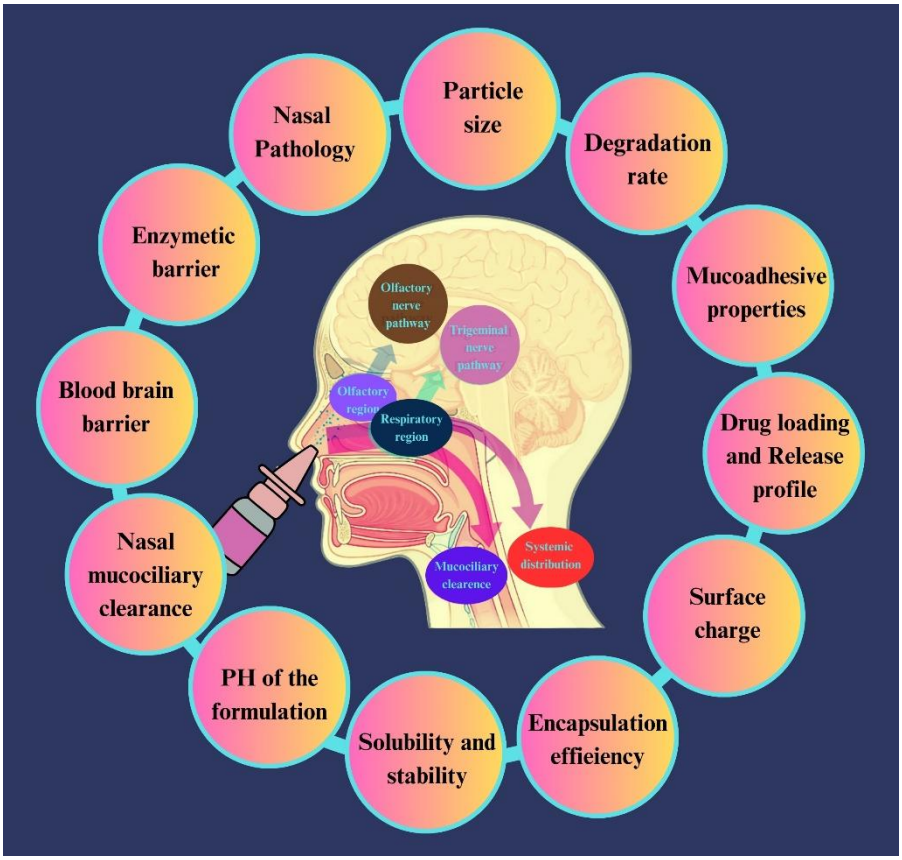


Figure 2: Factors affecting the controlled release of intranasal Nanoparticles

**2.4 Rapid onset and extended duration:** Rapid onset and extended duration of a nanoparticulate delivery system is required in some emergency conditions like pain management or migraine etc that involve a combination of physical, chemical, and surface modification strategies during nanoparticle development. [75-76]Attaching specific ligands, antibodies, or peptides to the nanoparticle surface can enhance their ability to quickly interact with specific biological targets or environmental factors.[77] For example, attaching antibodies or cell-specific ligands can speed up the delivery of drugs to specific tissues. [78]Modifying the surface charge of nanoparticles (positively or negatively) can improve their interaction with biological membranes, improving uptake and accelerating the action of the nanoparticles. [79-80]The shape of nanoparticles can influence their movement and uptake.[81] For instance, rod-shaped nanoparticles tend to enter cells faster compared to spherical ones, and some shapes are better suited for targeting specific tissues. [82]Incorporating stimuli-responsive materials, such as pH-sensitive, temperature-sensitive, or light-sensitive polymers, can make nanoparticles "triggered" to release their payload upon exposure to specific conditions. [83-84] This allows for rapid release once they reach the target site. Utilizing core-shell nanoparticles with an outer layer that dissolves or degrades upon exposure to specific stimuli (like an acidic environment or enzymatic activity) can enhance rapid action once the particles arrive at the site of interest. Using mesoporous nanoparticles, such as mesoporous silica, allows for a higher loading capacity of active agents and facilitates a

faster release. [85-86] These materials are porous, which improves both drug loading and the rate at which the active substance is released. [87]Controlling aggregations of nanoparticles can be achieved by addition of anti-aggregation agents like surfactants or stabilizers which ensure that they maintain high surface area and don't clump together.[88] Avoiding aggregation or clustering of nanoparticles within the system ensures that they remain active and can rapidly reach the target site. [89]High drug loading within nanoparticles improves the amount of active material available to be released, leading to a faster therapeutic effect.[90] Techniques like surface adsorption, encapsulation, or co-loading can be used to enhance drug loading capacity.[91]Modifying nanoparticles to facilitate faster diffusion through biological barriers (like the blood-brain barrier or cell membranes) can speed up their therapeutic action .[92-93] This could involve the use of surface coatings such as polyethylene glycol (PEG), which improves the solubility and bioavailability of nanoparticles.[94]Encapsulating nanoparticles in biocompatible coatings (like liposomes or polymers) can enhance their stability and control the rate of payload release, thereby improving their overall efficacy and the speed at which they act once administered. [95]

## 3. Anatomy and Physiology of nasal route:

The nasal cavity consists of several key structures that contribute to the absorption and distribution of intranasally delivered drugs, including nanoparticles.[96] The external opening of the nose, lined with skin and hair, which acts as a first line of defense against large particles and contaminants. [97] The interior of the nasal cavity, which is divided into two nostrils by the nasal septum. [98] The walls are lined with mucosa and hair, which help filter air and trap particles. [99] These are three bony structures (superior, middle, and inferior turbinates) covered by mucosal tissue that help warm, moisten, and filter the air. [100]The turbinates create turbulent airflow, which allows the drug to interact more effectively with the mucosal surfaces. [101]The lining of the nasal cavity consists of respiratory epithelium, which is rich in cilia (tiny hair-like structures) and goblet cells (that secrete mucus). [102] This mucosal layer plays an important role in drug absorption and clearance.[103] Located at the top of the nasal cavity, it is specialized for smell and is connected to the brain via the olfactory nerve. This region is significant for direct CNS delivery of drugs.[104] A sensory nerve that innervates the nasal mucosa and provides a pathway for drugs to enter the central nervous system, particularly via the trigeminal nerve to the brainstem. [105-106] The mucosal layer in the nasal cavity is continuously bathed in mucus, which serves as a protective barrier.[107] The cilia on the epithelial cells move in a coordinated fashion to transport mucus (and trapped particles) toward the throat to be swallowed or expelled. [108] This clearance mechanism is a challenge for drug delivery, but nanoparticulate systems can be engineered to resist rapid clearance by mucus. The nasal mucosa is generally more permeable than the gastrointestinal tract, allowing for faster and more efficient absorption of drugs.[109] However, the permeability can vary depending on the size, charge, and surface characteristics of nanoparticles. The nasal mucosa is highly vascularized, with a dense network of blood vessels (primarily capillaries), which aids the rapid absorption of drugs into the systemic circulation.[110] Nanoparticles can exploit these vessels for systemic delivery after absorption. The olfactory epithelium and trigeminal nerve are connected directly to the brain. When nanoparticles are delivered intranasally, they have the potential to bypass the blood-brain barrier via these nerve pathways. This direct route to the CNS is particularly useful for treating neurological disorders. [111]

## 4. Transport of Intranasal Nanoparticles to CNS via Trigeminal Pathway:

The trigeminal pathway involved in the sensory processing of stimuli from the face, including the nasal cavity. Intranasal administration of nanoparticles has become an increasingly popular method for delivering drugs to the central nervous system (CNS), as it can bypass the blood-brain barrier (BBB) and directly target the brain.[112] The trigeminal nerve has three main branches. Ophthalmic (V1): Carries sensory information from the forehead, scalp, and upper part of the nose. Maxillary (V2): Carries sensory information from the lower part of the nose, cheeks, and upper lip. Mandibular (V3): Carries sensory information from the jaw and chin. [113]The trigeminal nerve has its cell bodies located in the trigeminal ganglion, and its axons project to the trigeminal nerve nuclei in the brainstem (specifically, the spinal trigeminal nucleus and the trigeminal sensory nucleus). Sensory input from the nasal cavity is particularly carried by the ophthalmic (V1) and maxillary (V2) branches. [114]When nanoparticles are administered intranasally (via nasal spray or other delivery forms), they interact with the mucosal lining of the nasal cavity. The nanoparticles can be absorbed through the epithelial cells of the nasal mucosa. [115] Some of these particles will penetrate through the nasal epithelium and enter the trigeminal nerve endings present in the nasal mucosa, particularly in the upper parts of the nose (innervated by the ophthalmic and maxillary branches). [116]Activation of Trigeminal Nerve occurs once the nanoparticles come into contact with the trigeminal nerve fibers in the nasal mucosa, they activate these sensory nerve endings.[117] This can lead to direct transmission of the signal through the trigeminal nerve, either to the trigeminal ganglion or directly to the brainstem. From the trigeminal nerve, the signal is relayed to the brainstem and further sent to higher brain centers, such as the thalamus and cerebral cortex, for processing. [118]The nanoparticles themselves may also be transported via the trigeminal nerve fibers to deeper regions of the brain, including the medulla and even the cerebellum.[119] Nanoparticles may travel along the olfactory nerve and into the olfactory bulb, which directly connects to the brain, providing an efficient route for brain delivery bypassing the blood-brain barrier.[120] The trigeminal nerve can also relay particles directly into regions like the brainstem, cortex, and even into deeper structures

like the medulla, which is associated with autonomic regulation. [121]

## 5. Advantages of the Trigeminal Pathway for nanoparticulate drug delivery:

Bypassing the Blood-Brain Barrier (BBB) is an important criterion for Intranasal nanoparticles that follow the trigeminal pathway offer a promising route for delivering drugs to the CNS without needing to cross the blood-brain barrier, a major challenge in drug development. [122]Since the trigeminal nerve is connected to several areas of the brainstem and higher brain regions, nanoparticles delivered through this pathway can potentially target specific regions, offering therapeutic benefits for conditions like neurological disorders, pain management, and CNS diseases.[123]

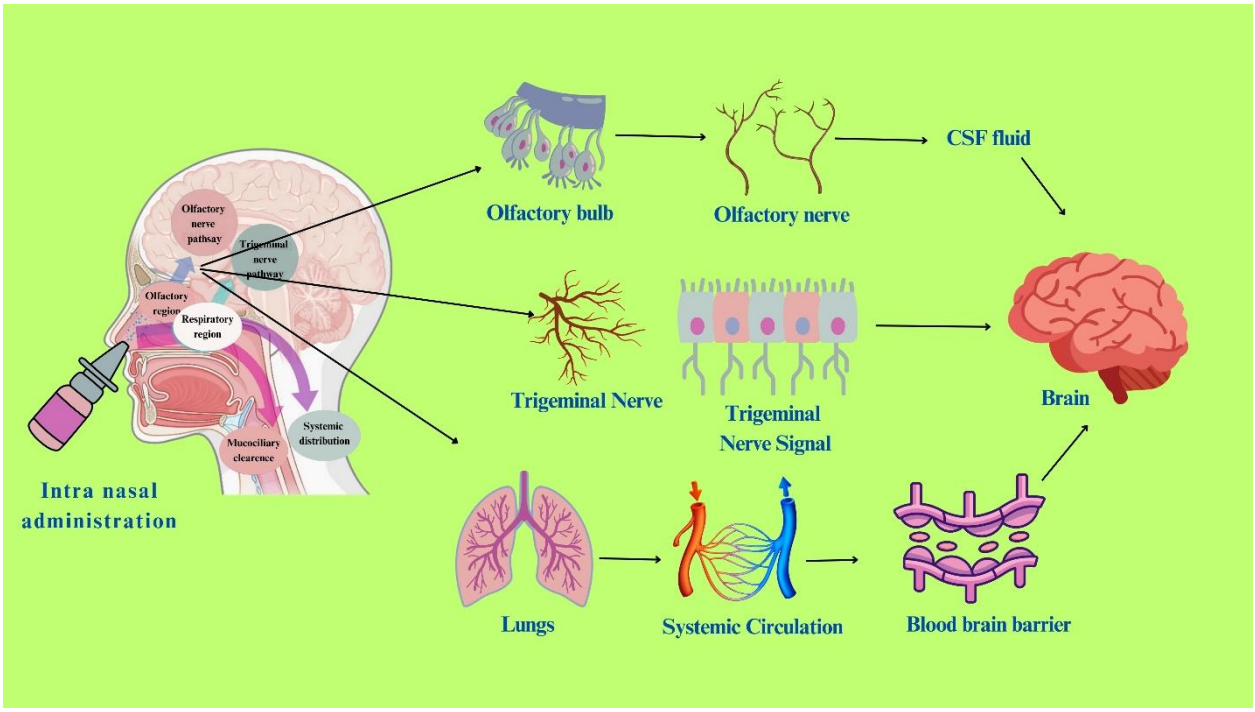


Figure 3: Absorption of nanoparticulate delivery system via olfactory nerve and trigeminal nerves to CNS

## 6. Physiological and Pharmacological interaction of Nanoparticle with Nasal Physiology via olfactory System:

Nanoparticles interact with the nasal physiology through a combination of physical and chemical mechanisms, including their size, shape, surface charge, and fictionalization.[124] These interactions influence the absorption and transport of Nanoparticle through the nasal mucosa and into systemic circulation or the CNS.[125] The nasal cavity is lined with a mucosal layer, primarily composed of epithelial cells, cilia, and mucus, which serve as the first line of defense against foreign particles.[126] The olfactory epithelium (located in the upper nasal region) and the respiratory epithelium (in the lower and middle parts) both play important roles in the absorption and clearance of nanoparticles.[127]Olfactory epithelium has specialized nerve endings (olfactory sensory neurons) that allow for direct neuronal transport to the brain whereas Respiratory epithelium is lined with cilia and goblet cells, produces mucus to trap and clear foreign particles.[128]The ciliary movement helps to clear nanoparticles or prevent their deeper penetration into the nasal mucosa. Nanoparticles can pass directly through the epithelial cells or paracellularly between the cells, depending on their characteristics. [128] It may be taken up by cells via mechanisms like phagocytosis (for larger particles) or pinocytosis (for smaller particles), allowing them to enter the bloodstream or reach deeper tissue.[129]Nanoparticles that interact with the olfactory epithelium can directly travel along the olfactory nerve to the olfactory bulb, then spread to the brain.[130] As described earlier, nanoparticles may be absorbed through the trigeminal nerve fibers in the nasal mucosa, leading to direct CNS targeting.[131] The surface properties (e.g., charge, hydrophobicity, and functionalization) influence the interaction with nasal epithelial cells and the subsequent release and distribution of the drug into the brain.[132]Nanoparticle surface modification such as PEGylation reduces particle clearance by the immune system and prolongs circulation time. Receptor-targeting ligands can enhance site-specific delivery to brain tissues or other targets. [133]

## 7. Pharmacokinetic of Intranasal nanoparticles:

The nasal mucosa is highly vascularized, allowing for the rapid absorption of drugs and nanoparticles. The drug particles are typically absorbed through the epithelial cells lining the nasal cavity.[134] Nanoparticles, owing to their small size and large surface area, can easily permeate the mucosal barrier and enter systemic circulation or reach the central nervous system (CNS).After absorption through the nasal mucosa, nanoparticles can enter the systemic circulation via the blood vessels of the nasal cavity. [135] The nasal route offers the advantage of bypassing the gastrointestinal tract and hepatic first-pass metabolism, which can lead

to higher bioavailability compared to oral administration.[136]Depending on the formulation (e.g., lipid-based, polymeric, or protein-based nanoparticles), the distribution of nanoparticles can be influenced by their physicochemical properties, such as surface charge, hydrophobicity, and size.[137]Once in the bloodstream, nanoparticles can be subjected to metabolism by liver enzymes, but they can also avoid hepatic first-pass metabolism due to their direct entry into systemic circulation.[138] The metabolic fate of nanoparticles depends on their material composition, and some may be metabolized to release the encapsulated drug or degrade into smaller components.[139]Certain nanoparticles (e.g., biodegradable ones) may degrade over time, releasing their therapeutic payloads as they are broken down by enzymes or under physiological conditions. The degradation products can be further metabolized by the liver or other organs, and eventually excreted from the body.[140]Nanoparticles that do not undergo metabolism may be eliminated via the kidneys. The size and surface properties of nanoparticles significantly affect their renal clearance.[141]Smaller nanoparticles (below 10 nm) are more likely to be excreted through the kidneys, while larger nanoparticles may undergo phagocytosis by the reticuloendothelial system (RES) in the liver and spleen.[142]Larger nanoparticles may be cleared via the bile and excreted in the feces. The composition of the nanoparticles affects their route of excretion, with some formulations favoring biliary clearance over renal.[143]

## 8. Pharmacodynamics of intranasal Nanoparticle:

Intranasal nanoparticulate drug delivery systems provide a novel approach for enhancing drug efficacy, particularly for central nervous system (CNS) disorders, by facilitating targeted drug delivery.[144]Upon intranasal administration, nanoparticles cross the olfactory epithelium/trigeminal nerve distributing the drug to different brain regions. Once distributed, Nanoparticles release the content that act on specific receptors, modulating neurotransmission and cellular responses. [145]Many CNS-active drugs (e.g., dopamine agonists, serotonin reuptake inhibitors) regulate neurotransmitter levels to exert their effects.[146] Drug-loaded Nanoparticle can target receptors such as NMDA, GABA, or opioid receptors, leading to neuro modulatory effects.[147]Some Nanoparticles facilitate direct intracellular drug delivery, enhancing therapeutic action at the molecular level.[148] InAlzheimer's disease**,** intranasal nanoparticles enhance brain uptake of neuroprotective agents like curcumin or rivastigmine, reducing amyloid-beta accumulation and oxidative stress.[149] For the treatment of Parkinson's disease**,** intranasal nanoparticles containing bio-molecules that interact with dopaminergic pathway and help to restore dopamine levels in the substantia nigra, improving motor control. Intranasal SSRIs or neuropeptides (e.g., oxytocin) exert rapid antidepressant and anxiolytic effects by modulating serotonin or oxytocin receptors.[150]

**Table1. List of suitable drug candidates for intranasal nanoparticulate delivery**

| S.No | Drug | Polymer | Method of Production | Particle size | Zeta Potential | Entrapment efficiency (%) | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|
| 1. | Estradiol | Chitosan NP | Ionic interaction-prepared lipid nanocarriers | 269.3±31.6 | +25.4 | 64.7% | The concentrations of estradiol-loaded NPs were quite high | 151 |
| 2 | Rivastigmine | Chitosan with tween 80 | Polymeric nanoparticles prepared using ion gelation method | 163.7±7.6nm | 45.30±6.21 mV | 85.3 % | Significant drug loading was seen using chitosan nanoparticles, with reduced accumulation in the liver, spleen, and heart. | 152-153 |
| 3 | Donepezil | Lutrol F127/Carbapol 934 | Melt emulsification high pressure hmozenization | 112.5±2.44 nm | -23.2mV | 98.7±4.01 % | Brain concentration is higher than that of | 154 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | the free drug. | |
| 4 | Curcumin | Lactoferrin | Desolvation method | 84.8±6.5nm | +22.8±4.3mV | 248.1% | When compared to free curcumin, the permeability of curcumin nanoparticles was significantly enhanced. | 155 |
| 5 | Caffeic acid | transferrin | Liposome | 139±9nm | ±56.30 | 23±4% | There was disaggregation activity against the Aβ42 peptide by Tf-CA liposomes. | 156 |
| 6 | Rhein and Polydopamine | Fe-Rh/Pda NPs | Metal nanoparticles | 75.14±173 | -2.27 – (-10.5mv) | 27.71±6.86 | Rhein was more bioavailable to the brain when encased in nanoparticles than was administered alone. | 157 |
| 7 | Galantamine | Chitosan/ Chitosan alginate complex NP | Ionotropic gelation | 240nm | +58mv | 67% | Prolonged release. There was no significant neurotoxicity caused by the new formulation. | 158 |
| 8 | Tacrine | Poly (n-butyl cyanoacrylate) with polysorbate 80 | Lipid nanocarriers synthesized via emulsion polymerization | 117.4nm | -10.0±0.9 | 22% | Compared to free tacrine and uncoated nanoparticles, tacrine concentrations in the brain were shown to be higher when poly (n-butyl cyanoacrylate) nanoparticles were coated with 1% polysorbate 80. | 159 |
| 9 | Doxorubicin | Stealth (PEG2000) and non- | Lipid nanocarriers synthesized via high-pressure | 118±0.92 | +22.5±8.68 | 38.40±8.94 | The outcome is a higher doxorubicin | 160 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | stealth SLN | homogenization | | | | concentration. | |
| 10 | Curcumin | mannose | Liposome | 100nm | -3.6±4.3 | 94.23±2.886 | The absorption and accumulation of curcumin liposomes in N2a cells were enhanced. | 161 |
| 11 | Estradiol | Polylactide-co-glycolide (PLGA) with tween 80 | Polymeric nanoparticles | 98.3±2.6 | 78.9±2.1 | 51.34±5.59 | Compared to free drugs, coated nanoparticles demonstrated superior brain absorption. | 162 |
| 12 | RHT (Rivastigmine Hydrogen Tartrate) | Eudragit RL100 | nanoprecipitation | 118±0.92 | +22.5±8.68 | 38.40±8.94 | Nanoparticles of eudragit loaded with RHT have the potential to increase nasal bioavailability by effectively adhering to the nasal surface. | 163 |
| 13 | Simvastatin | Simvastatin-Loaded PCL (poly-ε-caprolactone | Nanocapsules | 202.5±18.0 | -22.2±3.2 | 99.8±0.7 | Prepared NPs demonstrated great bioavailability and shorter delivery times. | 164 |
| 14 | Simvastatin | Simvastatin loaded Lecithin/chitosan nanoparticles | Nanoparticles | 212.6±7.2 | +40.4±2.1 | 99.3±1.1 | Prepared NPs demonstrated great bioavailability and shorter delivery times. | 165 |
| 15. | Buspirone HCL | BUH thiolated chitosan | Ion gelation | 226.7±2.52nm | +39.2±3.1 | 81.13±2.8 | Higher concentration in brain. | 166 |
| 16 | Agomelatine | Agomelatine with PLGA | NPs | 167.70±0.42 nm | -17.90mv±2.70 | 91.25±1.70 % | Absolute bioavailability and brain delivery of agomelatine were both greatly | 167 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | enhanced by intranasal injection of solid lipid nanoparticles. | |
| 17 | Duloxetine | Duloxetine nanostructured lipid carriers | Lipid carriers | 265.13±9.85 | 2.79±0.44mV | 98.13±0.50% | Better brain targeting & decreased side effects | 168 |
| 18 | Folic acid | | Niosomes | 3.05–5.625 | | 69.42% | High absorption through nasal cavity | 169 |
| 19 | selegiline | Chitosan | Selegiline Hydrochloride thiolated chitosan NPs | 186±21.45 | 70±2.71 | 215±34.71 | Attenuation of the oxidative stress and restoring the mitochondrial complex activity | 170 |
| 20 | Venlafaxine | Alginate | Venlafaxine alginate NPs | 173.7±2.5 | 37.50±1.74 | 81.3±1.9 | More enhanced excellent brain/blood ratios | 171 |
| 21 | Aripiprazole | Gellan gum (APZ-TFS-Gel) | Transferosome by using ion triggered deacetylation | 72.12±0.72nm | -55.56±1.9mv | 97.06±0.10% | Higher systemic and brain bioavailability | 172 |
| 22 | Haloperidol | GMS,comprito l ATO 888, precirol ATO 5 | Solid lipid nanoparticles using Modified emulsification-diffusion technique | 115.1±2.78 | -16.7 | 71.56±1.56 | Increased haloperidol concentrations in brain tissue as compared to free drug | 173 |
| 23 | Lurasidone | Oil (Camptex 335EP, Capryol 90) | Nanoemulsion prepared using high pressure homogenization | 48.07±3.29 | -0.20±0.01 | 97.87±0.702% | Increased concentrations of Lurasidone in brain | 174 |
| 24 | Huperzine A (Huperzia serrata) | Lactoferrin conjugatedN-trimethylated chitosan | NPs were prepared using emulsion solvent evaporation | 153.2±13.7nm | +35.6±5.2mV | 73.8±5.7 | Better permeability | 175 |
| 25 | Rutin | chitosan | NPs prepared using Inotropic gelation | 85-100nm | _ | _ | Better permeability than oral administration | 176 |
| 26 | Memantamine | PLGA | Nanoprecipiation followed by ultrasonification | 58.04nm | -23mV | 89% | Higher concentration of drug at the target site | 177 |
| 27 | Donepezil and | _ | Nano colloidal carrier prepared | 16nm | -7.22mv | _ | The concentratio | 178 |

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| | Memantine | | using low emulsion technique | | | | n in the brain is much higher than free drug | |
| 28 | Erythropoietin | Polysorbate80 | SLN | 219.9±15.6nm | _ | 41.4±3.6 | The results showed SLNs potential ability to hinder Aβ effects | 179 |
| 29 | Leuprolide acetate | Chitosan | Nanoparticles | 254.3±10.7 | 18.0±0.2mv | 85.6±0.8 | Great promise for AD was discovered for the chitosan nanoparticulate formulation of leuprolide acetate. | 180 |
| 30 | Escitalopram and Paroxetine | Lauroglycol 90 and PrecirolATO 5 | Nano emulsion prepared using High-pressurehomogenization | 165±2.01nm | 11.2±0.400 | 44.5±5.23 and 83.1±8.49 | Higher concentration of drug in the brain and lesser toxicity | 181 |
| 31 | Risperidone | Compritol888 ATO | SLNs prepared by solvent diffusion-solvent evaportaion | 148.05±0.85 | -25.35±0.45 | 59.65±1.18% | Higher concentration of drug achieved by using nano formulation as compared to free drug | 182 |
| 32 | Zolmitriptan | Triglyceride | Micro emulsion prepared using titration | 35±25nm | -38.90±2.05 | 98.77±0.83% | Effective delivery of drug to the brain | 183 |
| 33 | Amiloride | Carbitol | Nanoemulsion | 89.36±11.18nm | -9.83±0.12mV | 80.36% | Rapid onset of action due to direct nose-to-brain access | 184 |
| 34 | Rivastigmine | CPP peptide | Liposomes | 166.3±17.4 | -10.5±2.4 | 33.4±6.6 | Improved brain delivery and BBB penetration. | 185 |
| 35 | Ziprasidone | Gelucire43/01 and 44/14 | NLC was prepared using hot homogenization followed by ultra-sonification | 119.62 | _ | 70.83% | Higher concentration of drug in the brain as compared to free drug | 186 |
| 36 | Letrozole | Triacetin, tween 80, and PEG-400 | Nano emulsion by aqueous titration method | 95.59±2.34nm | -7.12±0.12mv | 97.37±1.13% | Improved anticonvulsant activity | 187 |

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| 37 | Piperine | Chitosan | Nanoparticles by dispersion | 248.50nm | +56.30mv | 81.70% | Increased bioavailability of drug | 188 |
| 38 | Erythropoietin | Polysorbate 80 | SLNs using double emulsion method | 219.9±15.6nm | -22.4±0.8mV | 41.4±3.6 | Enhanced neuroprotection | 189 |
| 39 | Queritin | PEG 660-stearate | Nanoemulsion using high pressure homozenization | 131.00±0.25 | +7.9±0.24 | >99 | Enhanced concentration of drug at the target site | 190 |
| 40 | Insulin | Poly(N-vinyl pyrrolidone)-co-acrylic acid nanogels | Nanogels | 75 | -12±6.9 | 74.03% | Changes in mucosal integrity were observed. | 191 |
| 41 | Temozolomide | Cyclodextrin conjugared Chitosan and PEG-adamantane polymer | Gold-nanoparticles by nucleophilic substitution | 31.3±20nm | -15mV | 82.89±8.14% | Intramuscular administration of temozolomide gold nanoparticles was performed. The results showed that the rat brain had a higher drug content. | 192 |
| 42 | Carbamazepine | Carboxymethyl chitosan | Nanoparticles | 218.76±2.41 | -33.3 | 80% | Greater drug concentration was found in several parts of the brain when carbamazepine-loaded dendrimers were used. | 193 |
| 43 | Haloperidol | Tween 20 | Dendrimers | 15.10±5.4 | 10.7±1.75 | _ | Haloperidol containing dendrimers were developed and administered through intranasal route. The study showed dendrimers can be a appropriate drug delivery system for drug targeting to brain for poorly water | 194 |

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| | | | | | | | soluble drugs. | |
| 44 | Bromocriptine | Chitosan | Polymeric nanoparticles were prepared using ionic gelation technique | 161.3±4.7nm | +40.3±2.7mV | 84.2±3.5 | Enhanced concentration of drug. | 195 |
| 45 | Tarenflurbil | PLGA | Nanocarrier by emulsification and solvent diffusion method | <200nm | -23.13±2.32 mV | 64.11±2.21 % | For intranasal delivery, tarenflubril was encased in PLGA nanoparticles. The efficiency of entrapment was enhanced. Evidence suggested that drug concentrations in the brain were higher. | 196 |
| 46 | Camptothecin | PEG, MPEG/ poly(ε-caprolactone) | Micelles | 88.5±20.2 | 10.4±2.84 | 62.5±9.17 | After the intratracheal injection of micelles loaded with camptothecin, rats with cerebral glioma tumours had an increase in survival time. | 197 |
| 47 | Doxorubicin | PLGA | Dendrimers | 156±10.85nm | -10.0±2.1mV | 19.01±1.58 % | Higher permeability through BBB via intranasal administration | 198 |
| 48 | Disulfiram | PEG2000 | Ion sensitive nanoemulsion | 63.4±1.1nm | -23.5±0.2mV | 89.02±0.32 | The local nasal administration with minimal systemic distribution may explain why disulfiram-loaded intranasal nanoemulsion successfully inhibited tumour | 199 |

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| | | | | | | | growth in vivo and prolonged the life span of glioma-bearing rats. | |
| 49 | Nicardipine | Chitosan | Polymeric nanoparticles | 439.6±11.9nm | +21.05±0.48 mV | 78 | Intracerebral haemorrhage treatment options may include nicardipine-loaded nanoparticles, which have shown rapid drug transport to the brain after intranasal administration. | [200] |
| 50 | Rasagiline | Chitosan glutamate | Ionic gelation technology was used to prepare NPs | 151.1±10.31 | _ | 96.43±4.23 | Enhanced bioavailability and brain uptake | [201] |
| 51 | Ropinirole | Chitosan | NPs prepared using ionic gelation technique | 173.7±2.32 | | 69.6±3.3 | Increased concentration of drug at the target site | [202] |
| 52 | Venlafaxine | Hyaluronic acid | Transbilosomes were prepared using film hydration | 185.6±4.9nm | -39.8±1.7mV | 69.6±2.6nm | Higher bioavailability of VLF to the brain | [203] |
| 53 | Zonisamide | Carbopol | Microemulsion | _ | _ | 54.95% | Enhanced bioavailability | [204] |
| 54 | Olanzapine | Chitosan | Ionotropic gelation | 322±18 | _ | 87.6±5.2 | Improved systemic absorption | [205] |

## 9. Conclusion and future prospect:

Nanoparticulate delivery system is considered as a novel and promising route for a number of neurodegenerative diseases. Bypassing the blood-brain barrier (BBB), a major obstacle in neuropharmacology and by the intranasal route the medications can directly deliver to the brain. The use of nanoparticles enables targeted delivery to specific brain regions, decreased systemic adverse effects, and regulated and sustained release of therapeutic medicines. Previous research revealed that, a variety of therapeutic compounds, including as tiny molecules, peptides, proteins, and genes, can be delivered through intranasal administration. Due to the non-invasive nature of the administration method, intranasal nanoparticulate delivery systems have demonstrated potential in improving bioavailability, enhancing therapeutic efficacy, and improving patient compliance for neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, and Huntington's disease. It has been observed from past research that, Intranasal nanoparticulate delivery systems possess the capacity to lessen neuroinflammation, encourage neuroprotection, and support neuro-regeneration, thereby providing therapeutic advantages for delaying or stopping the progression of disease. Even though intranasal delivery has several benefits, there are still issues that must be pointed out and resolved. These include enhancing the stability and pharmacokinetics of the drug-loaded nanoparticles, establishment of safety, overcoming nasal mucosal clearance mechanisms and optimizing nanoparticle formulations for improved targeting and release features. Additional research is

required to establish long-term impacts of intranasal delivery systems on the brain and general health. Combination medicines that target several pathogenic p athways of neurodegenerative illnesses may be delivered more easily via these platfor ms.

Intranasal nanoparticlebased systems may be customize d

to meet the demands of particular patients as our knowl edge of the genetic and molecular variances in neurodeg enerative disorders expands, improving therapeutic res ults. Although pre-clinical research has yielded encouraging outcomes, clinical translation is essential to the broad use of intranasal nanoparticulate devices. Commercialising these treatments successfully will require overcoming regulatory obstacles, establishing safety and efficacy, and solving manufacturing scalability. Intranasal nanoparticulate delivery systems have a bright future ahead for the management of neurodegenerative illnesses.

### List of abbreviations:

BBB: Blood-Brain Barrier

CNS: Central Nervous System

CSF: Cerebro Spinal Fluid

EPR: Enhanced Permeability and Retention

PEG: Polyethylene glycol

SSRI: Serotonin specific reuptake inhibitor

NP: Nanoparticle

SLN: Solid Lipid Nanoparticle

**Ethics approval and consent to participate:** This manuscript is a review. Hence, no experiments in animals or humans are included in this study, so ethical approval and consent are not required.

**Clinical Trial No:** The manuscript is a review article (not a part of Clinical trial), hence no Clinical trial no is applicable.

**Consent for publication:** This manuscript does not contain any personal data. Hence, no consent is required/Not applicable

**Availability of data and material:** Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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