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A comprehensive review on blood brain delivery methods using nanotechnology

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Abstract

A limited amount of the administered medicine can reach the brain. As a result, a higher dose of the drug must be administered, which, as expected, causes several undesirable side effects. For the past few decades, researchers in a range of professions have been working to address this highly important and frequently lethal condition. Nanomedicine is a field of research that has achieved promising findings in recent years. Nanomedicine is the science that combines nanotechnology, chemistry, and medicine. Many various forms of nano-medicine-based drug-delivery systems are currently being investigated with the express goal of improving drug delivery to the brain. This overview compiles and briefly summarizes some of the most significant advances in this crusade. Inorganic nano-particle-based drug delivery systems, such as gold and magnetic nano-particles, are discussed, as are several organic nano-particulate systems. Polymeric micelles and dendrimers are briefly described as organic drug-delivery nano-systems, while solid polymeric nano-particles are thoroughly investigated.

Keywords: Nano-particle, Nano-medicine, Drug delivery polymer, Targeting, Liposome.

Introduction

The brain is protected against a variety of brain disorders and traumas by the blood-brain barrier, an extremely intricate and well-organized multicellular structure that surrounds the brain and keeps out chemicals and invasive organisms. It does, however, also obstruct the drug's ability to reach the brain, making the treatment of many neurological conditions impossible.(Sarkar et al., 2017). Tight junctions (TJs), which are compact and extremely effective, set apart the BBB's highly specialized endothelial cells from the body's other endothelium. (Moura et al., 2019) The basal lamina, which is next to the astrocyte foot, and a continuous layer of pericytes encircle the endothelial cells. (Figure 1).(Lombardo et al., 2020)

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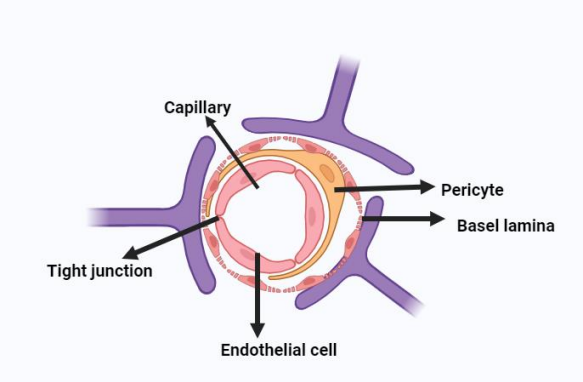

Figure 1: Blood brain barrier anatomy

Intracellular and valvar gaps are absent from the BBB, and the brain's entrance point to the outside world is severely constrained. Drug delivery to the central nervous system can be facilitated by combining polymer coatings with nanoparticles (NPs) to cross the blood-brain barrier. Numerous advancements in the detection and management of brain tumors, trauma, and nervous system problems have been made possible by this technique. The creation of novel NPs-based techniques and tactics aimed at medication delivery to the brain is shown in (Fig. 2).

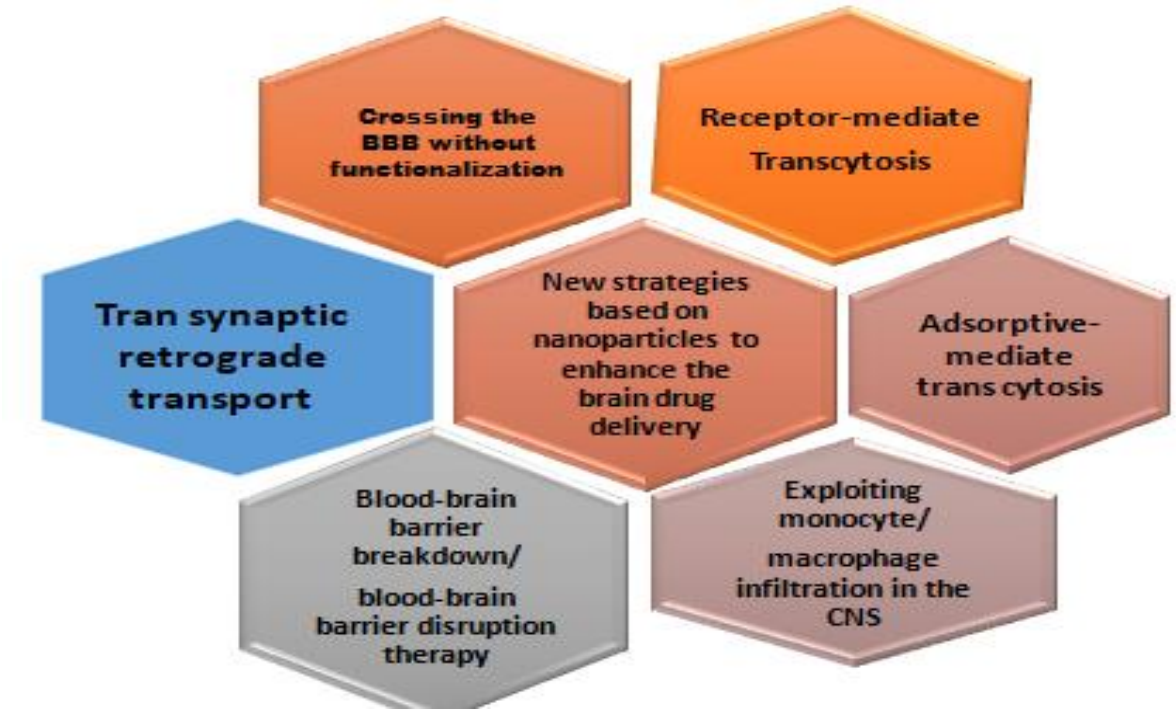

Figure 2: Development of new strategies based on NPs technology for drug delivery to the brain

By resolving the drawbacks of neuropsychiatric medications, nanotechnology creates new potential. For the diagnosis and treatment of neuropsychiatric disorders, nanotechnology offers a variety of nanomaterials with remarkable properties. Nanomaterials are a potent drug delivery vehicle that may efficiently pass the blood-brain barrier due to their high stability, substantial payload, and flexible architecture. (Tian-Qi Li, Li-Wen Huang, 2019). liposomes are now the most widely employed nanocarriers for a variety of hydrophobic and hydrophilic compounds that may be biologically active. Additionally, liposomes demonstrated improved drug solubility and regulated distribution (Sakshi*, 2024).In this paper, an effort has been made to provide a brief overview of the evolution of the blood-brain barrier in different types of brain illnesses and the associated approaches for creating nanoscale drug delivery systems that target the brain. An investigation into the many parameters of the manufactured nanosponges led to the discovery of several encouraging findings for the development of nanosponges in the future. (Kumar et al., 2022)

Central Nervous System Disorders Targeting Nano Scaled Pharmaceutical Delivery Devices

Alzheimer's Disease

The genetic risk factor APOE4 is linked to a poor neurological prognosis following traumatic brain injury, cerebral hemorrhage, and other neuropathological illnesses. It is also a prominent implicated gene for Alzheimer's disease. (Zlokovic, 2013) N-methyl-d-aspartate (NMDA) receptor antagonists and cholinesterase inhibitors are used to treat AD, although they only provide symptomatic relief and neither stop neurodegeneration nor reverse the illness. Different kinds of drugs that are not clinically licensed for the treatment of AD, innovative carriers, and various dose forms are some of the tactics that have been used to treat pathological illnesses. It is also a major genetic risk factor for Alzheimer's disease. (Lee & Minko, 2021) Numerous tactics based on nanotechnology are being researched to provide a more effective treatment. Their goals are to stop the development of amyloid plaques and fibrils, dissolve them, or eliminate the transitional metal ions that cause the harmful reactive oxidative species to arise in the body. Cholinesterase inhibitors, amyloid-targeted medications (antibodies, gold NPs), and metal chelators (copper, iron, and quinolone derivatives, such as clioquinol) are the three primary nanotechnological tools for treating AD.(Domínguez et al., 2014)

Parkinson’s Disease

Parkinson's disease (PD) is defined by the loss of approximately 50–70% of dopaminergic neurons in the substantia nigra pars compacta, a significant reduction in dopamine in the striatum, and the appearance of intracytoplasmic inclusions known as Lewy bodies,(De Giglio et al., 2011) The ABCB1 (P-Glycoprotein)-encoding PMDR1 genes are thought to be intimately associated with Parkinson's disease. In BBB endothelial cells, decreased MDR1 expression is linked to the development of Parkinson's disease. (ŞAHİN et al., 2020) The three medications that are most frequently used as pharmacological therapy for Parkinson's disease (PD) are dopamine agonists, monoamine oxidase B inhibitors, and L-dopa. Dopamine's direct precursor is levodopa. It has been the medication of choice for treating Parkinson's disease.(Domínguez et al., 2014)

Our goal was to create a nanosystem with a particular composition and set of physical and chemical characteristics that would enable BBB crossing and improve the distribution of dopamine to brain tissue. (Fig. 3) (Monge-Fuentes et al., 2021)

Huntington's Disease

The genetic neurological illness known as Huntington's disease (HD) is attributed to a CAG expansion in the gene that codes for the huntingtin (HTT) protein. The hallmarks of Huntington's disease (HD) include atrophy of the striatum and other brain regions, neuronal dysfunction, gradual loss of cortical pyramidal neurons and striatal medium-sized spiny neurons (MSNs), and motor, cognitive, and psychiatric problems.(Grabrucker et al., 2016). After intraperitoneal injection, high-rate brain delivery was successfully achieved in HD mice using biodegradable and biocompatible polymeric nanoparticles (NPs) modified with glycopeptides (g7) and loaded with cholesterol (g7-NPsChol), which per se is not blood-brain barrier (BBB)permeable. Unlike unmodified NPs, g7-NPs were able to pass the blood-brain barrier with ease and were found in diverse parts of the brain in glial and neuronal cells. Additionally, we discovered that in HD mice, repeated systemic administration of g7-NPs-Chol restored synaptic and cognitive impairment and somewhat enhanced global activity.

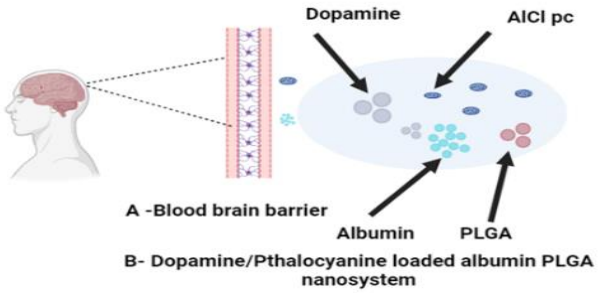

Figure 3: Schematic representation of dopamine/phthalocyanine-loaded nanosystem’s structural assembly (a) and its interaction with the blood-brain barrier (b) to ultimately enter the brain parenchyma and release the drug/compound of interest. AlClPc aluminum chloride phthalocyanine, PLGA poly (lactic-co-glycolic acid).

Brain Tumors

One way to categorize primary brain tumors is as gliomas. The causes of these brain tumors are often unclear, and they are among the most deadly and challenging forms of cancer to cure. (Baek et al., 2011) These formulations, which are based on lipids, have been demonstrated to raise the levels of chemotherapeutic chemicals in the brain, such as doxorubicin, paclitaxel, idarubicin, etoposide, and camptothecin. As a result, they are particularly appealing candidates for the treatment of brain cancers.(Brioschi et al., 2007) Magnetic nanoparticles, which are formed of a magnetic core (for example, iron oxide or magnetite) and a biocompatible polymeric shell (for example, dextran or starch), are the nanocarriers that are utilized to target brain tumors. For instance, the anti-EGFRvIII antibody that was attached to iron nanoparticles was shown to have a therapeutic impact in mouse models of glioma by increasing the survival rate of mice that were carrying glioblastoma.(Hadjipanayis et al., 2010)

Nanotechnology Approaches for Crossing the Blood-Brain Barrier

Novel insights into the workings of neural circuits and strategies for the diagnosis and treatment of brain disorders will come from the development of nanotechnology through integrated multidisciplinary efforts. (Ali *et al*., 2015)

Organic Nanoparticles

Polymeric nanoparticles

The most researched nanoparticle technology for brain delivery is polymeric nanoparticles. They can be made from natural or synthetic polymers.(Lombardo et al., 2020)

Due to their ability to undergo surface modification (e.g., PEGylation), nanosizing, bioactivity, controlled and sustained drug release, nontoxicity, bioavailability, biocompatibility, reticuloendothelial clearance bypass, and the encompassing of various active molecules including drugs, oligonucleotides, and peptides, these have developed into one of the most successful candidates for drug delivery applications. (Jyoti Ahlawat, 2020)

NPs made of polymers provide the following numerous benefits: The drug's ability to remain in the lesion can be extended by its large molecular weight. An active enhancer is, for instance, high molecular weight chitosan.54(2) Good biocompatibility as a result of less hydrolytic and enzymatic degradation.55 (3) Adjustable zeta potential, pH sensitivity, and solubility of the constituents to produce controlled in vivo drug release; and (4) pliable conjugated functional chemical groups on the polymer surface to target targets. (Tan et al., 2022)

Polymeric nanoparticles (NPs) possess great malleability and can display an extensive array of physico-chemical and biological attributes. Due to their great functional ability, solid nanoparticulate DDSs (SNPs) and many other forms of nanoparticles can be employed as delivery vehicles for medications that can be targeted either actively or passively to a variety of tissues.(Sahoo & Labhasetwar, 2003) The common ways used to functionalize SNPs for drug-delivery applications are summarized in Figure 4

Dendrimers

Dendrimers are artificial molecules that resemble trees and have several branching monomers extending from the center core.(Ahlawat et al., 2018) Generally, dendrimers are employed to transport hydrophobic substances to the targeted brain regions. Figure 5. Because of their easy surface modification, high biocompatibility and biodegradability, superior water solubility, and flexible molecular weight and shape, dendrimers are highly useful for drug administration. Dendrimers also have a passive targeting impact because of their increased permeability and retention (EPR) effect, a property that facilitates BBB penetration. (Leiro et al., 2018)

Dendrimers are appealing candidates for drug delivery because of their remarkable structural characteristics, which include their tiny size, low polydispersity, narrow molecular weight dispersion, well-defined globular shape, and relatively easy inclusion of targeting ligands.

Dendrimers' physicochemical characteristics and biocompatibility are dictated by their surface functional groups. (Agnieszka Z. Wilczewska1, Katarzyna Niemirowicz2, Karolina H. Markiewicz1, 2012)

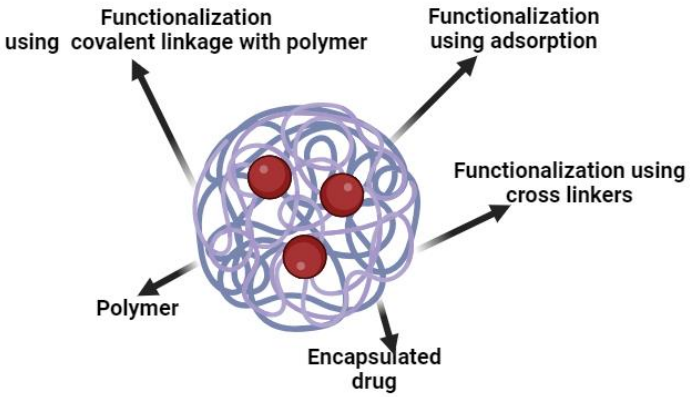

Figure 4: Schematic illustration of a functionalizable polymeric nanoparticle (Ayub & Wettig, 2022)

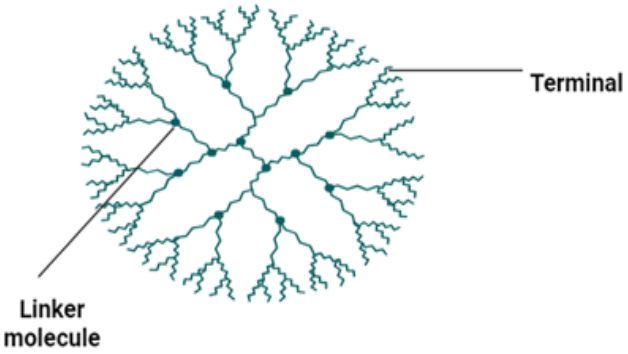

Figure 5: A dendrimer's general structure, which is made up of the terminal group, dendrons, and core. Usually, functional molecules and drugs are incorporated into the terminal group

Polymeric micelles (pm)

In recent years, polymeric micelles have been produced for medication delivery. These micelles exhibit shell-core structures with hydrophobic block polymers (such as L, D-lactone polycaprolactone) as the core and hydrophilic block polymers (typically PEGs) as the shell. These micelles develop spontaneously in amphiphilic copolymer solutions. The particle size of the polymeric micelles is reported to be between 10 and 100 nm. It is possible to load water-insoluble medications into the core Figure 6. These configurations enhance the bioavailability and stability of drugs. The medication is shielded from interacting with serum proteins and non-target cells by the micelle shell. When the loaded medication reaches the target cell, it is released via a diffusion mechanism. (Xu et al., 2013)

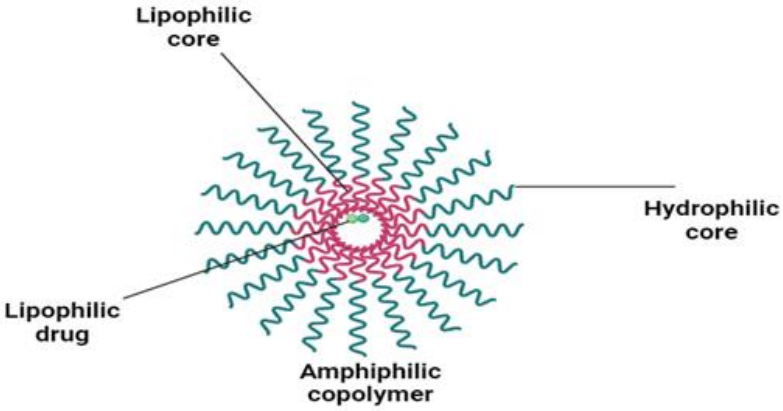

Figure 6: Diagram showing the structure of a polymeric micelle made of an amphiphilic polymer and a lipophilic medication contained in the lipophilic core

In addition to having certain issues and flaws with the mono system (low drug loading and poor stability), this binary micelle system also involves a long-term profile of in vitro drug release. Both poly(ethylene bioavailability in humans and rats) and mixed micelles were examined in an in vivo investigation. (I et al., 2008)

Liposomes

liposomes are tiny, spherical vesicles made up of one or more phospholipid bilayer concentric spheres divided by aqueous compartments. Figure 7 Because of their hydrophilic core and hydrophobic (lipophilic) tail, they are considered amphiphilic. The majority of their physical characteristics, including size, amphiphilicity, and surface charge, are modifiable based on the preparation technique and the type and amount of fat employed. Their dimensions might vary from 50 nm to 1 µm(Akbarzadeh et al., 2013). Many liposomal drug-delivery systems have been successfully used for brain drug delivery. For instance, Gurturk et al. prepared DSPE-PEG liposomes decorated with maltodextrin for the delivery of levodopa for the treatment of Parkinson's disease in their 2017 publication. The researchers obtained liposomes with decent drug loading and low polydispersity, with hydrodynamic diameters between 100 and 150 nm with a respectable amount of pharmacological loading. Research conducted in vitro revealed that levodopa included in maltodextrin-conjugated DSPE-PEG liposomes was statistically significantly more than that of non-targeted liposomes or the medication on its own. Maltodextrin is known to use RMT to traverse the BBB.

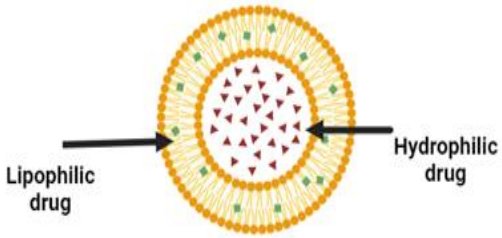

Figure 7: An illustration of a basic liposome consisting of a phospholipid bilayer and an aqueous center. Liposomes can contain both lipophilic (green) and hydrophilic (red) medications.

Nanoemulsions

A mixture of two or more immiscible liquids is referred to as an emulsion. Nanoemulsions are emulsions on a microscale, as the name implies. nanoemulsions are thermodynamically stable and can stay in a diphasic stage forever, in contrast to emulsions, which are thermodynamically unstable and phase separation is inevitable. The way the two look also differs; nanoemulsions are typically clear, while emulsions tend to be milky. Mixtures of oil, water, and surfactant with droplet sizes of colloidal dimensions—typically with droplet diameters of let100 nm—are referred to as nanoemulsion (Figure 8) (Kale & Deore, 2016)

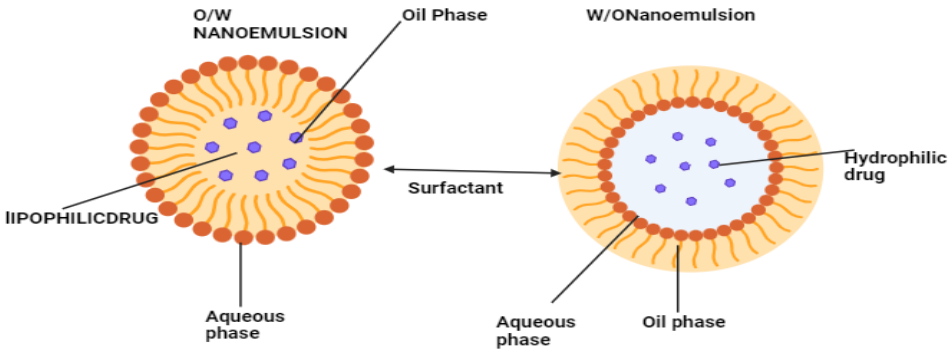

Figure 8: Diagram showing an oil-in-water nanoemulsion droplet with a lipophilic medication encapsulated in the organic core and a water-in-oil nanoemulsion droplet with a hydrophilic drug confined in its aqueous core (left).

Drugs that are both lipophilic and hydrophilic can be transported by nanoemulsion which is simple to manufacture. Nanoemulsions are extremely desirable instruments for drug administration because of their solubilization qualities, which are made possible by their small droplet size and great thermodynamic stability. You can transport both lipophilic and hydrophilic medications in microemulsions, and they are simple to make. Microemulsions are very appealing drug delivery techniques due to their small droplet size and great thermodynamic stability, which allow them to exhibit solubilization qualities. (Callender et al., 2017)A 2014 study by Patel et al. reported the preparation of drug-loaded microemulsions for intranasal delivery of Carbamazepine to the brain; the prepared formulations were reported to be stable for up to 6 months under standard conditions; the concentration of the drug Carbamazepine was found to be significantly higher compared to IV administration using in vivo models. Few studies report brain drug delivery using microemulsions, similar to niosomes. (Patel et al., 2016)

Inorganic Nanoparticles

Gold nanoparticles

The majority of research on gold nanoparticle distribution to the brain used gold nanospheres (AuNPs). A gold core and surface ligands that are covalently or non-covalently linked make up AuNPs. AuNPs possess a plethora of intriguing features. The BBB via RMT allows them to be readily synthesized, coated, or conjugated to carry a variety of cargos, including small chemicals, proteins, and nucleic acids.

Magnetic Nanoparticles (MNPs)

During the latter half of the 1970s, magnetic nanoparticles (MNPs) were initially utilized in medication delivery applications for the first time. It is possible to ensnare therapeutic chemicals within magnetic nanoparticles or attach them to their surface before administering them into the bloodstream. MNPs can be targeted by the use of standard active-targeting techniques (using RMT or AMT), or through the application of a magnetic field that is externally focused on the target site. This magnetic field can then facilitate the localization of the NPs at the desired location. (Qiao et al., 2012) (Figure 10)

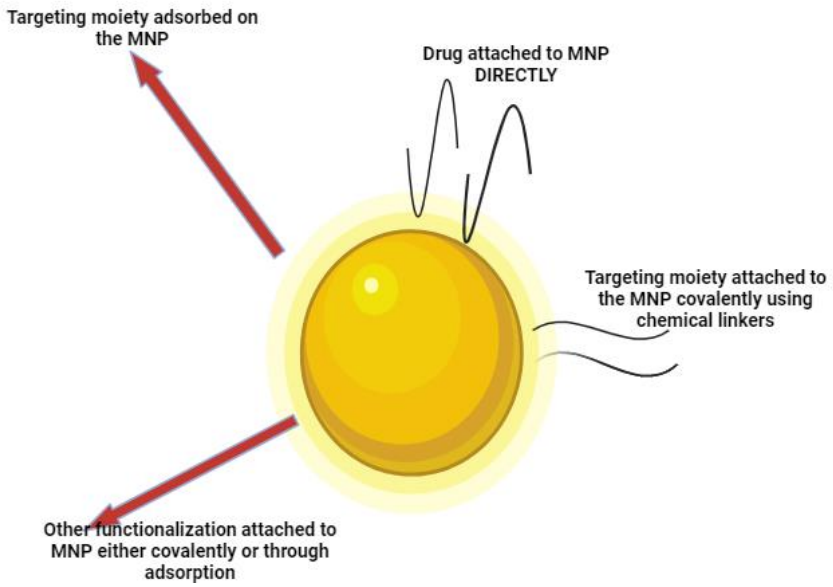

Figure 9: Schematic illustration of a nanoparticle made of gold. Drugs and other functionalizations can be adsorbable or covalently bonded onto the negatively charged surface of AuNPs.

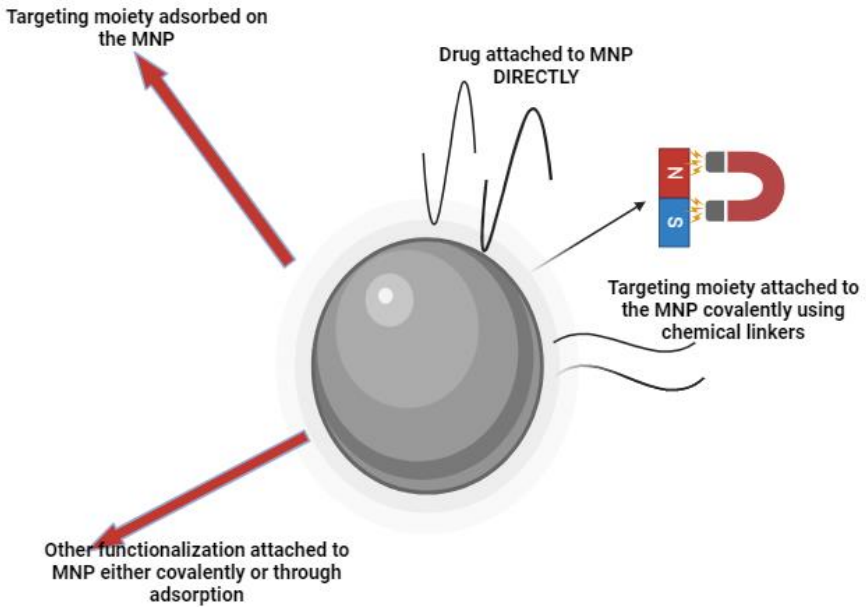

Figure 10: A a diagrammatic illustration of a magnetic nanoparticle (NP) that is functionalized and carries a medication. Using linkers, moieties, and medications that are targeted can either be adsorbed or covalently bonded to these molecules.

Conclusion

Many inorganic and organic NP-based drug delivery methods are being investigated for the delivery of drugs to the brain. Regarding drug-delivery applications, each of these many kinds of nanoparticles has pros and cons of its own, such as low drug-loading capacities, poor biocompatibility profiles, or undesirable physicochemical properties. Solid polymeric nanoparticles have garnered significant attention owing to their exceptional flexibility. The blood-brain barrier (BBB) is a big obstacle to delivering drugs to the brain, yet there is promising evidence from several research. While some of these nanoparticles have shown promise, there is still no guarantee of a safe way to deliver medicines to the brain. As a result, additional studies are required.

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