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A REVIEW ON THE APPLICATION OF DRUG LOADED NANOCARRIERS, LIMITATIONS, FUTURE PERSPECTIVES AND IMPLEMENTATION OF ARTIFICIAL INTELLIGENCE

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ABSTRACT: The central nervous system disorders represent a worldwide public health problem. Neurodegeneration is associated with many transitions in brain including synaptic disorder and neuro cognition decline. It is shielded by a barrier which controls the entry of compounds into the brain known as blood brain barrier (BBB), thereby regulating brain homeostasis. In achieving a therapeutic amount of drug to the proper site of action in the body and then maintaining the desired amount of drug concentration for a sufficient time interval to be clinically effective for treatment. Particularly, neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) are becoming further established in the elderly inhabitants of the society. These ailments usually encompass advanced degeneration & neuronal loss, rendering these disorders spread and difficult to treat. There are various types of pharmaceutical approaches to treat neurological disorders. The drug loaded nanocarriers are one of them. In this review, we will address the different applications of drug loaded nanocarriers in the treatment of various neurological disorders. Moreover, integration of artificial intelligence with nanotechnology, as well as the advantages and problems of artificial intelligence in the development and optimization of nanocarriers, are also discussed, along with future perspectives. The nanocarriers developed to enhance drug delivery across the BBB, include micelles, exosomes, liposomes, nanotubes, nanoparticles, nano emulsions, dendrimers, nanogels, and quantum dots, etc. The recent developments in nanocarriers implementation through size/charge optimization and surface modifications like PEGylation, targeting delivery, and coating with surfactants have been discussed, and a detailed description of the nanoscale pharmaceutical delivery devices employed for the treatment of central nervous system disorders has also been defined. This review provides a brief overview of the variety of carriers employed for central nervous system drug and diagnostic probes delivery.

INTRODUCTION: It is estimated that as many as 1.5 billion people world-wide suffer from some type of central nervous system (CNS) disorder at any given time¹.

The real cause of neurodegenerative disease is like a mystery and still under research.

Neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS)² usually involve progressive degeneration and neuronal death, rendering these disorders diffuse and difficult to treat. The development of nano-technological systems are useful tools to deliver therapeutics and/or diagnostic probes to the brain due to Nanocarriers

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having the potential to improve the therapeutic effect of drugs and to reduce their side effects³.

The nervous system (NS) is a complex responsible for establishing the body's basic functions, also regulating and coordinating its activities; consisting of two important systems, the first is the central nervous system (CNS) comprise brain and spinal cord and is considered central processing station. The second is the peripheral nervous system (PNS) which includes all other neural elements which transmits sensory information between the muscles, tissues and nerves from the rest of the body to the brain. Neurological disorder is a term used to describe a disease of CNS; as a result of physical injury to the brain or nerves, in other words; it affects the central or peripheral nervous system⁴. The central nervous system, one of the most delicate microenvironments of the body, is protected by the blood-brain barrier (BBB) regulating its homeostasis⁵.

Brain drug delivery strategies have not been widely used because they are risky, costly and unsuitable for less localized brain diseases⁶. The strategy of blood-to-brain delivery that involves improving BBB permeability of drugs or drug-carrier conjugates under normal conditions can minimize the above-mentioned side effects⁷⁻⁸. Nano materials have been widely investigated for brain drug delivery; in this review paper, we discuss various forms of Nano materials for blood-to-brain drug delivery through the intact BBB; the mechanisms of Nano materials-mediated drug transport across the BBB; and the future directions of this innovative area of research.

The passage of molecules through BBB depends on their structure, surface properties and chemical composition, allowing only low molecular weight (< 400–500 Da) and small lipophilic molecules to enter the brain with several folds of greater competence than large molecules⁹.

The structure and function of BBB can be changed in neurodegenerative disease; the barrier function of BBB is still generally stable in the treatment neurodegenerative diseases^{10, 11}.

Prime significance to investigate different vehicles which can enhance the BBB transportability of therapeutic drugs to target area the cationic vehicle

crosses the BBB via absorption mediated transcytosis. Some examples of commonly used nanocarriers are liposomes, nanoparticle, Nano micelles and exosomes. Drug delivery using Nano carriers may increase the bioavailability and stability of drugs and decrease the peripheral toxicity¹².

Nanotechnology represents the capacity to understand, manipulate, and control the matter at the level of individual atoms and molecules¹³. Therefore, the indication of nanotechnology for the development of non-invasive drug delivery strategies could lead to the design of novel and improved formulations to enhance the delivery of therapeutic agents across the blood-brain barrier. Numerous research studies have focused on the exploration of nanotechnology-based drug delivery systems, including nanoparticle, liposomes, dendrimers, carbon nanotubes, and micelles, which have the potential to deliver the desired quantity of the drug to the brain¹⁴⁻¹⁶.

Barriers to Drug Delivery for the CNS-Disease:

The CNS permeability of a drug is determined by the drug's ability to cross the blood– brain barrier (BBB). The brain is one of the most complex and important organs of living organisms. Therefore, it is necessary to protect it against the contamination with environmental and foreign substances which could lead to changes in the inner and outer.

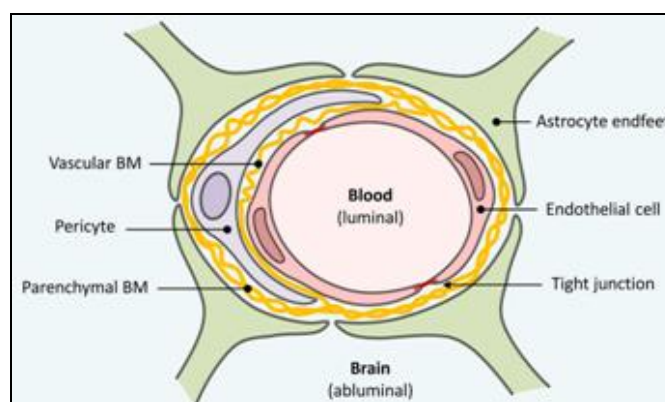


FIG. 1: SCHEMATIC DIAGRAM OF BLOOD BRAIN BARRIER

Concentrations of neuronal cells and subsequently to impairments in nerve conduction and dysfunctions in the body control processes¹⁷. The brain is a uniquely protected organ residing within the bony confines of the skull, thus making systemic delivery of drugs difficult.

Barrier layers are formed at three interfaces: blood vessels of the brain (blood brain barrier), the choroids plexus (Blood cerebrospinal fluid barrier) and the arachnoids layer of the meninges (blood–arachnoids layer)¹⁸⁻¹⁹ **Fig. 1.** The blood-brain barrier is the structure responsible for the protection of the brain, acting as a local gateway against the circulating toxins and cells through a selective permeability system. Brain capillary endothelial cells (BMEC), together with astrocytes, pericytes, neurons, and the basal lamina, constitute the neurovascular unit, the functional units of the BBB, which maintain the homeostasis of the brain microenvironment²⁰. Nanocarriers are small-size particles used for the controlled delivery of pharmaceutical agents that are encapsulated within the mentioned nanocarriers, and adsorbed or conjugated onto their surface²¹.

Nanoparticle for Drug Delivery to the Brain:

Nanoparticle for drug delivery to the brain is a method for transporting drug molecules across the Blood Brain Barrier (BBB) using nanoparticle. These drugs cross the BBB and deliver pharmaceuticals to the brain for therapeutic treatment of neurological disorders. These disorders include Parkinson's disease, Alzheimer's disease, schizophrenia, depression, and brain

tumors. Part of the difficulty in finding cures for these central nervous system (CNS) disorders is that there is yet no truly efficient delivery method for drugs to cross the BBB. Antibiotics, Anti-neoplastic agents, and a variety of CNS-active drugs, especially neuropeptides, are a few examples of molecules that cannot pass the BBB alone²² with the aid of nanoparticle delivery system; however, studies have shown that some drugs can now cross the BBB and even exhibit lower toxicity and decrease adverse effects throughout the body. Toxicity is an important concept for pharmacology because high toxicity levels in the body could be detrimental to the patient by affecting other organs and disrupting their function²³. Further, the BBB is not only the barrier for drug delivery to the brain. Other biological factors affect how drugs are transported to the body and how they target specific locations for action. Some of these pathophysiological factors include blood flow alterations, edema and increased intracranial pressure, metabolic perturbations, and altered gene expression and protein synthesis²⁴ though there exist many obstacles that make developing a robust delivery system difficult, and nanoparticle provide a promising mechanism for drug transport to the CNS.

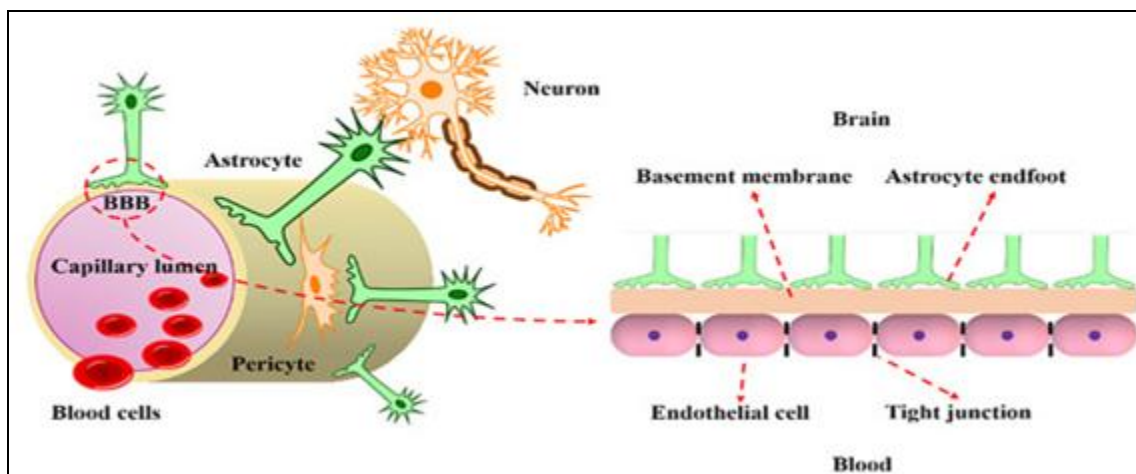


FIG. 2: CROSSING THE BLOOD BRAIN BARRIER WITH NANOPARTICLES

Nanocarriers are small-size particles used for the controlled delivery of pharmaceutical agents that are encapsulated within the mentioned nanocarriers, and adsorbed or conjugated onto their surface²⁵. Various materials may be used as nanocarriers; these includes²⁶ liposomes, micelles, polymeric and lipid-based nanoparticle, dendrimers, and carbon nanotubes. The average

size of cells in the human body is 10–20µm; thus, adsorption or uptake of the nano-sized drug–carrier conjugates by cells is possible, providing an opportunity to deliver drugs into cells. With the possibility of being surface functionalized with targeting ligands, nano carriers offer the capability of transporting drugs across the BBB dendrimers and carbon nanotubes **Fig. 2.**

Liposomes: Classic Dosage form to Penetrate BBB: Liposomes are nano-sized vesicles with an aqueous inner core enclosed by unilamellar or multilamellar phospholipids bilayers. Liposomes have been widely investigated for systemic delivery of therapeutics²⁷. Liposomes (LPs) are delivery systems with the capacity to encapsulate a large number of drugs and imaging agents. The structure of LPs allows for the delivery of a cargo loaded in the aqueous compartment or embedded in the lipid bilayers. They were the first generation of novel carriers for drug delivery²⁸. Liposomes with structure similar to cell membrane are biodegradable colloids and can be employed to carry a wide range of hydrophobic and hydrophilic

pharmaceuticals, such as small molecules peptide, proteins and RNAs, without changing their function and protecting them against degradation and potential immune responses **Fig. 3**. The glucose moiety of the ligands provided special affinity of the liposome with BBB endothelial cells, leading to an improvement of the transport rate. Doxorubicin liposomes conjugated with both foliate and transferrin also showed effectiveness in penetrating the BBB and targeting brain tumors²⁹. The brain delivery of liposomes is the low stability, as well as the difficulty of binding ligands to the surface as a result of the small number of available surface groups and steric hindrance.

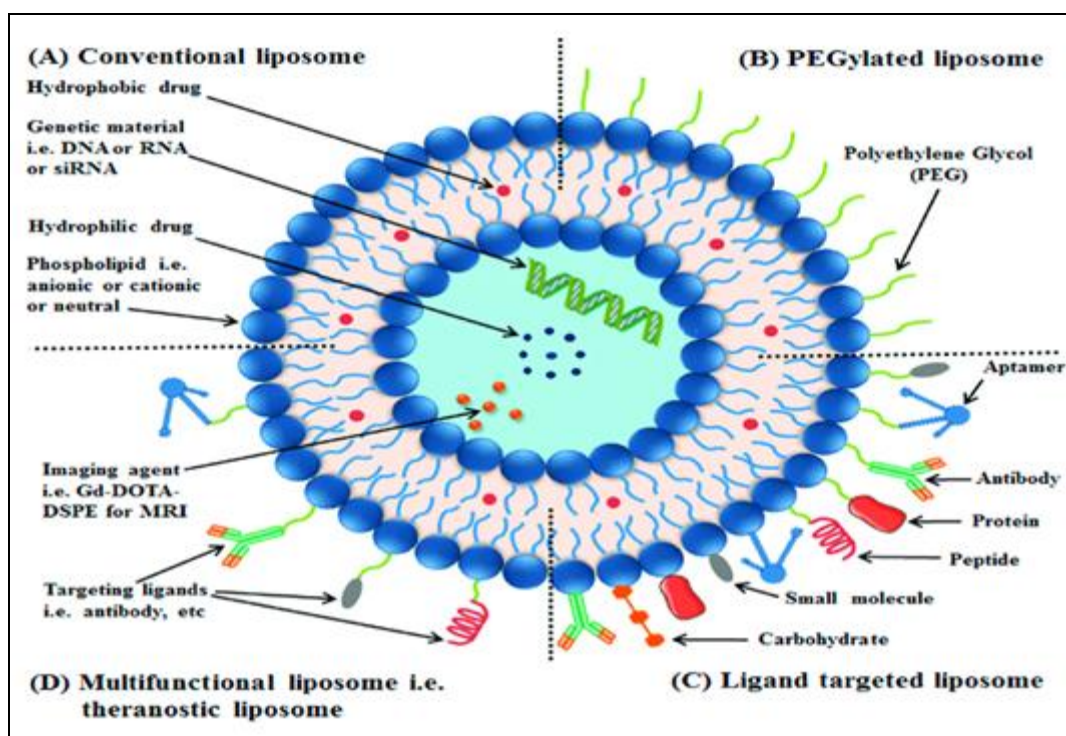


FIG. 3: LIPOSOMES: CONVENTIONAL LIPOSOMES ARE MADE OF PHOSPHOLIPIDS (A); PEGYLATED/STEALTH LIPOSOMES CONTAIN A LAYER OF POLYETHYLENE GLYCOL (PEG) AT THE SURFACE OF LIPOSOMES (B); TARGETED LIPOSOMES CONTAIN A SPECIFIC TARGETING LIGAND TO TARGET A CANCER SITE (C); AND MULTIFUNCTIONAL SUCH AS THERANOSTIC LIPOSOMES, WHICH CAN BE USED FOR DIAGNOSIS AND TREATMENT OF SOLID TUMORS (D).

There are several limitations of liposomes, including fast systemic elimination, quick metabolic degradation of the phospholipids, and stability issues after extended storage, inability to provide sustained release of drugs and moderately efficient for the entrapment of lipophilic compound³⁰. Initial studies employing very large liposomes were quite unsuccessful in transporting drugs across the BBB. When fluorescein or trepan blue were encapsulated in liposomes and injected

intravenously, they stained only the luminal side of the vasculature and not the luminal side or brain parenchyma, indicating failure of liposomes to cross the BBB³¹. After recognizing that the relatively large size of liposomes i.e., 0.2- 1.0 μm was responsible for rapid ingestion by the cells in the reticulo-endothelial system (RES), particularly in liver and spleen, liposomes were subsequently designed that were small unilamellar vesicles (SUVs), which ranged from 0.025 to 0.1 μm in

diameter³². The use of SUV liposomes was found to greatly retard the rate of clearance from blood as compared with large vesicles. Subsequently, most of the research on liposomes for the BBB delivery has focused on the use of these SUVs.

Several studies have demonstrated utility of liposomes in the BBB penetration in the treatment of cerebral ischemia. Among these studies were included encapsulation of ATP, Calpain inhibitor, antioxidants (ascorbic acid and α -tocopherol), CDP-choline, citicholine and superoxide dismutase in liposomes and their effectiveness to control ischemia induced neuronal damage when compared with free drug administration.

Transferrin Modified Liposomes: Transferrin receptors as one of receptors are of special grip for delivery therapeutic agents across BBB in order to enhance the targeting efficiency. The receptor is a trans-membrane glycoprotein with two subunits of 90kDa that are enclosed by a disulfide bridge, and each of these subunits can bind to one molecule of transferrin **Fig. 4**. However, as a target drug delivery system there are some problems about transferrin must be focused.

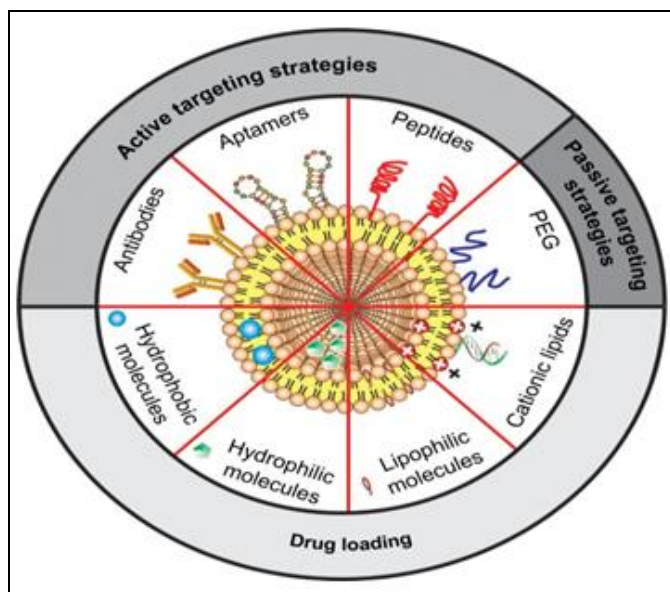


FIG. 4: PATHWAYS FOR CROSSING THE BLOOD–BRAIN BARRIER (BBB)

Transferrin is also expressed on hepatocytes, monocytes, erythrocytes, intestinal cells of choroid plexus and neurons besides BBB. Thus, Transferrin targeted liposomes also have high distributions in liver and kidneys³³. Transferrin receptor regulates the uptake of iron into the brain parenchyma.

It has been observed that transferrin functionalized fluorescein-loaded magnetic NPs (FMNs) were found located in the dendrites, synapse of neurons, cytoplasm and axons, indicating that they can effectively cross the intact BBB through transferrin.

Micelles: Polymeric micelles have emerged as candidates for brain targeting delivery. Their use as targeted delivery drugs and as diagnostic-imaging agents has gained much interest, since they have a number of physical and bio-chemical advantages over other types of nanocarriers³⁴.

Their particle size is usually within a range of 10 to 100 nm, and most of these amphiphilic polymers are biodegradable and biocompatible. Micelles serve as are excellent pharmaceutical carriers due to their ability to solubilize hydrophobic drugs, prevent drug degradation, increase their water solubility, extend their circulation time, biocompatibility, and have lower adverse side effects³⁵.

Amphiphilic surfactant molecules that spontaneously aggregate in water into a spherical vesicle consist of a shell and a core. Poloxamers, micelles made up of Pluronic block copolymers, they are the most studied micelles nanocarriers³⁶. The early drug release from the micelle nanosystem before it reaches its specific targets can be prevented by micelle fictionalizations, which increase their stability and improves their time in circulation³⁷.

Nano-particle: Nano particles are colloidal systems with compact / structure where the therapeutic agent is either entrapped within the colloid matrix or coated on the particle surface by conjugation or adsorption. The reason why nanoparticles are being widely used in treating neurodegenerative diseases is that they show following distinct characteristics:

1. Nano-particles possess relatively high drug loading and small size and deliver the active ingredient to the specific site at a controlled and sustained rate during the transportation.
2. Nano-particles, especially inorganic nano-particle, show excellent imaging performance.

These nanocarriers can be classified as polymeric or lipid-based NPs. Nanoparticle are defined as solid colloidal particles made of polymeric materials ranging in size from 1-1000nm³⁸⁻⁴⁰. They are used as drug carrier system in which the active compound is dissolved, entrapped, encapsulated and /or to which the active compound is adsorbed or attached. Examples of synthetic polymers used to prepare nanoparticles are poly (methyl methacrylate), poly (alkylcynoacrylate), acrylic copolymers, poly (D, L-lactide-co-glycoside), and poly (lactide)⁴¹. Nanoparticles have also been produced from natural proteins (albumin and gelatin) and polysaccharides (dextran, starch, and chitosan). Physicochemical studies have shown that coating of colloidal particles with block copolymers such as poloxamers and polyamines induced a steric repulsion effect, minimizing the adhesion of particles to the surface of macrophages, which in turn resulted in the decrease of phagocytes uptake and in significantly higher levels in the blood and non-RES organs including brain, intestine, and kidneys among others^{42, 43}.

Lipid-based NPs, such as solid lipid nanoparticle (SLNs), are an important class of colloidal systems in the area of modified drug delivery technology. SLNs are made from one solid lipid, while NLCs are from a mixture of spatially different lipids or from a blend of a solid lipid with a liquid lipid (oil)⁴⁴. Even if SLNs have low loading capacity for hydrophilic drugs, they are considered as very attractive nanovectors for delivering drugs to the brain, because of their low cytotoxicity and high biodegradability. They are generally made up by a hydrophobic core containing the drug, which is either dissolved or dispersed⁴⁵. SLN include widely used food lipids and waxes and commonly used emulsifiers include different kinds of poloxamers, Polysorbate, lecithin, and bile salts.

Polymeric NPs pass through the BBB by endocytosis followed by transcytosis through the BMEC lining the blood capillaries of the brain⁴. Drugs delivered to the CNS by polymeric NPs are P-gp substrates, which are actively exported from the CNS. The use of polymeric nanoparticles increases drug delivery to the brain, with reduced oxidative stress, inflammation and plaque load through the improved delivery of curcumin for treating Alzheimer's disease^{46, 47}.

Additionally, the *in-vivo* experiment regarding the co-delivery of Cisplatin and Boliden, an antioxidant agent, using the poly (lactide-co-glycolic) nanocarriers resulted in an effective target-specific delivery for therapeutic use in brain cancer therapy⁴⁸. In brief, it is possible that nanoparticle transport drugs across the BBB by any one, or combination of mechanisms.

Dendrimers: Dendrimers are versatile and highly branched structures consisting of repeating monomer units that are attached to and around a central core. Dendrimers possess exceptional structural properties such as small size, minimal polydispersity, narrow molecular weight distribution, well-defined globular shape, and a relative ease incorporation of targeting ligands, which make them attractive candidates for drug delivery⁴⁹. The surface groups of dendrimers can be conjugated with ligands for transport across the BBB, as well as for targeting specific cells such as tumor cells. Thus, dendrimers are promising tailor able delivery systems for improved delivery of drugs to the brain. The drug dendrimers conjugate showed a fast drug release profile at weak acidic condition and a stable state at physiological environment, as well as a good BBB transportation ability with the transporting ratio of 6.06% in 3h. Before, translation of Dendrimers into brain drug delivery use, it is necessary to address their biocompatibility issue. For example, PAMAM Dendrimers have been shown to be hemolytic and Cytotoxic⁵⁰. Some research results also showed that biotinylated PAMAM Dendrimers may prove to be more toxic compared to PAMAM Dendrimers alone⁵¹. One of the limitations of dendrimers is the variability of release mechanisms; drugs tend to be released before the Dendrimers can reach their target sites. Furthermore, their long-term safety profiles are relatively less established than other polymers⁵².

Exosomes New Emerging and Promising Nanocarriers: Exosomes, as one of natural endogenous nanocarriers, vary from 30nm to 150nm in size and have a typical lipid bilayers structure, which are reputed as "drifting bottle" in living body. It is secreted by a variety of cells: B cells, and T cells, Macrophages, dendrite cells⁵³. Exosomes distinguish themselves from other vehicles mainly in two features.

The one is immune privilege: as natural carrier systems with endogenous cellular tropism, exosomes can avoid the endosomal pathway and liposomal degradation, diminish clearance by the mononuclear phagocyte system, and increase drug transport to target tissue, just functions as “invisibility cloak”. Intercellular communication over vast distances makes it easier to transport proteins and nucleic acids, which are unstable medicinal agents^{54, 55}. Exosomes may represent a substantial advancement in the field of macromolecular drug delivery and may be a crucial step in the therapeutic use of SiRNA, while the use of exosomes as SiRNA vectors is still in its infancy. The cause-and-effect relationship between exosomes and pathogenesis of AD and PD is not clear enough related research is still at early stage. There are several problems waiting to be handled before they enter into clinical practice:

- (1) Exosomes are so complex in molecular constituents that safety issues and potential risk must be highlighted and evaluated comprehensively.
- (2) As brain target vehicle, it can't be overemphasized to improve the target ability of exosomes to enhance the drug concentration in brain area and avoid adverse effect. Proof of concept has been gained for exosomes-based brain drug delivery systems; several issues should be addressed before clinical evaluation such as the choice of exosomes donor cells, drug loading procedures, as well as the targeting peptides.

Quantum Dots: Quantum dots are a class of colloidal semiconductor nano crystals composed of a metalloid crystalline core (such as cadmium selenium) and an intermediate uncreative metallic shell (such as zinc sulfide) that shields the core⁵⁶. The outer coating of quantum dots can be chemically functionalized with bioactive molecules that promote aqueous solubility and desired bioactivity, enable targeting of specific molecules, as well as carrying therapeutic molecules⁵⁷.

It is widely known that the transferrin receptor is a kind of specific BBB transporter that allows selected bimolecular to move across the BBB; lysine-coated CdSe/CdS/ZnS quantum dots have

been synthesized followed by conjugation with transferrin while, Captopril-conjugated CdSe/ZnS-core/shell-typed quantum dots (QDs-cap) have been synthesized by the hot soap method with tri-n-octal phosphate oxide (TOPO) followed by the replacement of TOPO with Captopril by a thioexchange reaction. TAT, a cell membrane translocation peptide, has been successfully used to internalize nanoparticle. Research has shown that TAT-conjugated CdS/Mn/ZnS quantum dots can label the brain tissue within a few minutes after being intra-arterially delivered to a rat brain without manipulating the BBB; that type of TAT-conjugated quantum dots migrated beyond the endothelial cell line and reached the brain parenchyma. Because the same quantum dots without TAT did not label the brain tissue, TAT peptide was necessary for the quantum dots to overcome the BBB^{58, 59}.

Nano-emulsions: Nanoemulsions are heterogeneous dispersions of oil-in-water (O/W) or water-in-oil (W/O) formulations stabilized with surface-active agents, where diameter of the inner phase is reduced to nanometer length scale. For biocompatibility purpose, Nanoemulsions are usually made from edible oils, such as flaxseed oil, pine-nut oil, hemp oil, fish oil as well as safflower oil and wheat-germ oil, biocompatible surfactants such as egg phosphate dichloride which is one of the components of cell membrane lipids, deoxycholic acid, Stearylamine, dioleoyl trimethylammonium propane (DOTAP) and water. The versatility of nanoemulsions is based on the different types of oils and surface modifiers that can be used⁶⁰.

Emulsions which have droplet sizes between 5-200 nm are named as Nanoemulsions, ultrafine emulsions, submicron emulsions, translucent emulsions and mini-emulsions⁶¹. Nanoemulsions are developed systems for the delivery of biologically active agents for controlled release and drug delivery. They are promising systems for the fields of cosmetics, diagnostics, drug therapy and biotechnology⁶². Moreover, they possess great potential as a novel delivery system in food industry for fatty acids, polyphenols, natural colors, and flavors especially for producing functional foods⁶³.

Lipophilic active compounds have poor water solubility and thus introducing them into food and beverages is a big challenge for food industry. Using Nanoemulsions as a carrier system solve the solubility problem and also increase bioavailability of lipophilic active compounds such as vitamins and carotenoids ⁶⁴.

Carbon Nanotubes: Carbon-based materials such as fullerenes and nanotubes may be advantageous in biotechnological applications for the variety of properties and shapes that they offer ⁶⁵. Carbon nanotubes (CNTs) are cylindrical structures formed by graphite sheets with a diameter in the nanometer range; thus, their transport across the BBB is facilitated. It is known that this process plays a key role in the nanocarrier's toxicity. Functionalization requires a profound knowledge of the target organ and its transport mechanism ⁶⁶.

Carbon nanotubes can be single-walled or multi-walled, with open ends or closed with fullerene caps ⁶⁷. The permeation of amino-functionalized multi-walled carbon nanotubes through the blood-brain barrier has been studied in vitro, by using a co-culture model comprising primary porcine brain endothelial cells, primary rat astrocytes, and in vivo, through the systemic administration in mice. The results of the study could pave the way for

carbon nanotubes application in the delivery of drugs and biologics to the brain, causing no toxic effects on the cells ⁶⁸.

Nanogels: Nanogels are novel formulation of nanoparticles and offer the prospect of drug transport across the intact BBB. It has been reported that nanogels with surface charge exhibited better internalization property on cell membrane than neutral ones; Gil and Lowe synthesized polysaccharide-based nanogels containing poly (B-amino ester) and B-cyclodextrin for transporting doxorubicin and insulin across the BBB, such cationic nanogels enhanced the permeability of insulin across the *in-vitro* BBB model by 20% ⁶⁹. It is well established from the literature that lipophilic moieties easily penetrate the blood brain barrier in compared to hydrophilic ones; so surface functionalization towards lipophilicity of nanogels has been introduced as an accelerated encapsulated drug transport across the blood brain barrier. Azadia *et al.* prepared nano gels loaded with methotrexate (MTX) via an ionic gelation process using chitosan and sodium tripolyphosphate (TPP) as raw materials, the surfaces of the MTX-loaded nanogels were modified with polysorbate 80 to improve brain drug delivery ⁷⁰.

Challenges and Limitations of Brain Targeted Nanoparticles:

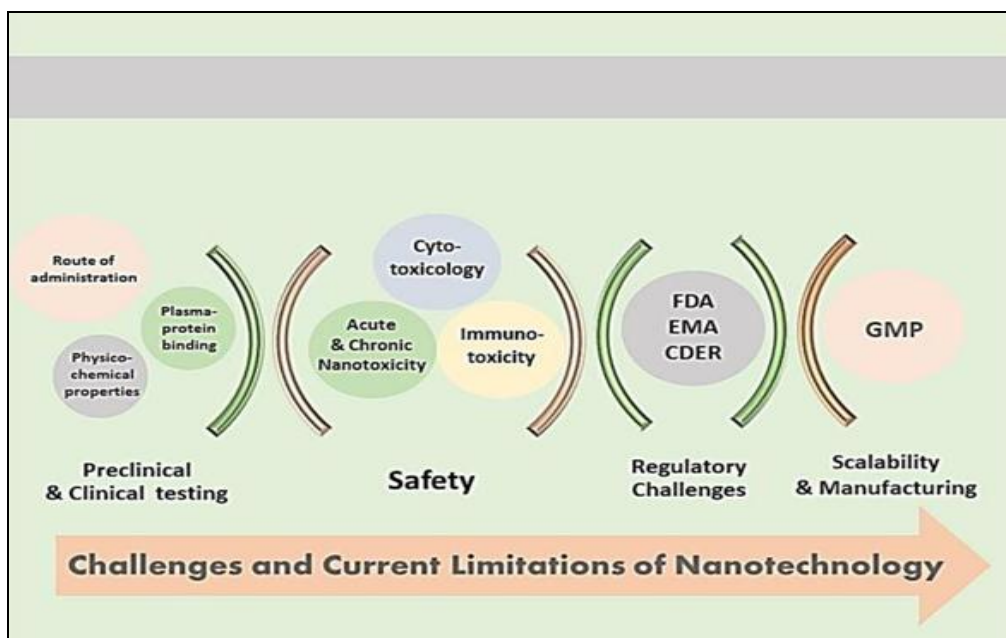


FIG. 5: PHARMACEUTICAL NANOTECHNOLOGY CHALLENGES AND CURRENT LIMITATIONS. FDA—FOOD AND DRUG ADMINISTRATION; EMA—EUROPEAN MEDICINES AGENCY; CDER—CENTER FOR DRUG EVALUATION AND RESEARCH; GMP—GOOD MANUFACTURING PRACTICES.

Even if nano-carriers are associated with various advantages like capability of transporting drugs across BBB or increased retention time in the circulatory system, their applications in a clinical scenario are restricted due to certain limitations. Foremost concern associated is the toxic effects exerted by the overexposure of nanomaterial, such as polymers. Owing to the major compositional percentage of Nano-drugs, polymers may get accumulated in the CNS due to repeated administration of Nano-carriers. It can cause both toxicity⁷¹ and immunogenicity⁷².

Therefore, rigorous regimes of experimental protocols are required to address as well curtail these problems before clinical implications. Primarily, it is indispensable to study the long-term toxicity profile of NPs in the brain, as it may limit the application of Nano-drug in clinics. Secondly, during the scaling up of the Nano-drug formulation process, from laboratory to industrial production, it is essential to maintain the encapsulation efficiency rate. The clinical efficiency of Nano-drugs may vary depending on their formulation and physicochemical properties while conjugating or en-capsulation drugs. Therefore, the formulation process optimization for large scale production is crucial for maintaining the encapsulation efficiency pace during physiological conditions. Additionally, the high cost of scaling up the Nano-drug synthesis process and the use of organic solvents during the synthesis of Nano-drugs also confines the process. Therefore, there is a need to find alternatives for producing cost effective and ecofriendly Nano materials⁷³. As another limitation, the use of pH dependent fluorescent tags (i.e. FITC) for the detection of exocytose nanoparticles may interfere with the interpretation of results⁷⁴. The use of natively fluorescent (quantum dots, Nano diamonds), luminescent (gold) and paramagnetic (ferrous oxide) can offer distinct advantages to overcome this drawback.

Integration of Artificial Intelligence (AI) with Nanotechnology:

AI in Pharmaceuticals and Drug Delivery: Lately, pharmaceuticals and drug delivery have become more and more important in the pharmaceutical industry due to the extended time, increased cost and lower productivity of recent molecular commodities. However, even existing formulation

development depends on classic trial and error experiments, which are time consuming, expensive and unpredictable. With the explosive growth of computing power and algorithms over the past decade, a new system called “computational pharmaceuticals” is integrating big data, AI and multiscale modelling approaches into pharmaceuticals, proposing significant potential change to the drug delivery paradigm. Nowadays, some actions are made to apply AI strategies to pharmaceutical product development, including pre-formulation physical and chemical properties and predicting activity, in vitro drug release, physical stability, in vivo pharmacokinetic parameters, drug distribution and in vivo–in vitro correlation⁷⁵.

In 2019, Run Han and colleagues applied machine learning methods to predict the physical stability of solid dispersion at 3 and 6 months⁷⁶. Furthermore, in 2021, Hanlu Gao and colleagues examined the dissolution behavior of solid dispersion by machine learning. A random forest algorithm was used to generate a classification model to distinguish between two types of dissolution profile, “spring-and-parachute” and “maintain supersaturation”, with an accuracy of 85%, sensitivity of 86% and specificity of 85% in 5-fold cross-validation. The random forest algorithm was employed to create a regression model to predict the time-dependent total drug release with a mean absolute error of 7.78 in 5-fold cross-validation⁷⁵.

Applications of AI in the Development and Optimization of Nanocarriers:

One current issue with drug delivery is its ability to target multiple receptors in the body, reducing the performance of a particular function⁷⁷. Nanocarriers were found to have benefits in targeting drugs to specific cells or tissues, as they can be functionalized to target disease-specific cells, thus, preventing toxicity from being triggered in healthy cells⁷⁸. Various properties of nanocarriers responsible for drug delivery are the size, shape, chemical composition and surface properties. However, preparing the optimal nanocarrier DDS is challenging⁷⁹. The optimization of the nanocarrier–drug compatibility can be aided by AI and computational approaches to evaluate drug loading, drug retention and formulation stability⁷⁸. The nanotechnology field is experiencing drastic differences in the technique

and efficiency of experiments. A large number of laboratories currently use automated systems; however, the scaling-up of nanocarriers and AI-based databases has excellent promise in translation. The objective of integrating automation and AI proposes the chance to enhance targeted therapeutic nanocarriers for specific cell types and patients⁸⁰.

Molecular modelling investigations of nanocarrier DDSs have primarily focused on (i) evaluating nanocarrier formation and conformation, (ii) evaluating nanocarrier delivery and interactions, (iii) evaluating nanocarrier surface properties and (iv) nanocarrier adsorption on different surfaces⁸¹.

There are a growing number of experimental tests to verify the properties of nanocarriers in vitro, in vivo and in disease areas. In 2020, Yuan He and colleagues used machine learning methods to predict nanocrystals⁷⁹. The 910 particle size data and 310 PDI data covered high-pressure homogenization, wet ball-milling and anti-solvent sedimentation methods. The LightGBM models showed satisfactory performance of nanocrystals created by high-pressure homogenization and wet ball-milling methods⁷⁵.

In addition, cost-effective theoretical computational techniques can assist in avoiding the demand for numerous experiments with various drug combinations. Among these theoretical techniques, molecular dynamics and Monte Carlo simulations are the most widely used. In this way, simulations can clarify quantitative measurements that are difficult to obtain experimentally⁷⁷. It is not easy to determine which nanocarrier scaffold is suitable for a particular application⁸². Additionally, each nanocarrier can be optimized to show the preferred behaviour. In this regard, developing a repository that helps researchers to identify a suitable nanocarrier scaffold and their functional groups for specific drug encapsulation and release would represent a major advance. Efforts have been made to create a database repository of nanocarriers, where scientists can obtain 3D structures and physical and chemical properties, in "Collaboratory for Structural Nanobiology"⁸³. Like the Protein Data Bank, this repository acts as a focal point to explain, organize and verify these structures, enabling correlations between the structures of

nanocarriers and their toxicological, physical, chemical and biological data. Another repository that compiles the available literature related to various categories of nanocarriers, including metallic nanocarriers, polymers or dendrimers, is called the Nanomaterial Registry. eNanoMapper is a complete database that specifically focuses on the safety information of nanomaterials⁸⁴.

AI Problems in the Development and Optimization of Nanocarriers and Pharmaceuticals: The recent evolution of AI technologies has played a vital role in the rational design and optimization of nanocarriers and pharmaceuticals. The successful application of various AI techniques has decreased development time, assured product quality and promoted successful research and development of pharmaceuticals. However, while implementing machine learning algorithms, a familiar problem is data loss. The high cost of pharmaceutical trials and long research, preparation and optimization time cause this problem since large pharmaceutical companies usually strictly save their records and data. Moreover, there is no satisfaction anymore for people with the suitable performance of machine learning models but who also hope to understand their working mechanism. Interpretable machine learning methods can provide more in-depth insights into the development of pharmaceutical formulations.

In the future, greater integration of the pharmaceutical industry and AI techniques will provide more opportunities for research and development in the pharmaceutical field. Additionally, a repository of nanocarriers in the 3D atom is still missing, which may also provide researchers with the opportunity for nanocarriers' conjugation with various functional groups. Such a repository would allow researchers to smoothly assess the appropriate scaffold for performing molecular simulations⁸⁵. Moreover, there is an urgent need for more researchers interested in handling and analysing data⁸¹.

Future Perspectives: Advances in surface technology of nanoparticles have allowed nanocarriers to engage applicants for future work involving targeted drug delivery. The utilization of nanotechnology in medicine has a great influence on human health in terms of diagnosis, prevention

and treatment of illness. Numerous nanocarriers have been authorized for clinical use, and they are currently used to diagnose and/or treat several types of cancer. Additionally, there are different formulations, which are now in different stages of clinical trials. Nanocarriers are intended to deliver drugs by different mechanisms: passive targeting, active targeting, solubilization and activated release. Nanocarriers increase therapeutic effectiveness, decrease the effective dose and decrease the danger of systemic, adverse effects. Key problems associated with the clinical development of nanocarriers were discussed, comprising biological difficulties, large-scale fabrication, biocompatibility and protection, intellectual activity, authority rules and whole cost efficiency compared to current therapies.

It is recommended to create an individualized therapeutic plan for nanomedicines, tailored according to the patient's individual genetic and illness profiles. Scientists should consider reducing the complexity of nanocarriers and consider the final dosage form for human use so that the formulation is clinically applicable for therapeutic use.

Advances in nanotechnology have produced distinct opportunities to address challenges related to immunology and vaccine development, where the various architectures of nanoparticle systems modify novel platforms for the production of highly effective vaccines.

The accumulation of nanodrugs in unwanted tissues leads to toxicity problems. Therefore, in clinical studies, consideration should be given to the determination of the biological distribution of nanoparticles after systemic administration.

Lately, nanocarriers were widely investigated in vaccines against SARS-CoV-2 (that leads to COVID-19), with several effective late-stage clinical testing. Corporations, such as Moderna and BioNTech, utilize nanocarriers to encapsulate mRNA, which encrypts for a COVID-19 allergen. Since 30 November 2020, Moderna and BioNTech/Pfizer have met their main effectiveness cut-offs in phase III clinical tests and have claimed for urgent user authorization. Recent results strongly suggest that nanomaterials have a bright

future in the field of solid tumor therapy, which has led to the emergence of the need for more rational combinations of chemotherapeutic drugs and nanocarriers.

Additionally, nano targeted radiopharmaceutical moieties must be developed to diagnose and treat cancer. Safety assessments of nanomedicine will be an important topic to be developed in the future, in addition to its potential implications for the global economy; so, special regulations of nanotechnology are warranted.

CONCLUSIONS: Nano-carriers have been widely studied as drug delivery vehicles for transporting drugs to various tissues/organs for targeted delivery. The BBB is recognized as the major obstacle to the treatment of neurological disorders, as it hinders the delivery of many potentially important therapeutic and diagnostic substances to the CNS. These Nano-systems are showing a great potential as drug carriers to the brain, thanks to many advantages associated with their use, and are becoming an alternative to the present surgical and conventional methods. However, there is a need for further optimization of Nano system design and development of CNS therapeutics with enhanced activity and improved BBB permeability. According to the various mechanisms of drug transport across BBB by Nano carriers, only penetration of drug-carrier conjugates into the brain parenchyma via transcytosis or endocytosis exhibit suitability for all types of brain drugs. Therefore, to obtain a practical delivery platform for brain drugs, it is suggested here that the development of a versatile delivery platform should focus on their capability as well as efficiency to be transcytosis or endocytosis. Lastly, to achieve the minimal effective drug concentration in brain parenchyma while the maximal safety drug concentration is not exceeded in other organs, the drug transport efficiency across the BBB by Nano carriers should be elevated. From this viewpoint, it is necessary to explore new approaches facilitating endocytosis of Nano carriers by the brain capillary endothelial cells, although, in the brain parenchyma the efficiency of drug accumulation is not only determined by drug uploading and release profile, but also by crossing BBB, which are relatively easy to be engineered.

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