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Nanopharmaceuticals: A Boon to the Brain-Targeted Drug Delivery

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Abstract

Brain is well known for its multifarious nature and complicated diseases. Brain consists of natural barriers that pose difficulty for the therapeutic agents to reach the brain tissues. Blood-brain barrier is the major barrier while blood-brain tumor barrier, blood-cerebrospinal (CSF) barrier and efflux pump impart additional hindrance. Therapeutic goal is to achieve a considerable drug concentration in the brain tissues in order to obtain desired therapeutic outcomes. To overcome the barriers, nanotechnology was employed in the field of drug delivery and brain targeting. Nanopharmaceuticals are rapidly emerging sub-branch that deals with the drug-loaded nanocarriers or nanomaterials that have unique physicochemical properties and minute size range for penetrating the CNS. Additionally, nanopharmaceuticals can be tailored with functional modalities to achieve active targeting to the brain tissues. The magic behind their therapeutic success is the reduced amount of dose and lesser toxicity, whereby localizing the therapeutic agent to the specific site. Different types of nanopharmaceuticals like polymeric, lipidic and amphiphilic nanocarriers were administered into the living organisms by exploiting different routes for improved targeted therapy. Therefore, it is essential to throw light on the properties, mechanism and delivery route of the major nanopharmaceuticals that are employed for the brain-specific drug delivery.

Keywords: nanocarriers, nanoparticles, nanopharmaceuticals, ligand, brain diseases, targeted drug delivery, nanomedicine, route of administration

1. Introduction

Brain besides being a fascinating organ is also known for its complexity. From outside, this delicate organ is protected by a bony structure called skull while internally it is sheltered from noxious substances via some complex barrier systems. These protective barriers impede the treatment strategies adopted for therapeutic purposes [1]. The management of CNS disorders such as dementia, epilepsy, panic disorders, meningitis, and brain tumors greatly depends on the means of attaining higher drug levels at the targeted sites. Physico-chemical properties of the drug molecule mainly dictate its ability to penetrate these barriers and achieve a therapeutic outcome. Thus the ultimate pharmacological response obtained by the potential drug depends on multiple factors like its effectiveness, its uptake or penetration through protective barriers or its ability to bind with specific carrier proteins for efficient transport across the membrane [2]. Among these barriers, blood-brain barrier (BBB) presents one of the types that hinder the transport of the medicinal compounds for treating

brain ailments. BBB serves as both physical and transport barrier and is present at the interface of blood and brain. It is a tight junction made of microvascular endothelial cells, astrocytes, and pericytes [3]. Therefore, the development of newer therapeutic strategies is the need of the hour to overcome these transport hurdles.

1.1 Barriers in delivering drug to brain

1.1.1 The blood-brain barrier (BBB)

It is a tight physical junction present at the interface of CNS and blood circulation. It consists of endothelial cells that do not have fenestrations and thus restrict the influx of ions and other solutes into the brain from surrounding blood capillaries. Astrocytes and pericytes surround endothelial cells and thus make it almost an impermeable barrier. BBB allows paracellular transport of small lipophilic compounds (<400 Da) via passive diffusion. This barrier also offers active transport of some hydrophilic compounds by the means of transport proteins (e.g., P-glycoprotein) present at the junction. The transcellular pathway that is used by some compounds to enter the brain includes different mechanisms such as passive diffusion, specific transporters, and transcytosis [4].

1.1.2 Other barriers

Among the primary brain tumors, gliomas are considered the most common. These tumors make a barrier at their early stage termed as blood-brain tumor barrier (BBTB). Although BBTB is permeable at the core of glioblastomas, however, it closely resembles BBB at the peripheral regions. This combination of BBB and BBTB leads to an additional hindrance for drug delivery to reach the glioblastoma cells and thus requires newer drug development strategies to aid drug delivery to the tumor site [5].

Efflux pumps also serve as additional barriers in drug delivery to the brain that are present in endothelial cells lining. These efflux pumps are made up of protein complexes called adherens junctions primarily regulate the permeability of the endothelial barrier [6].

Blood-cerebrospinal fluid also acts as a barrier that limits the free movement of molecules and drug compounds across the brain by strictly regulating the transfer of solutes between the blood and CSF [7].

2. Drug delivery to brain: potential hurdles to overcome

Mainly lipophilic drugs are used to treat CNS ailments and possess a molecular weight below 400 Da and log P between -0.5 and 6.0 [8, 9]. For drugs that are ionized at physiologic pH, it is their unionized fraction that determines the concentration gradient across the BBB for passive diffusion [2]. By considering these facts, a drug should be designed in such a manner that it has optimal lipid solubility so that it penetrates BBB and maintains a therapeutic concentration in the brain. But this is not that simple because only increasing the lipophilicity of the drug molecule via certain chemical modifications may not attain the desired pharmacokinetic effects as it may lead to decreased systemic solubility and bioavailability. It may also have increased protein binding and higher uptake by liver and reticuloendothelial system which ultimately leads to increased metabolism thus leading to diminished active drug concentration at the target site [2]. There are certain drug molecules that penetrate the BBB besides what their lipid solubility suggest. This penetration is attributed to the carrier-mediated transport of these polar compounds present at the tight junctions [10].

3. Nanopharmaceuticals: an approach to achieve brain targeting

Brain targeting is potentially difficult because of multiple barriers. Recent advances in nanotechnology present opportunities to overcome such limitations and to deliver the drug to the brain targets. Nanopharmaceuticals are the relatively newer field that employed “therapeutic containing nanomaterial” with unique physicochemical properties due to their small size (one to several 100 nm), high

Route	Brand	Nanocarrier	Indication	Manufacturer
SC	Copaxone	Glatiramer acetate	Multiple sclerosis	TEVA
IV	DepoCyt®	Cytarabine encapsulated in multivesicular liposomes (20 µm)	Lymphomatous malignant meningitis	Leadiant Biosciences
Epidural space injection	DepoDur®	Morphine sulfate encapsulated in multivesicular liposomes (17–23 µm)	Chronic pain	Pacira Pharmaceuticals
IV	Opaxio®	Paclitaxel covalently linked to SLN	Glioblastoma	Cell Therapeutics
Intratumoral Injection	NanoTherm®	Aminosilane-coated superparamagnetic iron oxide (15 nm) nanoparticles	Local ablation in glioblastoma, prostate, and pancreatic cancer	Magforce
Oral	Avinza®	Morphine sulfate nanocrystals	Psychostimulant	Pfizer/King Pharma
Oral	Focalin XR®	Dexmethylphenidate HCl nanocrystals	ADHD	Novartis
Oral	Ritalin LA®	Methylphenidate HCl nanocrystals	ADHD	Novartis
SC injection	Plegridy®	Polymer-protein conjugate (PEGylated IFN Beta-1a)	Multiple sclerosis	Biogen
IM injection	Invega Sustenna®	Paliperidone	Schizophrenia	Janssen Pharms
IV	AmBisome®	Amphotericin B liposome	Cryptococcal meningitis	Gilead Sciences, Inc.
IV	Abelcet®	Amphotericin B liposome	Cryptococcal meningitis	Enzon Pharma
IV	DaunoXome®	Daunorubicin liposome	Pediatric brain tumors	Under Phase I trial
IV	Doxil®/Caelyx®	Doxorubicin HSPC, cholesterol, and DSPE-PEG2,000	Glioblastoma and Pediatric brain tumors	Phase II Phase II
IV	Myocet®	Doxorubicin EPC and cholesterol	Glioblastoma	Phase II
IV	SGT-53 (SynerGene Therapeutics)	Cationic liposome with anti-transferrin antibody	Glioblastoma	Phase II
—	Cornell Dots	Silica nanoparticles with a fluorophore, PEG-coated	Malignant brain tumors imaging	Phase I

SC, subcutaneous; IM, intramuscular; IV, intravenous; ADHD, attention deficit hyperactivity disorder; IFN, interferon; DSPE, distearoylphosphatidylethanolamine; EPC, egg phosphatidylcholine; PEG, polyethylene glycol.

Table 1.
 Marketed nanopharmaceuticals for brain disorders.

surface to volume ratio and flexibility to alter their properties [11]. An alternate definition can be pharmaceuticals engineered on the nanoscale for the therapeutic purpose [12]. Nanopharmaceuticals comprised of different nanomaterial like polymers, lipids, amphiphilic material, metals, inorganic elements, carbon nanotubes, dendrimers, etc., to constitute nanocarriers which can be fabricated in different sizes, shapes, morphology, surface charges and surface groups for the brain-specific targeted delivery of the drug across barriers. Nanopharmaceuticals mediated drug delivery system has the power to penetrate drug moieties across CNS, either passively or actively, and improve bioavailability and therapeutic efficacy of the drug even at a lower concentration. Currently, available marketed nanopharmaceuticals for the brain are mentioned in **Table 1**.

4. Nanopharmaceuticals: brain targeting mechanisms

Nanopharmaceuticals could able to breach blood-brain barriers through various mechanisms. On the simple edge, their smaller size leads to passive delivery of the drugs through transcellular route across brain's epithelial cells or choroid plexus. Criteria for the simple passive diffusion across the barriers are molecular size less than 400 Da, low hydrogen bonding capacity and lipophilicity [13, 14]. Therefore, lipophilic and tailored nanocarriers could deliver the drug through this mechanism.

While extremely hydrophobic molecules like nutrients (glucose and amino acids) pass through active diffusion mechanism with the aid of special transporter proteins. On the other hand, hydrophilic and larger molecules like transferrin and insulin pass through receptor-mediated transport across the membrane [15]. BBB majorly comprised of the endothelial layer which possessed tight junctions; the presence of proteins, namely occludins, claudins and adhesion molecules in the tight junction, make it a tougher barrier [16].

Nanopharmaceuticals are custom-made to surpass the brain barriers through these mechanisms:

- Lipophilic nanocarriers (liposomes, solid lipid nanoparticles SLN) fuse with the endothelial cells and transport the drug through the transcellular pathway or endocytosis. Moreover, nanoparticles provide a sustained drug release pattern in the bloodstream, enabling higher drug concentration to cross BBB [17].
- Furthermore, nanoparticles are functionalized with ligands or specific surfaces to trigger receptor-mediated transcytosis or carrier-mediated transport across BBB. Attachment of ligands like lactoferrin, transferrin, insulin facilitated receptor-mediated transport. Cationized ligands and peptides like albumin cross through receptor-mediated absorptive transport. Nanoparticles surface can be modified to utilize active transport system comprising P-glycoproteins, L-transporters, nucleoside transporter, ionic transporter, multidrug-resistant proteins that transfer the molecules into the brain by consuming adenosine triphosphate (ATP) [17]

Liposomes have been extensively studied and even FDA approved nanocarrier for brain disorders. Surface modulation of liposomes with functional proteins, peptides and polyethers aided targeted drug delivery for brain diseases [18]. PEGylated liposomes and glutathione-PEGylated liposomes evade body's reticuloendothelial system and facilitate enhanced drug uptake across BBB [19]. Moreover, transferrin-modified liposomes [20], TAT peptide-conjugated liposomes [21], glucose-modified liposomes [22], and transferrin-folate bound liposome effectively deliver the drug

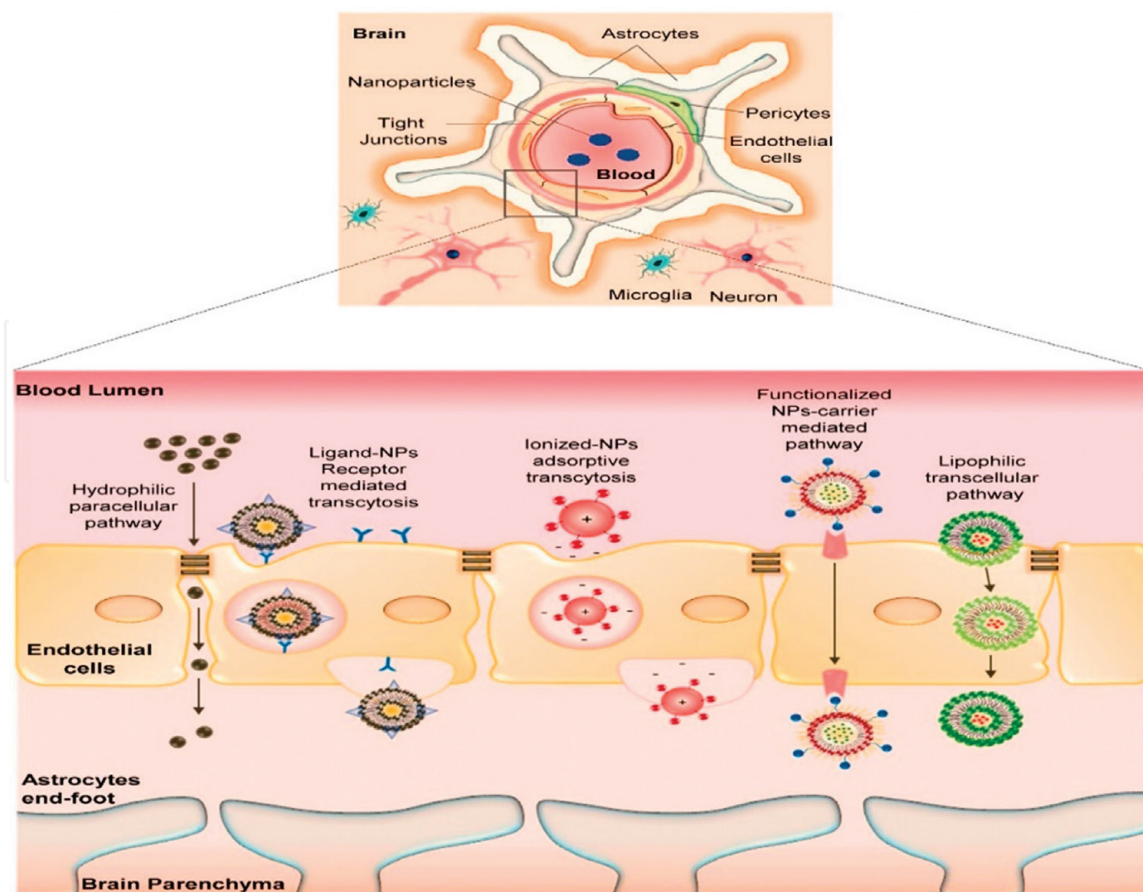


Figure 1. Different pathways for nanopharmaceutical mediated transport across the blood-brain barrier (Under Creative Commons Attribution License 4.0, <https://creativecommons.org/licenses/by/4.0/>) [96].

across the barrier to treat multiple sclerosis [23]. Similarly, transferrin bound SLN and thiamine coated SLN were found to be efficacious in the treatment of cerebral malaria and increased drug uptake in the brain [24]. Mechanisms of transport across BBB are shown in **Figure 1**.

Polymeric nanoparticles accumulate in the brain tissue by both passive and active mechanisms. Chitosan-poly lactic-co-glycolic acid (PLGA) nanoparticles showed enhanced delivery of coenzyme Q to the brain of transgenic mice through absorption mediated endocytosis [25]. In another study, PLGA was coupled with Tet-1 peptide to achieve neuronal targeting of curcumin in the treatment of Alzheimer's disease. Retrograde transportation of curcumin across the barriers destroyed amyloid aggregates and scavenges oxidative radicals in the brain [26]. Similarly, ligand attached polymeric-lipidic nanoparticles like nerve growth factor (NGF) loaded poly butyl cyanoacrylate (PBCA) liposomes considerably deliver the drug across the BBB cholinergic system in the amnesic rodent model [27]. Likewise, inorganic nanocarriers show promising outcomes in terms of brain targeting. Amine functionalized multi-walled carbon nanotubes adopted transcytosis mechanism to pass BBB [28]. A natural substance wheat germ agglutinin-horseradish peroxidase (WGA-hrp) was conjugated to gold nanoparticles (AuNPs) and administered in the IM injection into the mice. Results were remarkable in terms of drug penetration across BBB [29].

Dendrimers are the excellent drug carriers; their surface functionalization with folic acid, peptides, aptamers, amino acids, biotin, antibodies facilitated more site-specific targeting. To penetrate CNS barriers, dendrimers were conjugated with transferrin, lactoferrin, D-glucosamine, and leptin for more effective brain drug delivery [30].

Some other nanoparticulate systems like nanoemulsion and nanogel can be functionalized with targeting moieties (transferrin, insulin, peptides) for CNS drug delivery. Nanogels made up of PEG-polyethylenimine (PEI) and N-vinylpyrrolidone/ isopropyl acrylamide have been tested to ensure CNS drug delivery potential [30].

5. Nanopharmaceuticals classification on the basis of routes of administration

BBB mediated drug uptake restrictions prompt scientists to investigate drug delivery potential of the nanopharmaceuticals to the brain through various routes. The ultimate objective was to enhance drug penetration across BBB and to reduce disease index. Up till now, the most commonly employed route was systemic administration through Intravenous (IV) injection. Other natural routes like oral, intranasal (IN), intrathecal (IT), intraperitoneal (IP) have been used as well. Some novel strategies like cerebral devices, implants, Ultrasound-guided nanoparticle delivery, osmotic delivery gain much attention in the recent era. Different nanopharmaceuticals are illustrated in **Figure 2**. List of all nanopharmaceuticals delivered through different routes have been mentioned in **Table 2**.

5.1 Oral administration

The oral route is the most convenient, non-invasive and compliant mode of administration. However, brain targeting through the oral route was not investigated largely mainly due to indirect systemic entry through absorption from the gastrointestinal tract (GIT). Harsh GIT environment, slow onset of action, shorter half-life, first pass elimination and reduced systemic absorption hampered drug

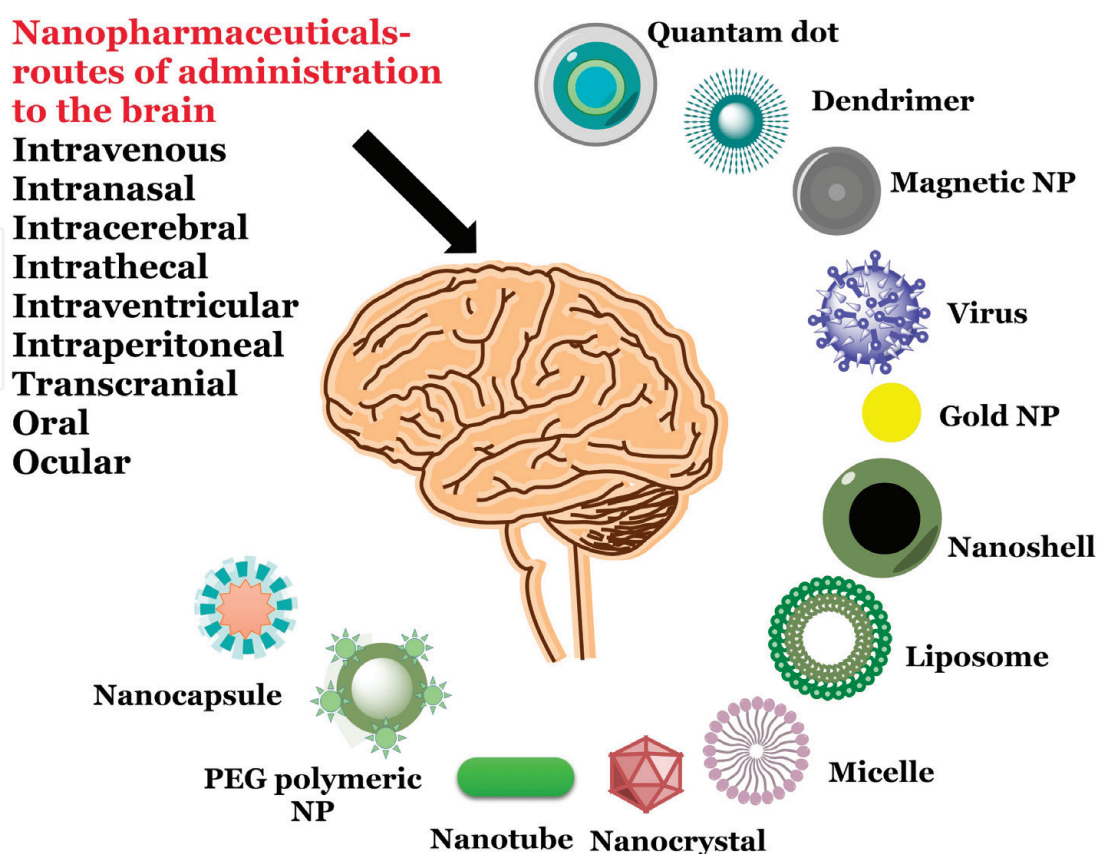


Figure 2. Nanopharmaceuticals classification on the basis of route and nanocarriers.

Route	Drug	Particle size	Nano component	Active ligand	Indication	References
Oral	Dalargin	~100 nm	poly (butylcyanoacrylate) nanoparticle	Tween 80-PEG 20000	Analgesic effect	[33]
Oral	Indomethacin	~320 nm	Lipidic core	poly (ϵ -caprolactone) coat	Glioblastoma treatment	[31]
Oral	Saquinavir	100–200 nm	polyunsaturated fatty acids (PUFA), Lipoid-80 and deoxycholic acid		Increase oral bioavailability and brain distribution	[32]
Oral	Estradiol	138.8 \pm 4.3 nm	polylactide-co-glycolide (PLGA) nanoparticles	Tween 80 coated	Alzheimer's disease treatment	[34]
Intraperitoneal (IP)	None	220 \pm 35 nm	Iron oxide (Fe ₃ O ₄) nanoparticles	coated with a carbon shell derived from glucose	Brain cells localization	[36]
Intranasal (IN)	Bromocriptine	161.3 \pm 4.7 nm	Chitosan nanoparticle	—	Parkinson's disease	[48]
IN	Clonazepam	15 \pm 10 nm	Microemulsion	—	Increase brain/blood uptake ratio	[52]
IN	Nimodipine	30.3 \pm 5.3 nm	Microemulsion	—	High brain uptake	[53]
IN	Risperidone	15.5 nm-nanoemulsion; 16.7 nm-mucoadhesive nanoemulsion	Nanoemulsion; mucoadhesive nanoemulsion	—	Schizophrenia treatment	[54]
IN	Diadanosine-dideoxyinosine (dd)	269–382 nm	Chitosan nanoparticles	—	Increase brain/plasm, CSF/plasma ratio	[12]
IN	Rivastigmine	143.1 to 3300 nm	Chitosan nanoparticle	—	Alzheimer's disease	[50]
IN	Venlafaxine	167 \pm 6.5 nm	Chitosan nanoparticles	—	Major depressive disorders and anxiety disorder	[51]
IN	Duloxetine	137.2 \pm 2.88 nm	Nanostructured lipid carriers	—	Behaviorial improvement in major depressive disorder	[55]

Route	Drug	Particle size	Nano component	Active ligand	Indication	References
IN	Coumarin	100 to 600 nm	methoxy-PEG-polycaprolactone	—	Enhanced brain penetration	[58]
IN	Vasoactive intestinal peptide (VIP)	90–100 nm	PEG-PLA nanoparticles (NP)	—	Protein translocation across BBB	[79]
IN	Sumatriptan	23.1 ± 0.4 nm	Micellar nanocarrier	—	Migraine therapy	[56]
IN	Zolmitriptan	23 nm	Micellar nanocarrier	—	Migraine therapy	[57]
IN	FITC labeled	5 nm	AuNP	FITC	Brain specific delivery	[80]
Intravenous (IV)	Azidothymidine	—	Transferrin anchored PEG nanoparticles	—	Viral infection	[81]
IV	Valproic acid	—	Nanoparticles	—	Epilepsy	[82]
IV	Tacrine	35.58 ± 4.64 nm	PBCA NPs	—	Alzheimer's disease	[83]
IV	Cabazitaxel	24–68 nm	PEG modified Cellulose (Cellax) NPs	—	Glioblastoma	[84]
IV and intratumoral	Docetaxel/SiRNA	110–150 nm	Peptide modified Cationic liposomes	—	Glioma	[85]
IV/Intranasal	Catalase	9.5 nm	Exosomes	—	Parkinsonism	[86]
IV	HCFU	50 nm	Nanogels	—	Glioma	[87]
IV (MRI)	Curcumin	<100 nm	Magnetic NPs	—	Detection of amyloid plexus in Alzheimer's	[88]
IV	Sunitinib/anti-miR-21 oligonucleotide	<190 nm	NPs	—	Glioblastoma	[89]
IV	Monoclonal antibody (OX26)	300–600 nm	PEG-chitosan NPs	—	Cerebral ischemia	[90]
Focused ultrasound+IV	FE ₃ O ₄ /SPANH	—	Nanoparticles	—	Malignant glioma	[91]

Route	Drug	Particle size	Nano component	Active ligand	Indication	References
Convection-enhanced delivery	CPT-11	96–101 nm	Liposomes		Intracranial tumor	[92]
Intrathecal	Fasudil	100 nm	Liposomes		Subarachnoid hemorrhage	[93]
Intracranial	Paclitaxel	3 mm	Nanoscale PLGA implants		Intracranial glioblastoma	[94]
Neural probes	Dexamethasone	400–600 nm	PLGA nanoparticles in alginate hydrogel		Glial inflammation	[95]

PEG, polyethylene glycol; PLA, polylactic acid; FITC, fluorescein isothiocyanate; SPAnH, poly[aniline-c-sodium N-(1-one-butyric acid)] aniline; PBCA, poly(n-butyl cyanoacrylate); HCFU, N-hexylcarbonyl-5-fluorouracil.

Table 2.
Nanopharmaceuticals administration through various routes.

therapeutic efficacy and bioavailability. Thus, oral drug delivery failed to deliver the therapeutic moiety to the brain efficiently. In this regard, nanopharmaceuticals must possess the properties to bear harsh enzymatic environment, overcome first pass metabolism and efficiently permeate through the intestinal epithelial barrier to reach the systemic circulation.

Scientists developed lipid nanocore surrounded by poly (ϵ -caprolactone) and orally administered to the mice. The concentration of the loaded drug, indomethacin, was successively increased in the brain and efficiently treat glioblastoma in the mice model without causing BBB vessel alteration. This could serve as a basis for safe and effective brain targeting via oral route [31].

Similarly, orally administered saquinavir-loaded nanoemulsion significantly delivers the drug across BBB. Nanoemulsion was stabilized by deoxycholic acid which overpasses first-pass elimination of the drug. The oily phase, polyunsaturated fatty acids (PUFA) facilitates rapid transport to the brain. It laid the foundation for effective brain targeting through oral route [32].

Researchers formulated poly (butyl cyanoacrylate) nanoparticles, double coated with Tween 80 and polyethylene glycol (PEG)-2000 for the oral delivery of the dalargin to the brain. Dalargin is a hexapeptide, anti-nociceptive agent which could not cross BBB. However, its nanoformulation showed promising analgesic effects in the mice model, which demonstrated the potential of the nanoformulation for brain targeting via oral route [33].

Orally administered Tween 80 coated PLGA deliver estradiol successfully to the brain. The therapeutic efficacy in elevating Alzheimer's disease was parallel to the nanoformulation administered intramuscularly [34]. In short, oral delivery of drug-loaded nanopharmaceuticals achieved preliminary success but still need to be further explored in the near future.

5.2 Intraperitoneal administration (IP)

Intraperitoneal administration involved peritoneal cavity of the abdomen. The route is still under investigation. It has an advantage of delivering a larger amount of the drug and it is employed when a vein for the IV injection is not easily located. In addition, it can be employed when animals are not ready for oral administration. However, the route is currently limited to pre-clinical research in small animals and need to be scaled up [35].

Iron oxide nanoparticles were fabricated with the aim to target subcellular compartment of the brain cells. For this purpose, iron oxide nanoparticles with different shapes (round, biconcave, spindle, nanotube) were synthesized and coated with glucose derived fluorescent carbon layer. In-vivo administration through IP route indicated biconcave nanoparticles localized in the nuclei and nanotube-shaped nanoparticles located in the cytoplasm of the brain cells. While the carbon coated surface on iron oxide nanoparticles facilitated attachment of several therapeutic moieties on the nanoparticles for their delivery inside the brain cells [36]. Therefore, the IP route could serve as a major route to deliver the drug across the brain barriers.

5.3 Intravenous administration (IV)

Systemic route including IV drug delivery to the brain involves the receptor-mediated and adsorptive mediated transcytosis. It is the most exploited route of administration for the nanoparticles because of the immediate action systemically and locally by targeted delivery. Polybutyl cyanoacrylate (PBCA) was first used for the synthesis of the NPs intended for the brain. Analgesic dalargin was incorporated in the PBCA NPs

with Polysorbate 80 coating and a marked level of analgesia was seen in the animal studies after IV administration of the NPs [37]. PBCA NPs with doxorubicin coated with Polysorbate 80 were studied for their brain delivery in the rats and showed the promising result in 2–4 hours as compared to the uncoated NPs after IV drug delivery [38]. In a similar study, Polysorbate 80 coated PBCA NPs with a size of 280 nm were evaluated for the delivery of Loperamide across BBB following IV injection. Results were quite promising in the *in-vivo* nociceptive studies on mice [39]. Musumeci et al. prepared the docetaxel loaded nanospheres using PLGA and observed the biphasic release of drug following IV administration. An *in vitro* study using a biomembrane model made of dipalmitoylphosphatidylcholine (DPPC) was conducted and confirmed the significant release of the drug across the membrane, making it a potent drug delivery approach for crossing BBB [40]. An *in vitro* study was conducted on brain endothelial cell lines and glioma cells using nanocarrier system made with PLGA/PLA and a detailed sketch of cellular uptake, cytotoxicity and therapeutic efficiency were obtained. Furthermore, the animal studies confirmed the uptake of NPs in the brain following IV administration [41]. In one study, male Sprague Dawley rats were used for establishing the efficacy of curcumin as an anticancer drug with neuroprotective properties. The study group demonstrated that how the nanoparticles can increase the circulation time of curcumin in the body and penetration across the BBB, especially the distribution of NPs in the hippocampus. Half-life and mean residence time of curcumin increased after IV administration of NPs across the BBB [42]. Liu et al. demonstrated the effect of breviscapine loaded PLA NPs in rats after IV administration. NPs with an average particle size of 319 nm were distributed in the liver, spleen and brain. The prepared NPs had longer circulation life because they evaded the RES and crossed BBB [43]. Poly (alkyl cyanoacrylate) NPs can deliver several drugs like loperamide, doxorubicin, tubocurarine, etc., across the brain based on the principle of LDL receptor mediate endocytosis after injection of these NPs into the blood by IV administration. Prior to *in vivo* studies, these NPs were coated with surfactants like Poloxamers and Tween for the enhanced drug uptake by brain blood capillaries [44]. Some of the latest techniques of treating brain disorders include delivery of neurogenic genes, mRNA and siRNA. One such study was reported by Son et al. for the delivery of rabies virus glycoprotein (RVG) labeled disulfide containing polyethyleneimine (PEI) nanomaterial to the brain. *In vivo* studies revealed promising data after the infusion of RVG peptide linked nanomaterial in 6 weeks old male BALB/c mice. [45] MRI-driven targeting of the brain using iron oxide NPs of around 100 nm was reported by the group of researchers. Mice were injected with the NPs suspension and were kept in the magnetic field for 30 minutes. There was 5-folds increase in the accumulation of NPs in the glioma cells in the presence of a magnetic field as compared to undirected NPs following IV administration. This approach can be used as a non-invasive therapeutic and diagnostic tool in the various dimensions of health [46]. However, the associated issues like rapid body clearance through the reticuloendothelial system and unintended organ distribution must be overcome for appropriate brain-specific drug delivery.

5.4 Intranasal administration (IN)

Recently, intranasal (IN) route for the drug delivery to the brain proved to be a reliable and non-invasive mode to cross BBB while possessing the ability to deliver a wide range of drug moieties like smaller molecules, larger macromolecules, growth factors, viral vectors and even stem cells to the brain. The transport involves either olfactory or trigeminal nerve which has a direct link from the brain and terminated in the nasal cavity at respiratory epithelium or olfactory neuroepithelium [47]. The nasal mucosa is the target tissue for the drug administration and possessed features like a larger surface area, porous endothelial membrane, huge blood flow, the absence of first-pass elimination and readily accessible. Olfactory region of nasal

mucosa provide nose to brain targeting feature and could be able to treat various CNS disorders like depression, pain, Alzheimer's disease, glioblastoma, multiple sclerosis etc. Several dosage forms, sprays, suspensions, nebulizers, aerosols, gel, solutions can be utilized for IN drug delivery [47]. On the other hand, barriers like mucociliary clearance from nasal mucosa, enzymatic degradation and low degree of permeability across nasal epithelium hinder the drug targeting efficiency to the brain. As a solution, nanopharmaceuticals were used which overcome the clearance and other nasal problems due to their unique nature.

One of the studies demonstrated IN administration of chitosan nanoparticle to deliver bromocriptine, a dopaminergic agonist, to minimize motor function disorder associated with prolonged levodopa usage in the Parkinson's disease. Results were promising in terms of motor function [48]. Didanosine-dideoxyinosine (ddI) is an antiretroviral therapy (HAART) and available in oral dosage forms, however, faced extensive degradation and elimination in GIT which decreases its bioavailability. To overcome the issues, dd loaded chitosan nanoparticles were administered through IN route. Results indicated higher brain to plasma, CSF to plasma and olfactory blood to plasma ratios in the case of IN delivered dd nanoparticles. It shows that nanoformulation can be directly delivered to the brain compartment through IN route [49].

Another research group fabricated rivastigmine loaded chitosan nanoparticle for inhibiting acetylcholinesterase in the brain through IN administration. The free drug had severe bioavailability issues and distributed to the non-targeted site with severe side effects when administered through oral or IV route. Here, chitosan nanocarrier and administration through nasal route enhanced brain uptake with higher brain/blood ratio. It further highlighted the role of nanocarrier and route in brain targeting [50]. Similarly, Venlafaxine (VLF) chitosan nanoparticles were administered to the brain through the nasal route for the treatment of major depressive disorders and anxiety disorder with improved brain uptake and enhanced bioavailability [51].

Another study showed microemulsion and mucoadhesive delivering clonazepam, an anxiolytic, sedative, hypnotic, anticonvulsant drug to the brain. The brain/blood uptake ratio of the intranasal microemulsion and mucoadhesive microemulsion were significantly higher than the IV administered microemulsion, indicating the effectiveness of IN route for brain-specific drug delivery [52]. Similarly, the microemulsion was used for the IN delivery of nimodipine to the brain cells. The microemulsion leads to 3-fold more drug uptake by the olfactory bulb than the IV route. AUC ratio of brain to plasma and cerebrospinal fluid (CSF) to plasma were higher after IN administration in comparison to IV injection. Thus, it could be a promising approach to treat neurodegenerative disorders [53]. Risperidone nanoemulsion and mucoadhesive nanoemulsion were administered through IN route for the treatment of schizophrenia. The composition of nanoemulsion included glyceryl monocaprylate as an oily phase, tween 80 as a surfactant and mixture of propylene glycol and transcucol as a co-surfactant. While mucoadhesive microemulsion had chitosan polymer which induces mucoadhesive properties. The nanoemulsion and mucoadhesive nanoemulsion improved risperidone bioavailability, prevent first pass metabolism and bypass BBB to achieve desired drug concentration at the targeted site. The brain/blood uptake ratio and drug transport efficiency were found to be significantly higher through nasal administration in comparison to the IV injection [54].

Furthermore, nanostructured lipid carriers comprising duloxetine was prepared and delivered to the brain via IN route for the treatment of the major depressive disorder. The results revealed prolonged drug release and therapeutic effect as demonstrated from improved behavior analysis after 24 hours [55].

Furthermore, micellar nanocarrier (amphiphilic nanocarriers) of sumatriptan was developed to treat an acute migraine to improve cerebral blood flow. Limitations

of the drug associated with oral dosage forms and subcutaneous administration like poor bioavailability, shorter plasma half-life, and hepatic elimination have been resolved to much extent through incorporation in micellar nanocarrier. And increased brain concentration of the drug and site-retention can be achieved via nose to brain drug delivery [56]. Similarly, zolmitriptan-loaded micellar nanocarriers were prepared to target brain serotonin receptors and inhibit cranial vessel inflammation. Micellar nanocarriers were administered through nasal route with enhanced characteristics like lower particle size, higher permeation across nasal mucosa, appropriate flow rate, ability to load hydrophilic as well as hydrophobic drugs, enhanced site-retention and ultimately enhanced drug therapeutic activity [57].

Another polymer methoxy-PEG-polycaprolactone was used to encapsulate coumarin with promising brain penetration and myelin binding properties, while administered through nasal route [58]. Bioadhesive nanocarriers reported in the above studies overcome many hurdles associated with a nasal route like protection of drug against enzymatic degradation, enhanced permeability, and avoidance of mucociliary clearance. However, IN delivery of nanopharmaceuticals should be further improved with targeting moieties and incorporation of cost-effective approach.

6. Alternate routes and strategies

6.1 Conventional enhanced delivery (CED)

Potential brain barriers can be by-passed by injecting the drug directly into the tissues using catheter. Such a direct delivery of therapeutic agent to the target site is termed as conventional enhanced delivery (CED). Many pre-clinical studies adapted CED to infuse nano-formulations directly into the brain [59]. C57BL/6 J mice were used to infuse a 10 μ L solution of lipid nanocapsules (LNCs) having an average size of 70 nm into their skull at an infusion rate of 0.5 μ L/min [60]. An alternate method for direct infusion was also reported in which drug-loaded micelles were injected by making small incisions on the skull. A foremost shortcoming CED technique is its invasiveness which requires high anesthetic doses prior to incisions, which resulted in the death of the experimental rats [61]. This technique also requires the optimization of certain factors like pH and osmolarity to surpass any brain damage [62].

6.2 Intracarotid delivery

Administering the drug into the carotid artery provides an alternative solution to direct delivery. This direct systemic delivery requires a catheter to directly inject drugs into the bloodstream. In a study, the efficacy of direct systemic delivery was reported almost twice to that of CED in terms of brain damage [63]. IV route is also used to deliver the drug directly into systemic circulation. Ferrociphenol-loaded lipid nanoparticles were infused to manage glioma via the IV route. The outcomes showed that mean survival of the rats was 28 days while mean survival rate recorded for CED was of 24 days [62, 64].

6.3 Intratumor delivery

Poly(lactic acid) (PLA) and poly(dimethylaminoethyl methacrylate) (PDMAEMA) were used to synthesize amphiphilic star-branched co-polymeric nanoparticles for intratumor delivery of the drugs for treating brain tumors. In a study, this system was used to deliver combined DOX and miR-21 inhibitor (miR-21i) into LN229 glioma cells directly. These micelles protected miR-21i from lysosome degradation

and the release of DOX to the nucleus, which ultimately decreased the miR-21 expression. This combined DOX and miR-21i delivery surprisingly displayed an anti-proliferative efficiency compared with separate treatment of DOX or the miR-21. The outcomes revealed that this co-polymeric system was a better option for delivering genes and hydrophobic therapeutic agents [65].

6.4 Other parenteral routes

Delivering the drug directly into the brain is another way of treating brain disorders. This local drug delivery has been approved by the US FDA [66]. Intrathecal administration of nanopharmaceuticals delivers the nano-drugs in the CSF. However, this route of administration is most commonly used for anesthetics and neurotic pain [67]. This route is under experimental phases in humans. It includes two different ways of delivering the therapeutic moiety, either by infusion in the intralumbar region or intraventricularly using an Ommaya reservoir placed subcutaneously and connected to the brain with a catheter [68]. Thioflavin-T was delivered by intrahippocampal injection for targeting the β amyloid in the brain using the nanoparticles. The data reported localization of thioflavin-T in the intracellular and extracellular spaces of the brain, which prevented the formation of β -amyloid aggregates in the Alzheimer's disease. This same method can be adapted to deliver the anticancerous drugs as well as other analgesic peptides [69]. In an *in situ* perfusion study conducted on mice, Polysorbate 80 coated PBCA NPs loaded with the tubocurarine were able to cross the BBB after intraventricular drug administration. There was a marked effect on the EEG epileptiform spikes [70]. Intraarterial drug delivery has an advantage over the other conventional systems of drug delivery because of the increased dose delivery at the desired site of the brain. This route can also be exploited for the immun0-targeting. However, this route has some limitations like a dilution of the drug because of cerebral blood flow [71].

6.5 Ultrasound guided drug delivery

Ultrasound facilitated drug penetration through brain barriers is yet another option for safe and reversible targeted drug delivery [72]. In this technique, ultrasound radiations are employed to generate shear stress on the vascular endothelium for a transient and reversible perforation in the BBB which facilitates the nanoscaled drug delivery to the targeted site. It appeared in a research outcome that docosahexaenoic acid binding with low-density lipoprotein NPs can penetrate the BBB by the application of ultrasound sonication. A near IR fluorescent dye examination revealed about 60 times greater accumulation of sonication facilitated drug delivery to the targeted site. The main advantage reported was lack of cytotoxicity or neuronal damage due to pointed ultrasound irradiation [73]. PEGylated PLA nanoparticles delivery to the brain was facilitated via ultrasound-induced perforation. β -specific antibody 6E10 was conjugated on PEG-PLA along with the coumarin 6 and DiR as fluorescent probes to assess the target site accumulation. Ultrasonication facilitated NPs penetration was about 2.5-fold more than the complementary non-sonicating therapy [74]. Ultrasound techniques can be used to aid the enhanced delivery of PEG-b-poly(l-Lysine) coupled with siRNA into glioma cells by 10-fold in conjunction with a newer gas-cored nanobubble [75].

7. Future prospects for nanopharmaceuticals delivery

Another targeted approach to the brain for delivering drugs is through the ocular route. The ocular route has so many advantages like reduced peripheral toxicity and

direct delivery of therapeutic moiety in the target site [76]. Ocular and intranasal drug delivery for the brain was compared by a group, in which nerve growth factor (NGF) was used for treating Alzheimer's disease. However, it was found out that intranasal drug administration was more effective and potent for brain disorders and ocular route did not perform well. However, many scientists are working for making the ocular route a success because of it being the compliant and non-invasive route [77]. There has been a huge room for the administration of nanocarrier through ocular route to the brain. Nanocarrier can facilitate drug delivery to the brain because of their size, site-retention properties and enhanced adhesion to the lacrimal fluid. The route can be exploited for the delivery of drugs and genes to CNS by avoiding systemic exposure via nanopharmaceuticals [78].

8. Conclusion

Brain-targeted drug delivery is a difficult matter due to anatomic and pathophysiological brain barriers. The current advances in nanotechnology provide a solution in the form of nanopharmaceuticals, drug containing nanocarriers, to cross the CNS barriers and to target the brain tissue in various disorders. Nanopharmaceuticals' mode of administration into the body is an important aspect, which ultimately effects drug concentration in the brain and drug therapeutic effect. Current chapter highlighted the routes of administration through which nanopharmaceuticals can be delivered to reach the brain. Every route has pros and cons, nanopharmaceuticals overcome the route associated limitations in the delivery of drug to the brain due to their peculiar physicochemical properties and surface modulation. Translation this research area into the clinic still require investigations, as safety is the foremost concern and distribution to other body organs must be eradicated. Moreover, there is a need to control the drug delivery rate when nanopharmaceuticals reach the brain for safer action.

Conflict of interest

The authors declared no conflict of interest.

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