Chapter 3

Nanodrug Delivery System for Brain Targeting

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Conventional drugs face limitations crossing into the brain allowing for only ideal drug candidates. These candidates should possess properties such as high lipophilicity, moderate molecular weight, charge, etc. This leaves out many other drugs and prevents entry into the brain. The brain protects itself via several barriers that limit drug entry and reduce effectiveness. These barriers include the blood-brain barrier, the blood-cerebrospinal fluid barrier, and the arachnoid barrier. These barriers reduce the efficacy of drugs in the therapy of brain-related diseases. This has necessitated the development of novel strategies such as nanodrug delivery systems, to target drugs to the brain for effective therapies. Nanodrug delivery systems such as liposomes, carbon dots, viral vectors, polymeric micelles, etc., are increasingly being tested in preclinical models and clinical trials in the management of

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brain-related diseases. So far, some successes have been recorded for diseases such as Parkinson's disease, Alzheimer's disease, Huntington's Disease, Multiple Sclerosis, etc., While nanodrug systems show promise in future applications, some limitations affect the use in clinical settings. This chapter highlights the current advances in nanodrug delivery systems and their benefits in brain targeting to enhance clinical outcomes.

3.1 Introduction

Targeted drug delivery systems have received increasing attention in the past several decades to achieve better therapeutic outcomes and reduced side effects [1]. There are numerous examples of targeted drug delivery systems undergoing clinical trials; however, clinical translation of targeted drug delivery systems is relatively slow [2]. Major efforts have been made to identify high-affinity ligands and identify nanodrug delivery system strategies, particularly for enhanced brain targeting [3–5].

Nanodrug delivery systems (NDDS) are drug delivery systems for the delivery of medications in nano sizes (1 billionth of a meter) to specific organs. These systems are encapsulated in vesicles or polymer matrices with one or more medicinal compounds [1, 2]. They provide a means of administering medications to improve drug delivery and efficacy at the targeted organ [6]. They are also used to improve drug stability and water solubility, prolong cycle time, boost target cell or tissue absorption rate, and limit enzyme degradation, hence improving drug safety and effectiveness [7–9]. They have unique properties which make them suitable for targeting drugs to specific organs such as the brain where drug uptake could present some challenges.

3.2 Physiological Barriers of the Brain to Drugs

The brain is one of the most important organs in the human body and no harm must come to it [10]. The blood-brain barrier (BBB)—a highly selective, partially permeable barrier between the brain and the rest of the body is one of the most important defense systems of the brain [11]. The blood-brain barrier has

a very strict regulation of solutes, ions and molecules that it permits into the central nervous system (CNS) and brain. This is a result of the tight junctions formed by densely packed endothelial cells and a complex efflux transporter system which actively removes molecules from the brain and the cerebrospinal fluid transporting them back into the systemic circulation [11–13]. the BBB's highly selective nature has posed a big challenge for scientists to treat CNS or brain disorders or diseases, as many of the drugs that need to reach the brain to be effective are unable to do so [14].

For decades, drug delivery to the brain in the treatment of CNS disorders has been faced with the problem of poor drug targeting. Irrespective of the development of active drugs in the therapy of diseases, efficacy may still be limited due to low drug delivery across the BBB. Endothelial cells are an integral part of the BBB structure and they are encompassed by pericytes with tight junctions in between. They utilize a high amount of ATP to maintain the structure of the barrier. Endothelial cells regulate the permeability of substances from the circulatory vasculature into the neuronal system [15]. The blood is separated from the brain parenchyma by endothelial cells that line the capillaries in the brain. The brain capillaries' endothelium monolayer serves as a vital interface for the exchange of nutrients, gases, and metabolites between blood and brain, as well as a barrier for neurotoxic plasma components and xenobiotics [16, 17]. Astrocytes enable strong attachment of endothelial cells and maintain strong tight junctions. It is the most common cellular component type in the brain and is involved in several functions such as gliotransmitter release, dopamine metabolism, glutamate uptake, etc. [17]. Pericytes are found between endothelial cells and astrocytes and very essential in maintaining homeostasis. It also enables angiogenesis and the increase of endothelial cells [17]. Besides all cellular components, the non-cellular component (the basement membrane), is a composite of four proteins, all of which help in the support and anchoring of cells. Collagen IV is essential for the maintenance of the Basement membrane, but not for its formation. The role of laminin is not well known, but nidogen, the third protein, stabilizes the network between the two former proteins. Perlecan is large in size but invaluable in embryogenesis [18]. All components of the basement membrane

work to protect the brain from the entry of exogenous compounds and regulate the movement of blood solutes across the barrier.

The BBB is not the only physiological barrier that limits brain drug delivery, another barrier is the blood-cerebrospinal fluid (CSF) barrier [19]. The choroid plexus regulates the flow of drugs via the blood to the CSF. Drug transfer via the choroid plexus and the BBB occurs via unrelated pharmacokinetics. The choroid plexus is not as tight as the BBB in limiting the entry of substances owing to the difference in the cells forming the barrier. At an inverse proportion to the drug's rate, the molecules penetrate the CSF [20]. While the drug enters the CSF much more easily than the BBB, it exits rather quickly. A drug injected into the CSF compartment travels quickly from the brain to the bloodstream like "a slow intravenous infusion". Almost all drugs enter into the CSF irrespective of the ability to cross BBB. There is minimal entry into the brain parenchyma and drugs rapidly exit into the blood.

The arachnoid barrier, which also limits the entry of drugs from the circulatory system into the brain, may be considered a part of the blood-CSF barrier. The arachnoid barrier cells form one of the three layers of the meninges covering the CNS. The meninges are made up of an outermost dura layer (adjacent to the skull) and two innermost layers (leptomeninges), which include the arachnoid mater [21]. The subarachnoid space accounts for more than 80% of the cerebrospinal fluid space thereby playing a major role in the level of drugs transported into the CSF [22]. The spinal cord and blood-spinal cord barrier are rate-limiting factors in the entry of drugs into the other part of the CNS. This barrier regulates the entry of endogenous and exogenous substances into the spinal environment [23].

These physiological barriers limit the entry of drugs for brain targeting and necessitate the use of novel methods such as nanodrug delivery systems in the treatment of central nervous disorders.

3.3 Strategies for Effective Brain Targeting

Currently, several strategies are effective for brain drug delivery. While some are invasive, others are not invasive. The reasons for

this special delivery system for the brain stem from the unique nature of the organ and the number of barrier systems in place to protect this delicate organ. The strategies that have been used are discussed in the following section.

3.3.1 Exosomes

Studies have shown exosomes to be of advantage as a useful delivery system for drugs to the brain [24, 25]. Exosomes are vesicles secreted from cells; in this case, endothelial cells are used to produce exosomes which are then used in brain targeting. Exosomes work as vesicles for the drug which can easily cross the BBB [24]. When compared to nanoparticulate drug delivery systems like liposomes and polymeric nanoparticles, using exosomes as drug delivery vehicles have several advantages [26]. Exosomes are intracellular vesicles for the natural transport of substances outside the cell, thus, can be adapted for drug delivery. Despite the potential advantages of exosomes, some issues limit its clinical applications-choice of donor cell for exosome (because exosomes can vary in composition depending on the source), further toxicity studies, etc. [24].

3.3.2 Blood Permeability Enhancers

Some compounds can enable the transport of drugs to the brain by temporarily opening the BBB. These molecules, known as permeability enhancers, are effective in overcoming the BBB and provide efficient drug targeting. In a study by Liang et al., a new glioma-targeting approach based on enhancer-modified albumin nanoparticles was created to safely and efficiently deliver medications to glioma areas in the brain [27]. Breitkreuz et al. [28] also utilized a new compound, MO1, to effect a transient increase in BBB permeability resulting in improved delivery of paclitaxel to the mouse brain leading to reduced orthotopic glioblastoma growth [28].

In recent years, ultrasound has become well known for enhancing the entry of medications across the BBB [24]. Ultrasound can improve medication administration to the brain by improving distribution via a BBB that is already impaired, such

as in tumors and by disrupting the BBB in normal brain tissue [29]. When used together with microbubbles in the brain, ultrasound can increase BBB permeability and enable drugs to easily cross the barrier. Microbubbles are micro-sized vesicles with rigidity maintained by lipids and polymers. The outer layer (shell) can be attached to different moieties, whether in diagnostic (imaging agents) or therapeutic agents (drugs) [30]. The mechanical index magnitude can affect the properties of the microbubble. It can cause to oscillate (sonoporation) or implode (sono-permeabilization). The oscillating activity (cavitation) can help open up membranes and blood vasculature [30]. Both components (ultrasound and microbubbles) affect the extent of permeability. This technique has been applied in the therapy of different diseases [30].

3.3.3 Chemical Modification

Chemical modifications such as prodrug formation involve the modification of the drug structure for it to cross the BBB, then it is metabolized to the original drug in the CNS. The use of prodrugs has been applied in the delivery of dopamine to the brain. Due to its polar nature, hydrophilic dopamine cannot cross the BBB, hence, it is administered as L-dopa which enters the CNS and is converted to dopamine [31]. The use of prodrugs is also seen in the delivery of azidothymidine to the brain via the simple formation of the ester prodrug [32, 33]. Another study utilized a prodrug ester in the transfer of ketoprofen across the BBB [34]. The formation of dimers as a prodrug has also been applied in the CNS delivery of anti-HIV drugs like abacavir [32]. The necessity for a drug to be hydrophobic enough to cross the BBB underlies the basis for the formation of prodrug forms which are often non-polar enough to cross the barrier [24]. Yue et al. (2018) experimented with the use of a dual-targeting prodrug in the delivery of Ibuprofen to the CNS [35]. Several prodrugs are currently utilizing the L-type amino acid transporter 1 (LAT-1) which is found in the BBB. LAT1 belongs to a larger family of L-transporters that help to transfer some amino acids across membranes into cells in the body [36]. The ability of LAT1 to detect specific amino acids and physiological hormones as important

endogenous substrates and several medications as exogenous substrates determine its impact on human metabolism [36].

3.3.4 Transport Systems

The use of transport systems also represents another mode of drug delivery to the brain. These transport systems are endogenous structures that physiologically transport endogenous molecules across cell membranes. It is thus exploited in the delivery of drugs as well by modifying the structures of the drugs to resemble endogenous molecules recognized by the transporters. Examples of transporters used to mediate drug transfer across the BBB include the above-mentioned LAT1, glucose transporter type 1 (GLUT 1), monocarboxylic acid transporter type 1 (MCT1), equilibrative nucleoside transporter type 1 (ENT 1), and cationic amino acid transporter 1 (CAT1) [37]. It is also possible for two or more modes of drug delivery to be combined as seen in the delivery of L-dopa in the treatment of parkinsonism which combines a prodrug to resemble an L-amino acid which is then taken up by LAT1 (prodrug + transport system) [31].

3.3.5 Direct Administration

Another method of bypassing the BBB is the direct administration of the drug into the brain. This may either be intracerebral or intracerebroventricular. The intracerebral route involves the administration of the drug through microinjection guide sleeves that are implanted stereotaxically to enable the targeted entry of the drug to a specific part of the brain [38]. The latter requires the administration of the drug via the ventricles of the brain [38]. Unlike the other systems, these methods are invasive and require special care. Intracerebroventricular administration has long been utilized for several CNS diseases such as refractory pain, infection in the brain and brain tumors [39]. The same route can be applied whether, in the treatment of meningitis, where antimicrobials are administered intracerebroventricularly, or in chemotherapy, treatment of CNS lymphoma. Some existing strategies in brain drug delivery are presented in Table 3.1.

Table 3.1 Strategies in brain drug delivery

S/N	Delivery system	Uses	Refs
1.	Direct administration (Intracerebroventricular or Intracerebral)	Administration of anti-epileptic drugs	[40]
2.	Prodrug	Administration of dopamine	[31]
3.	Prodrug	Treatment of HIV infection in the brain	[33]
4.	Prodrug transport systems (LAT1)	Administration of ketoprofen, an anti-inflammatory drug	[34]
5.	Transport system (MCT1)	Brain cancers	[41]
6.	Viral Vector delivery	Gene therapy	[42]
7.	BBB disruption (Ultrasound)	Delivery of irinotecan to the brain in an animal model	[43]
8.	Polymeric micelles	Treatment of premature ejaculation using dapoxetine	[44]
9.	Solid Lipid Nanoparticles	Administration of clozapine, an antipsychotic	[45]

3.4 Characteristics of an Ideal Drug Candidate for Effective Brain Targeting

Effective brain targeting requires essential characteristics drugs should possess. Typically, this would depend on the intended mode of transport across the BBB (exosomal delivery, transporter-mediated, viral-vectored, etc.). These characteristics would enhance adequate exposure and optimal drug delivery. Due to the nature of the BBB, an essential characteristic is its high lipophilicity, which determines the membrane transport and action binding ability [46]. Moreover, it is a parameter that determines the ability of drugs to bind to active sites and is very important for pharmacokinetics-absorption, distribution, metabolism, excretion; pharmacodynamics and toxicity properties [46]. It is measured in terms of the partition coefficient (Log *P*), which is a measure

of the distribution of the drug in the organic phase (unionized) ratio to the amount in the aqueous phase (ionized). Drugs with high lipophilicity can enter the CNS via solubilization into the lipid layer of the endothelial cells or diffusion. For an ideal drug candidate, the Log *P* value ranges between 1.5 and 2.7 [47].

Only when a drug's molecular weight is less than or substantially equal to 400–600 Da can its lipophilicity be used as a measure of BBB transit [48]. The molecular weight of an ideal drug for brain targeting entering the brain compartment via passive diffusion requires a molecular weight <400 Da or between 400–600 Da. The rate of diffusion across membranes relies on the molecule's ability. The larger the molecular weight, the more the number of hydrogen bond donor molecules and acceptor moieties and the lesser the lipophilicity and thus, the ability to diffuse across the blood-brain barrier [49]. Ideal drug candidates for brain drug delivery require high lipophilicity, small molecular weight and a low number of hydrogen bonds (<8) [50].

The charge is another essential requirement for crossing the BBB. The cell membrane of the BBB is negatively charged and the use of an equally negatively charged compound may create a form of repulsion and limit diffusion. Polymers, cationic lipids, albumin, and nanoparticles are examples of positively charged materials that can interact with the negatively charged cell membrane and internalize via adsorptive endocytosis [51]. Carrier-mediated drug delivery requires essential properties such as the high affinity of the drug for the cell transporter [52]. Transporters recognize endogenous molecules, hence the need to enable drugs to acquire similar properties to enhance affinity. In some cases, the formation of a prodrug is necessitated. An ideal drug candidate should be able to revert to its active state on entering the brain compartment and retain activity. For nanomedicines, properly understanding the pharmacokinetics, toxicity, and distribution properties of drugs and conjugates is essential in enhancing the clinical application of medicines for brain drug targeting [53]. The key characteristics of ideal drug candidates for brain targeting are shown in Fig. 3.1.

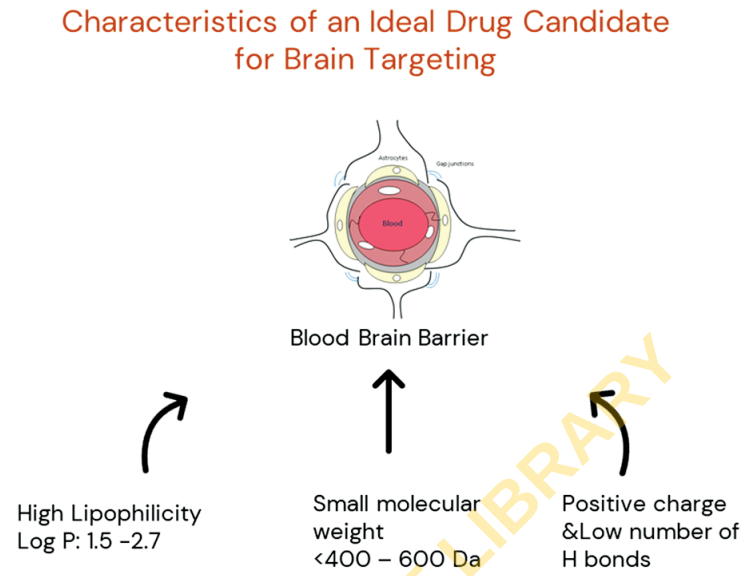

Figure 3.1 Key characteristics of ideal drug candidates for brain targeting [53].

3.5 Nanodrug Delivery System Strategies for Enhanced Brain Targeting

Different strategies have been employed for the formulation of nanodrug delivery systems to enhance drug delivery to the brain. These strategies include the following:

3.5.1 Micelles

Micelles are uni-layered amphiphilic nanocarriers that allow the controlled release of encapsulated drugs [10, 54, 55] They are characterized by their unique spherical shape, with the hydrophobic part(s) set apart from the hydrophilic part(s), which leads to the formation of an inner hydrophobic core surrounded by external hydrophilic terminals [11]. Their stability in physiological environments is a result of their amphiphilic nature, which results in long circulation times, providing them with sufficient time to reach the target tissue [56].

Despite the long systemic circulation, they have poor cellular binding and uptake [57]. Due to their amphiphilic nature, both lipophilic and hydrophilic drugs can be loaded into micellar DDSs. However, micellar drug delivery systems possess low drug loading capacities compared to other systems. In a study by Yin et al., doxorubicin-loaded poly(lactic-glycolic) acidlysoGM1 micelles was developed with an encapsulation efficiency of about 61%. These micelles easily crossed the BBB and accumulate inside the brain parenchyma of mice and zebrafish used in the in vivo studies through micropinocytosis and lysosomal pathways [10, 55].

Amphiphilic block copolymers generate nano-sized encapsulating structures known as polymeric micelles. The formation of micelles is based on the ability of these block copolymers to aggregate/coalesce into a larger spherical vesicle when present in an aqueous solvent [58]. Micelles can vary based on the forming polymers. While some of these polymers are largely hydrophobic, others are more hydrophilic. Polyethylene oxide, for example, contains hydrophilic blocks while poly propylene oxide contains hydrophobic blocks. A combination of these two creates a highly useful polymeric micelle in the solubilization of drugs [59]. Polymeric micelles are particularly well suited for drug administration because of their inherent and adjustable characteristics [60]. They are commonly characterized by a hydrophilic, water-loving coating known as the 'corona' with an inner lipophilic or hydrophobic 'core' [61] due to the amphiphilic nature of forming copolymers. Polymeric micelles provide useful advantages due to their unique properties of solubility, low toxicity, compatibility with biological systems, structure, arrangement, etc., hence their diverse use in various treatment applications [62]. They are also uniquely target-specific. The interesting nature of the micelle enables it to protect the coated drug from degradation, and enhance its solubility, particularly for poorly soluble drugs [62]. In the treatment of brain diseases, micelles are useful in the delivery of anti-cancer drugs. Polyethylene glycol (PEG micelles) help deliver drugs such as doxorubicin and camptothecin, which were found to be effective in the treatment of glioblastoma. Its applications are not limited only to brain drug targeting, but to other organs as well due to its target specificity and

bioavailability. An advanced application of micelles in drug delivery is the ultrasound micelle drug delivery, which is a form of augmentation that utilizes ultrasound waves in stimulating the release of drugs from the micelles [58]. Interestingly, this modification involves the use of ultrasound which is comprised of waves that are transmitted through the skin without any need for invasive procedures or surgery, and rupture or stimulate the release of drug-containing micelles in specific locations of the body, minimizing avoidable side effects [58].

3.5.2 Liposomes

Liposomal drug delivery is a major means of overcoming restrictions of BBB transport. It has been shown that liposome surface modifications can improve the circulation time in blood, the therapeutic index, and the bioavailability, as well as change the drug distribution to the brain [63]. Liposomes are composed of phospholipids and cholesterol formed into small spherical-shaped vesicles consisting of one or more phospholipid bilayers that can hold various therapeutic molecules including drugs, vaccines, nucleic acids, and proteins [10]. In general, the components of the liposomes make them biologically inert, non-immunogenic, and biodegradable, with low inherent toxicity [64]. Liposomes can be used as carriers for biologically active compounds and have been widely used as a drug delivery system (DDS) to improve drug efficacy and eliminate drug-related toxicity or unwanted effects [65–67]. Even though liposomes have lipophilic characteristics, they are very large and cannot simply diffuse across cell membranes or between BBB cells [68]. Instead, liposomes cross the BBB via transport systems, such as adsorptive-mediated transcytosis (AMT), receptor-mediated transcytosis (RMT), and carrier-mediated transcytosis (CMTs) [69, 70] To efficiently cross the BBB, instead of using conventional liposomes, further surface modification is possible. This includes cationic liposomes, specifically targeted liposomes and long-circulating liposomes; to which immunoliposomes belong (see Table 3.2). Liposome-based strategies can be classified as physiological since the liposome adds physiological interactions to that of the drug on its own, whereby it influences drug distribution characteristics [63].

Table 3.2 Types of liposomes [63]

Liposome type	Description
Conventional liposome	Entraps hydrophilic compounds such as small molecules or biological-based compounds in the liposome's core and lipophilic compounds in the phospholipid bilayer membrane Compounds are stabilized thus avoiding early degradation in the systemic circulation
Non-specific targeted liposome	
Cationic liposome	Increases drug transport across the BBB by maximizing liposome-endothelial tissue retention while lipid surface can facilitate adsorption of polyanions, such as DNA and RNA
Anionic liposome	Monocyte can bind to anionic liposome and facilitates drug transport across the BBB via the mononuclear cell migration pathway
Cationic PEGylated liposome	Enhances the brain uptake by increasing plasma concentration and tissue retention
Specifically targeted liposome	Polyethylene glycol (PEG) acts as a shield to protect liposomes from plasma protein binding or RES uptake. Thus, it increases plasma concentration. However, PEGylation is only able to prolong liposome circulation without improving BBB penetration
Long-circulating liposome	Achieved by conjugating liposome or PEGylated liposome to single functional ligand or multiple ligands to facilitate a specific binding to the BBB surface receptors or carrier proteins Targeted delivery leverages the delivery efficiency of liposomes to the brain, and improves the therapeutic index by increasing target site drug accumulation while decreasing peripheral toxicity. This opens a possibility for reducing dose or dosing frequency Targeted ligands can be antibodies, cell-penetrating peptides, or endogenous molecules, e.g., transferrin, GSH, ApoE, and lactoferrin

3.5.2.1 Immunoliposomes

Immunoliposomes; antibody-directed liposomes have been recognized as a promising tool for the site-specific delivery of drugs and diagnostic agents [71]. However, the in vivo use of classical

immunoliposomes is hampered by the very rapid clearance of immunoliposomes from the circulation by the reticuloendothelial system [72]. This obstacle can be avoided if gangliosides or PEG-derivatized lipids are inserted within the bilayer of the conventional liposomes, as these modifications will prolong considerably the liposome half-life in circulation [71, 73, 74]. In a study by Huwyler et al., [71] immunoliposomes were used to target an encapsulated drug, daunomycin, to the rat brain in vivo. This was achieved using vector-mediated drug delivery systems, which have been previously used for peptides or peptide nucleic acids [75] to apply small molecule drug delivery to the brain. Thus, micromolar drug concentrations in the brain were achieved using BBB drug delivery vectors with increased carrying capacity by logarithmic orders. As micromolar concentrations of many small drug molecules in the brain are required for pharmacological activity. This was possible with the use of PEG-conjugated immunoliposomes and monoclonal antibodies that target the brain and BBB receptors [71].

3.5.3 Dendrimers

Dendrimers are highly branched spherical polymers that are now used as drug delivery systems due to the ease with which they can be produced and modified compared to other nanotechnology-based drug delivery systems and their size. Dendrimers are sometimes referred to as "starburst" polymers as a result of their branching. They are made up of three main, distinct components; an initiator core, to which interior layers (i.e., generations) of repeating subunits (dendrons) are radially linked, and the terminals, where the functionalization (such as the linking of bioconjugates such as proteins or antibodies onto the dendrimer surface), as well as drug loading, takes place [76–79].

One of the most studied classes of dendrimers used in the delivery of therapeutics to the brain are the polyamidoamine dendrimers, which have an ethylenediamine ($C_2H_4(NH_2)_2$) core, amide (RC(=O)NR0R00) branches (where R, R0 and R00 are organic groups or hydrogen atoms) forming the walls of cavities and amino ($–NH_2$), hydroxyl (–OH), or carboxylic acid (–COOH) functional groups as terminals [80, 81]. These dendrimers are

small, highly stable, highly water-soluble, and functional groups can easily be attached to them, making them very suitable for the delivery of therapeutics [82]. The amino-terminated variants of polyamidoamine dendrimers are the most popular in pharmaceutical research owing to their ease of bioconjugation using a variety of protein and/or peptide ligands [11]. Through the use of chemical linkages or encapsulation, drugs can be conjugated to the amino terminals of polyamidoamine dendrimers [80]. Drug delivery systems based on Dendrimers can use any among the transport system at the BBB to travel across it due to the significant variation in size and other physical characteristics of dendrimers [81].

3.5.4 Polymeric Nanoparticles

Polymeric nanoparticles are solid, colloidal particles formed by polymers in which drugs can be dissolved, adsorbed, or encapsulated [83, 84]. They have gone forward to be one of the most successful candidates for drug delivery systems owing 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 [10, 85]. Similarly to other solid nanoparticulate drug delivery systems, polymeric nanoparticles can be used for the active or passive targeting of drugs to different tissues as a result of their high functional ability, exhibiting a broad range of physicochemical and biochemical characteristics [77]. The different types of polymeric nanoparticulate drug carrier systems are discussed below:

3.5.4.1 PLGA nanoparticles

Currently, attention is being paid to PLGA nanoparticles as potential nanocarriers of drugs across the BBB owing to their high biocompatibility, biodegradability and functional ability [86, 87]. This is because the hydrolysis products of PLGA; lactic acid (LA) and glycolic acid (GA) in aqueous environments are easily metabolized and eliminated from the body through the Krebs cycle

[87]. PLGA nanoparticles on their own do not have a sufficiently long half-life after IV administration however, this can be significantly prolonged by using the polymer's highly modifiable end-group [87, 88]. PLGA has a poor uptake by cells due to its negative surface charge thus, it does not readily cross the BBB. These problems can be solved through the use of crosslinkers, surface adsorption and end-group modifications [87, 89].

Barbara et al. [90] showed that PLGA nanoparticles loaded with curcumin and decorated with the glycopeptide "g7" significantly reduced b-amyloid aggregation, which is a significant indicator of Alzheimer's disease [90] while Wang et al. [91] showed increased accumulation of trimethylated chitosan conjugated PLGA nanoparticles (TMC-PLGA NPs) in the periventricular region of the cortex and the third ventricle of the brain with negligible cytotoxicity using an in vivo model. The researchers believe adsorptive-mediated transcytosis to be responsible for TMC-PLGA NPs' ability to cross the BBB [91].

3.5.4.2 PEG nanoparticles

PEG like PLGA has low toxicity levels in the body, is biocompatible, though not biodegradable, is easily eliminated from the body by the kidneys, and is a highly modifiable polymer for drug delivery [92]. Thus, PEG is a commonly used polymer in several pharmaceutical applications, including nanomedicine [86]. Covalently linking PEG onto another molecule (i.e., polymer, NP, drug, protein, antibody, etc.), is known as PEGylation. It is a common technique used for the conferring of function on several nanoparticulate drug carriers. An example of such an FDA approved drug is doxorubicin (used in the treatment of ovarian cancer, breast cancer, multiple myeloma and Kaposi's sarcoma) sold under the brand name DOXIL® (in the US) by Tibotec Therapeutics—a division of Ortho Biotech Products in New Jersey, USA [93, 94].

3.5.4.3 Copolymer nanoparticles

Copolymers are polymers made from more than one single type of monomer. The surface modification to PLGA NPs by PEGylation of drug-loaded PLGA nanoparticles (PEG-PLGA NPs) for brain drug

delivery is an effective technique as the nanoparticles possess noticeably improved BBB permeating properties [86, 95]. Jeong et al. [96] first synthesized the triblock copolymer PLGA–PEG–PLGA (PEP), which has exhibited a considerable increase in the delivery of encapsulated drugs to the brain in a study conducted by Chen et al. [97].

3.5.5 Nanoemulsion

These are nano-sized (<200 nm) heterogeneous dispersions of water-in-oil or oil-in-water stabilized using a suitable emulsifier [98, 99]. They are appropriate for the delivery of both the hydrophilic and lipophilic drugs and their permeation through the BBB via receptor-mediated transcytosis (RMT) is facilitated by surface functionalization with suitable ligands. Nanoemulsions are commonly made of vegetable or animal oils, e.g., peanut oil, flaxseed oil, sunflower oil, hemp oil, wheat germ oil, fish oil, egg phosphatidylcholine, etc., making them highly compatible with biological membranes. Stability issues, however, limit its application [100].

Recent studies have shown the use of nanoemulsions for direct nose-to-brain delivery of drugs as well as drug delivery through the parenteral route [101]. Ling Tan et al. [102] used parenteral nanoemulsion for brain targeting of carbamazepine to treat seizures and evaluated its pharmacokinetic efficiency. The study revealed a higher pharmacokinetic profile and lower side effects of the drug when delivered as nanoemulsion than when delivered as the free drug solution [102]. In another study, Abdou et al. [103] assessed the brain targeting efficiency of encapsulated zolmitriptan; an anti-migraine agent nanoemulsion as a mucoadhesive and delivered it via the intranasal route. They found that the mucoadhesive intranasal nanoemulsion significantly enhanced the drug permeability, AUC and bio-availability in the brain [103].

3.5.6 Viral Vectors

Viruses are known to replicate by attacking their host to introduce their genetic material into the host cell [11]. This genetic

material is composed of instructions to produce more viruses. Thus, viruses end up taking over the host cell completely to fulfil their own needs with eventual taking over of more host cells [104, 105]. The genetic material that guides the replication of viruses can be substituted with instructions that would be beneficial for the host, such as instructions to attack, poison and destroy cancerous cells. In essence, viral vectors can be used to deliver specific genes to treat or prevent diseases through gene therapy [106, 107]. In addition to gene therapy, viral vectors have recently been used as drug carriers, in which the drugs are encapsulated or infused with a vector that can be functionalized for targeted delivery [11]. Viral vectors compared to other drug delivery systems in gene transduction to the brain have about 80% transfection efficiency and long-term expression of transgenes within the non-dividing cells [10]. Lentivirus, herpes simplex virus (HSV), adenovirus (AdV) and adeno-associated virus (AAV) are examples of the viral vectors that have been used to achieve drug delivery into the brain [10]. Viral vectors as drug delivery systems, however, still have issues linked to the high cost of production and their safety, as the administration of viruses carries a certain level of risk [24, 108, 109].

3.5.7 Carbon Nanotubes

Carbon nanotubes (CNTs) are nanoscaled cylinders of graphene sheets, which have become a promising nanocarrier system for therapeutic agents in many brain-specific therapies [10]. The potential activity of CNTs is due to their ability to undergo surface functionalization easily with specific chemical compounds, which leads to the variation in their physical and biological properties [101, 110]. Polymer-coated carbon nanodots and chemically functionalized multiwalled carbon nanotubes (MWCNTs) can easily bypass the BBB and also form an interface with neurons based on several in vitro and in vivo models experiments. Thus resulting in enhanced uptake of CNTs at the site of a tumor [101, 110]. The limitations associated with CNTs include toxicity, high cost of production, no control over CNT length and chirality, batch-to-batch variation, and polydispersity in CNT type.

3.5.8 Carbon Dots (CDs)

These are a new class of zero-dimensional carbonaceous nanomaterials. Compared to traditional inorganic quantum dots or noble metal nanoclusters, CDs display improved properties thus, making them promising luminescent nanocarriers and probes [10]. One of the most fascinating characteristics of CDs is their fully color-tunable fluorescent from the blue to the near-infrared regions and the ease of surface modification for targeted delivery. CDs are mostly used in the biomedical field due to their physical and optical properties that included feasible fluorescence, adjustable stability, and water solubility. These made them powerful tools for use in chemo- or biosensing based on their tunable luminescence properties. The synthesis of CDs is cost-effective. While CDs have good biocompatibility and low toxicity, their limitations include photobleaching, instability, particle-particle aggregation, creation of a nonhomogeneous mixture, inability to be stored for very long, and size-induced toxicity; sizes <5 nm showed more toxic effects than sizes > 10 nm [111].

3.5.9 Carbon Nano-Onions (CNOs)

These onion-like carbonaceous zero-dimensional nanostructures are synthesized by thermal annealing of nanodiamonds at very high temperatures and pressure in an inert atmosphere [112, 113]. They are composed of an average of six to eight graphitic shells with sizes ranging between 5 to 6 nm and the distance between two graphitic layers being 0.335 nm. They appear to be suitable candidates for biomedical applications due to their unique electronic and structural features, which include a broad absorption band, a large surface area to volume ratio, the ability to reversibly accept multiple electrons, biocompatibility, and thermal stability [114]. Limitations to their use include poor dispersibility of CNOs in aqueous solution due to their hydrophobic nature resulting in bioaccumulation and hence the toxicity of these nanocarriers, batch-to-batch variation due to the method of synthesis, and difficulty to easily bypass the BBB due to their high molecular weight, which could lead to disruption of the integrity of the

BBB [114]. As a result of the poor solubility of CNOs, surface functionalization is carried out to avoid aggregation in organic and inorganic solvents due to intermolecular interactions such as van der Waals forces between the original nanostructures.

3.6 Mechanisms of Nanodrug Release

Nanodrug delivery systems are considered not only for the ability to convey drugs to the target site but also for the ability to release the drugs. There are a variety of mechanisms of drug release from different nanodrug delivery systems. Ensuring that polymers or composite materials or any form of nanocoating are easily degradable in the active site is essential for activity. Maintaining favorable release kinetics is highly paramount for overall drug efficacy. For liposomes, drugs are released after the dissolution of the lipid layers [115]. This occurs when the cellular membrane lipids fuse with the lipophilic layers of the liposome, releasing drug contents [116]. Polymeric micelles release drugs via a diffusion mechanism of the drug and the rate at which the polymer is depolymerized [117]. Common mechanisms that underlie the different nanocarrier systems include diffusion, disintegration, dissolution, stimuli-controlled release and chemical interaction [118]. The stimuli-controlled release mechanism is observed in ultrasound micelle drug delivery. In this mechanism, an ultrasound device is used to stimulate the rupture of polymeric micelles in target tissues. This form of controlled release utilizes pressure waves. Other types of stimuli include temperature, pH gradient, etc., some of which are internal stimuli. This way, enhanced target specificity is achieved via the external or internally stimulated drug release mechanism [58]. The diffusion mechanism is usually observed in polymeric-encapsulated drugs in which drug dissolution first occurs within the capsule before it diffuses across the polymer nanocapsule into the target site [118]. For drugs with matrix-type nano-enclosure, there is no polymeric barrier hence the initial fast release of drugs is observed [118].

Some types of dendrimers release drugs via a degradation mechanism by which the polymers are degraded enzymatically or hydrolytically in vivo at the target site. Polymers such as polylactic

acid (PLA) are bulk degraded, while in cases, where water entry into the matrix occurs much slower than the rate of degradation, surface erosion is typically observed [118]. In some cases, special drug release mechanisms are employed via surface changes. This is observed in liposomes adapted into pH-sensitive liposomes to trigger release in the acidic or basic medium of tissue [119] or with magnetic resonance imaging [120]. For polymeric micelles, the rate of drug release can be determined by the hydrophobicity and molecular weight of copolymers [118]. Some polymers show responses to heat and ultrasound as well.

3.7 Applications of Nanodrug Delivery Systems in Brain-Related Disorders

Nanodrug delivery systems are increasingly applied in the treatment of brain-related disorders, enhancing outcomes and improving the quality of life. There is a wide range of brain-related disorders affecting different parts of the brain resulting in different signs and symptoms. Examples of these include Parkinson's disease, Alzheimer's disease, Amyotrophic lateral sclerosis/multiple sclerosis, Huntington's disease, frontotemporal dementia, prion diseases, and; brain tumors, epilepsy, stroke, HIV encephalopathy, etc.

3.7.1 Parkinson's Disease

Parkinson's disease is a neurodegenerative disease evident by the following symptoms: tremors, rigidity, akinesia and postural instability resulting from the loss of dopaminergic neurons in the nigrostriatal region [121]. While it is inheritable, studies have shown that it may be caused by a combination of genetic and environmental factors. Commonly used drugs in the management of Parkinson's include dopamine agonists such as ropinirole, pramipexole; levodopa, and monoamine oxidase-B inhibitors such as rasagiline, and selegiline. While these treatments have been effective in improving symptoms, novel nano delivery systems help with new treatments and modifying disease therapies. In preclinical studies, the use of liposomes in loading dopamine

into the brain has been tested [122]. For sustained release, polymeric nanoparticles have also been tested for other drugs such as ropinirole, apomorphine, selegiline, etc. [123]. Poly ethylene glycol attached to nanoparticles can be used to increase retention time and reduce the clearance of these drugs [123].

Nanoparticles in Parkinson's disease have useful advantages not only in increasing retention time but also in cell targeting, triggered release, anti-aggregation, etc. For instance, phenylboronic acid can be used to modify nanoparticles for the triggered release of apomorphine [123, 124]. This helps to prevent unwanted side effects by enabling release only in selective environments. Nanoparticles may sometimes have useful therapeutic effects, such as gold nanoparticles, which have shown protective effects in clinical trials for patients with Parkinson's [123, 125].

3.7.2 Alzheimer's Disease

Alzheimer's disease (AD) is a progressive disease in which the brain cells undergo atrophy and die. This leads to symptoms such as loss of memory, difficulty performing tasks, and inability to cater for oneself, then eventually leads to death. It is characterized by the presence of abnormal protein build-up in the brain and it is accountable for the majority of dementia around the world. In preclinical models, polymeric nanoparticles coupled with poly ethylene glycol have been tested in the management of AD [126]. A study was undertaken in which memantine was loaded into biodegradable polymeric NPs generated by the double emulsion process to improve the efficacy of memantine against AD. Targeting the AD brain with memantine-loaded NPs can reduce Aβ plaques and AD-related inflammation significantly [127]. Zinc-loaded polymeric nanoparticles tested in animal models in the management of AD showed sustained effect and target specificity [126]. Nanogels containing deferoxamine have also been found useful in the management of Alzheimer's disease [128].

3.7.3 Huntington's Disease

Huntington's disease (HD) is a rare disease in which the brain's nerve cells continue to degenerate and this usually affects cognition,

functional abilities, and locomotion, and may also cause psychiatric disorders. Symptoms usually appear in middle age after a person has had children, however, the disease can appear during any period between childhood and senescence [129]. Huntington is found in all human and mammalian cells, with the largest quantities found in the brain and testes; modest amounts can also be found in the liver, heart, and lungs [130]. The function of the wild-type protein, as well as the pathophysiology of Huntington's disease, are yet unknown. Common drugs used to control the jerking include tetrabenazine and deutetrabenazine. In the management of Huntington's disease, intranasal administration of chitosan nanoparticles loaded with siRNA was found effective in lowering Huntington's disease gene expression [131]. To replenish selenium levels associated with HD, selenium nanoparticles were also tested in preclinical models to regulate cognitive decline [132].

3.7.4 Brain Tumors

Brain tumors and cancers are a group of related disorders characterized by the abnormal proliferation of cells without regulated apoptosis. Brain cancers are more complicated because of difficulty inaccessibility, hence the need for novel systems such as nanodrug delivery systems. A wide variety of nanosystems have been tested for selectivity, ability to cross BBB, enhance retention time, etc. Based on evidence that nanoparticles can accumulate in tissue sites with tumors, they can be used to treat intracranial tumors [133]. Polymeric nanoparticles made from polymers such as poly (D,L-lactide-co-glycolide) are approved for use in clinical applications. The hydrophobic shell of polymeric micelles also serves as a useful means of encapsulating anti-cancer drugs such as platinum [134]. Nanoliposomes are also useful in enhancing the cytotoxicity of anti-cancer drugs in tumors such as glioblastoma [134].

3.7.5 HIV Encephalopathy

HIV encephalopathy is an HIV complication which occurs when the virus reaches the CNS resulting in mental symptoms and disorders. The emergence of nanomedicine may be used to

manage this disease through nano-ARTs. A variety of nanoparticles have been tested and these include gold nanoparticles, silver nanoparticles, etc. The inhibition of CCR5 by TAK-779, an effective agent by conjugation of gold nanoparticles with a fragment is an example [135]. Silver nanoparticles were also found to be effective against the virus in vitro [135].

3.8 Nanodrug Delivery Systems at the Clinical Trials Stage

Nanodrugs have been tested in various animal models under preclinical settings. Now, they are increasingly being tested in humans at different phases of clinical trials. Some of the nanodrug delivery systems at the clinical trials stage are shown in Table 3.3.

Despite the great advantages of nanodrug delivery systems, nanoneurotherapeutics still possess certain limitations that hamper their full implementation in clinical settings. One limitation is that as the size of the particles reduces to the nanoscale, certain physicochemical properties changes, which may result in unintended effects.

Table 3.3 Nanodrug delivery systems at the clinical trials stage

Nanodrugs	Disease/condition	Phase of clinical trials	Year
AGuIX nanoparticles with radiotherapy plus concomitant temozolomide	Glioblastoma	Phase I/II	[136]
Novel nanosensor array	Multiple Sclerosis	Diagnostic	[137]
NA-NOSE artificial olfactory system	Multiple Sclerosis	Diagnostic	[138]
Nano-sized gadolinium particles	Brain tumor	Phase I	[139]

Nanoparticles have larger surface areas and hence tend to become sticky with each other. The increased surface area of nanoparticles as a result of their smaller size causes an increase in chemical reactivity, which may impact how these nano-sized particles will react under different conditions and in the presence

of cell membranes [140]. This may lead to the production of reactive species that may cause oxidative damage and cause toxicity. In addition, unpredicted effects may occur when they cross other membranes and barriers besides the blood-brain barrier. Nanoparticles may also cause damage to the lungs, although unclear [140]. Gold nanorods have been reported to be cytotoxic due to the formulation.

The other major factor that may hinder the progress in the use of nanomedicines is ethical concerns. Risk assessment, risk management, and risk communication in clinical trials are currently the most important ethical challenges in nanomedicine. To win and sustain public support, it is critical to educate members of society on the benefits and risks of nanomedicine [141].

3.9 Future Research Direction/Development

Nanotherapeutics hold unlimited potential in the management and treatment of diseases, especially for CNS disorders such as Alzheimer's disease, Parkinson's, mania, depression, schizophrenia, brain tumors, cancer, etc. The field is dynamic and rapidly evolving with researchers all over the world inventing and discovering new liposomes, nanoparticles, extracellular vesicles, and medical devices to improve drug delivery to the brain [142]. Future research points in the direction of fully elucidating the unique properties of nanomedicines and the influence of nanosize on the behavior of molecules. Numerous in vitro models would be required to ascertain this to suggest the direction for regulatory understanding. Evaluation of compounds on a nanoscale and their impact on biological processes points the arrow for new research.

Many more developments will likely spring up in the nanodrug delivery system for brain drug targeting in the coming years. Overcoming significant challenges in some systems like exosomes, for example, could be alleviated with artificial exosomes that do not precipitate host immune reactions in the patients. Achieving precision in cell targeting could provide a gainful step in transformative systems in brain drug delivery. Nano-based drugs are yet to be fully implemented in clinical settings suggesting the need for more studies [142, 143]. While the permeation

of the BBB is the priority for nanosystems, protection from neurotoxicity is important. More data is needed on the toxicity profile of nanodrug delivery systems to ensure safety and suitability [142].

Nanomedicine is indeed exciting and provides a unique way of solving formulation and delivery problems. Brain drug targeting is much more desirable since it eliminates the need for invasive delivery processes. In the future, more research may also be directed towards personalized treatments-pharmacogenomics. Pharmacogenomics ignores a 'one-size-fits-all' approach, studies the individual response to drugs based on expressed genes, and provides care to the patient uniquely. With a unique combination of a nano approach in this field, particularly in cancer treatment where it has achieved significant results, enhanced decisions can be made in enabling optimal outcomes [144].

It is conceivable that nanodrug delivery systems will be largely optimized across the management of an array of brain diseases following increased profile studies, characterization, and pharmacokinetic analyses. Increasing industrial acceptability and reducing manufacturing costs are largely key to facilitating availability and use, and application in clinical settings.

3.10 Conclusion

The applications of nanomedicine in brain targeting are immense and extremely useful in the treatment of brain diseases. Whether glioblastoma, multiple sclerosis, Parkinson's, Alzheimer's or any other disease, existing drugs can be modified to improve delivery, enhance retention and reduce clearance, and new drugs can be formulated in nano delivery systems to improve therapeutic outcomes. Future research may further help eliminate limitations and improve their application in clinical settings.

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Multiple Choice Questions

1. Which one of the following is a nanodrug delivery system?

   A. Tablets
   B. Capsules
   C. Liposomes
   D. Syrups

2. _____ are spherical colloidal structures that possess an outer lipid bilayer.
   A. Liposomes
   B. Dendrimers
   C. Micelles
   D. Capsules

3. The surface of Liposomes can be modified with _____ to increase retention time in circulation.
   A. Ethylenediamine
   B. Poly ethylene glycol
   C. Poly propylene glycol
   D. Micelles

4. _____ is a dynamic structure that regulates the entry of substances into the brain and exit out of, and is key to maintaining its homeostasis.
   A. Cell membrane
   B. Blood-Brain Barrier
   C. Skull
   D. Blood

5. One of the following is not part of the blood-brain barrier?
   A. Endothelial cells
   B. Astrocytes
   C. Pericytes
   D. None of the above

6. One of the following is not a major protein found in the basement membrane of the blood–brain barrier
   A. Laminin
   B. Perlecan
   C. Keratin
   D. Nidogen

7. How many layers of meninges cover the central nervous system?
   A. 1
   B. 2
   C. 3
   D. 4

8. Prodrug formation belongs to what type of strategy for brain drug targeting?
   A. Chemical modification
   B. BBB permeability enhancer
   C. Transport systems
   D. Direct administration

9. Drugs with high lipophilicity are able to cross the blood-brain barrier via:
   A. Disintegration
   B. Erosion
   C. Solubilization
   D. pH-gradient transfer

10. Amphilic block Copolymers constitute _____
    A. Liposomes
    B. Micelles
    C. Opsonins
    D. Vectors

11. Polymeric micelles are characterized by an inner lipophilic _____ and an outer hydrophilic _____ respectively.
    A. Core, corona
    B. Corona, core
    C. Polymer, block
    D. None of the above

12. Coupling antibodies to surfaces of liposomes result in the formation of _____
    A. Micelles
    B. Dendrimers
    C. Immunoliposomes
    D. Exosomes

13. Three different layers make up dendrimers and they include core, corona and _____
    A. Middle layer
    B. Branching layer

C. Outer layer
D. Inner layer

14. _____ contains minuscule droplet sizes.

A. Liposomes
B. Micelles
C. Nanoemulsion
D. Viral vectors

15. Which one of the following is not used as a viral vector?

A. Adenovirus
B. Adeno-associated virus
C. Herpes virus
D. Ebola virus

16. Which one of the following is fluorescent in nature?

A. Carbon dots
B. Carbon nanotubes
C. Liposomes
D. Micelles

17. Common mechanisms that underlie the release of drugs from different nanocarrier systems include:

A. Diffusion
B. Stimuli-controlled release
C. Chemical Interaction
D. All of the above

18. Nanodrug delivery systems (NDDS) are tested in the treatment of all but one of the following brain diseases:

A. Parkinson's disease
B. Alzheimer's disease
C. Duodenal ulcer
D. Huntington's disease

19. _____ is attached to nanoparticles to enhance retention time and reduce clearance of drugs

A. Micelles
B. Poly ethylene glycol
C. Poly lactic acid
D. Liposomes

20. _____ can be used to modify nanoparticles for triggered release of apomorphine
    A. Ethanol
    B. Poly ethylene glycol
    C. Phenylboronic acid
    D. Benzoic acid

21. Curcumin in the management of Alzheimer's Disease is faced with the following issues:
    A. Low bioavailability
    B. Poor stability
    C. All of the above
    D. None of the above

22. Huntingtin is found in all mammalian cells with the largest quantities found in:
    A. Brain
    B. Testes
    C. All of the above
    D. None of the above

23. Polymeric nanoparticles made from _____ polymer are approved for use in clinical applications
    A. Poly ethylene glycol
    B. Poly (D,L-lactide-co-glycolide)
    C. Polyacrylamide
    D. Poly propylamide

24. Which one of the following minerals were tested as nanoparticles in Huntington's?
    A. Calcium
    B. Magnesium
    C. Nickel
    D. Selenium

25. _____ and _____ nanoparticles have been tested in the management of HIV encephalopathy
    A. Gold and silver
    B. Selenium and zinc

C. Iron and gold
D. Selenium and silver

26. Nano-sized gadolinium particles were tested in the treatment of brain tumors in _____ of clinical trials.

A. Phase I
B. Phase II
C. Phase III
D. Phase IV

27. AGuIX nanoparticles with radiotherapy plus concomitant Temozolomide were tested in clinical trials in the management of _____

A. Alzheimer's disease
B. Huntington's disease
C. Glioblastoma
D. Multiple sclerosis

28. Which one of the following is not a limitation of nanoneurotherapeutics?

A. Ethical concerns
B. Toxicity
C. Tissue selectivity
D. Lung damage

29. Which one of the following is not an advantage of nanodrug delivery systems?

A. Tissue selectivity
B. Increased drug concentration in the brain
C. Increased efficacy
D. Increased deposition in vital organs

30. Production of reactive oxygen species may cause _____.

A. Enhanced treatment outcomes
B. Oxidative damage
C. Tissue selectivity
D. Reduced clearance

Answer Key

1.	C	**2.**	A	**3.**	B	**4.**	B	**5.**	D	**6.**	C
7.	C	**8.**	A	**9.**	C	**10.**	B	**11.**	A	**12.**	C
13.	B	**14.**	C	**15.**	D	**16.**	A	**17.**	D	**18.**	C
19.	B	**20.**	C	**21.**	C	**22.**	C	**23.**	B	**24.**	D
25.	A	**26.**	A	**27.**	C	**28.**	C	**29.**	D	**30.**	B

Short-Answer Questions

1. The use of prodrug is also seen in the delivery of Azidothymidine to the brain via the simple formation of the _____ prodrug.
2. The blood is separated from the brain parenchyma by _____ that line the capillaries in the brain.
3. _____, _____ and _____ barriers limit drug entry into the brain.
4. The oscillating activity of ultrasound devices that can help open up membranes and blood vasculature is known as _____.
5. Dendrimers release drugs via degradation mechanism by which the polymers are degraded by _____ or _____.
6. Common mechanisms that underlie the release of drugs from different nanocarrier systems include _____, _____, _____, _____and _____.
7. Curcumin, however beneficial, is faced with the problem of _____ and _____.
8. The increasing surface area of nanoparticles leads to a rise in _____.

Answers

1. Ester
2. Endothelial cells
3. Blood-brain barrier, blood-cerebrospinal fluid barrier and arachnoid barrier

4. Cavitation
5. Enzymatic activity, hydrolysis
6. Diffusion, disintegration, dissolution, stimuli-controlled release, and chemical interaction
7. Low bioavailability, stability issues
8. Chemical reactivity

Long-Answer Questions

1. Briefly describe the role of liposomes as a nanodrug delivery system in enhancing drug delivery to the brain.
2. Explain the difference between micelles and dendrimers.
3. How does chemical modification increase drug delivery to the brain?
4. Explain the various characteristics of ideal drug candidates for brain targeting.
5. Elucidate the various advantages of nanomedicine in brain targeting as compared to conventional drug administration.