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Review Article

Brain-Targeted Drug Delivery System: A Novel Approach

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Abstract

A targeted drug delivery system is based on a technique that continuously administers a predetermined dosage of a therapeutic agent to a sick location of the body. The targeted drug delivery goal is to raise the relative amount of the treatment in the target tissues while lowering it in the non-target tissues. This technique's intrinsic benefit has been reduced drug dose and adverse effects. Drug targeting in the brain is one of the most challenging issues in pharmaceutical research because the blood-brain barrier acts as an impermeable barrier for systemically delivered therapeutics and the brain extracellular matrix contributes to the poor distribution of locally delivered drugs. In the treatment of various Central nervous system (CNS) diseases, general approaches that can improve drug delivery to the brain are of great interest. Drugs are less harmful and more effective when they are administered close to where they would be most effective. Extreme research studies have recently concentrated on the development of fresh strategies for more successfully delivering medications to the brain in response to the shortcomings of the traditional delivery mechanism. This study thoroughly explains the obstacles involved in brain-targeted drug delivery, the process of drug transfer through Blood Brain Barrier, different techniques for brain-targeted drug delivery, and some recent breakthroughs in brain-targeted drug delivery.

Keywords: Blood-brain barrier, Brain-targeted, Cerebrospinal fluid, Nanoparticles, Liposomes, Convection-enhanced drug delivery.

Introduction-

A smart drug delivery technology that is particularly good at getting medications to patients is targeted drug delivery. Unlike the targeted release system, which releases the drug in a dose form, the traditional drug delivery system includes the drug being absorbed through a biological membrane. [1] A targeted medication delivery system is based on a technique that continuously administers a certain dosage of a therapeutic substance to a body part that is afflicted with a disease. This helps to maintain the necessary medication levels in the body's tissues and plasma, preventing any drug-related harm to healthy tissue. Because of the high degree of integration in the medication delivery system, chemists, biologists, and engineers must work together to optimize it. When implementing a targeted release system, the following system design criteria must be considered: drug properties, drug side effects, the route taken for drug delivery, the targeted site, and the disease. [2] The development of targeted delivery, in which the medicine is only active in the target location of the body, is one of the current efforts in the field of drug delivery. Drug targeting technology shown in figure-1. The primary goals of the targeted medication delivery system are to extend, localize, target, and engage with sick tissue while keeping the patient safe. [3] Direct administrations of drugs into the Central nervous system (CNS) can achieve targeted action in the central nervous system. [4] The blood-brain barrier can dramatically reduce the efficiency of a wide variety of medications (such as antibiotics, antineoplastic medicines, and Neuropeptides-CNS stimulant pharmaceuticals) due to its persistent impediment effect. Most large molecules and 98 % of tiny molecules do not penetrate the blood-brain barrier, according to some recent research. [5,6] The following parameters are thought to be optimal for a compound to transport through the blood-brain barrier (BBB) [7]:

- Unionization of the compound is required.
- The log P number needs to be close to 2.
- Its molecular weight must be under 400 Da.
- Between 8 and 10 total hydrogen bonds should not be present.
- Only 2% of medicines with tiny molecular weights are predicted to pass through the blood-brain barrier (BBB).

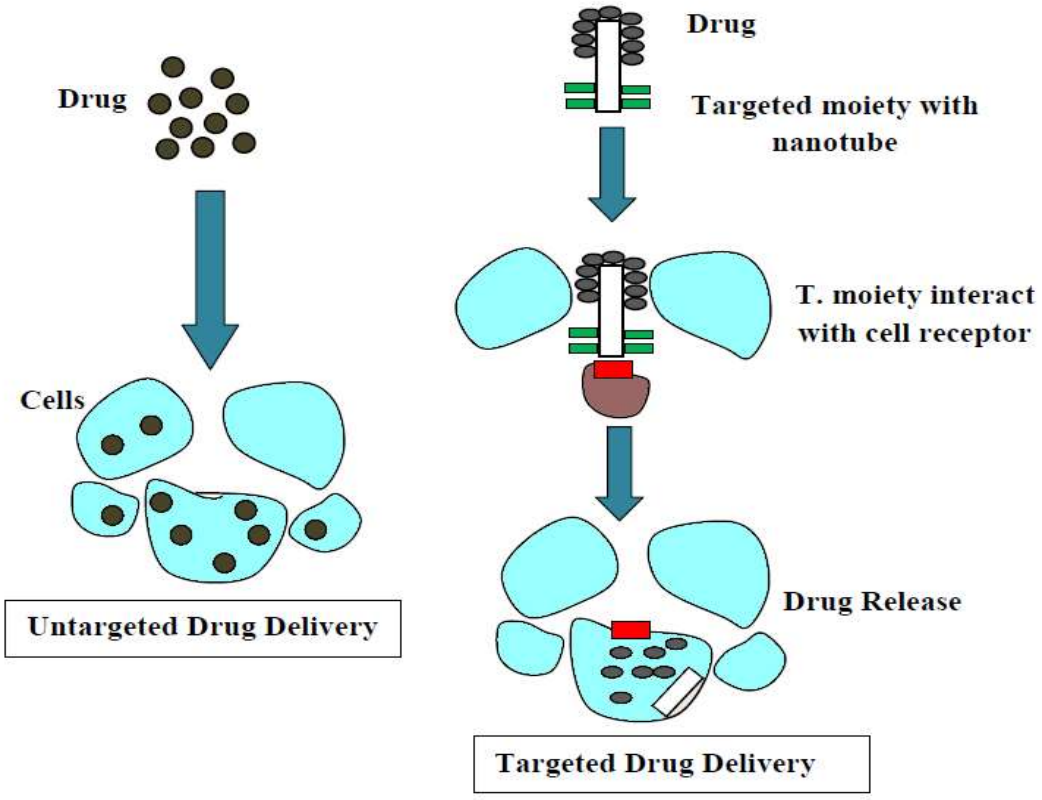


Figure 1: Drug targeting technology [8]

Barriers in brain-targeted drug delivery-

Consideration of several obstacles to drug delivery to the brain can highlight the ineffectiveness of systemically administered medications to effectively treat many Central nervous system (CNS) illnesses. The barriers of brain shown in figure-2. [3]

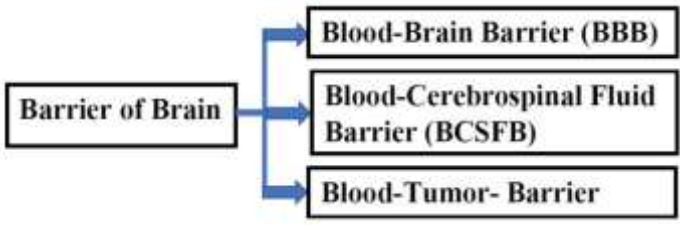


Figure 2: Barriers in brain-targeted drug delivery system [3]

A. **Blood-Brain Barrier (BBB)**- The blood-brain barrier (BBB) is a highly selective permeability barrier in the central nervous system that separates circulating blood from brain extracellular fluid. [3] The basal membrane, surrounding endothelial cells, and brain cells like pericytes and astrocytes build and maintain the blood-brain barrier, an enzymatic and physical barrier. In brain capillaries, BBB tight connections develop between endothelial cells to stop chemicals from entering the brain paracellularly. [9] An estimated 95% of the blood-brain barrier (BBB) surface area is made up of micro-capillaries, which have small diameters and thin walls compared to the vessels in other organs and appear to be the main pathway by which chemicals reach the brain. In brain capillaries, intercellular cleft, pinocytosis, and fenestrate are nonexistent; exchange must be trans-cellularly. As a result, the blood-brain barrier (BBB) can only be penetrated passively by lipid-soluble solutes that can readily diffuse through the capillary endothelial membrane. [10]

B. **Blood cerebrospinal fluid barrier (BCSFB)**- Another barrier preventing blood from reaching the brain is the blood-cerebrospinal fluid barrier (BCSFB). It divides the cerebrospinal fluid from the blood (CSF). However, this barrier is not regarded as a key pathway for drug uptake because its surface area is 5000 times smaller than that of the blood-brain barrier (BBB). [11–14] The cerebrospinal fluid (CSF) and brain parenchymal interstitial fluid can exchange molecules, and the blood-cerebrospinal fluid barrier (BCSFB) carefully controls the entry of blood-borne molecules into the cerebrospinal fluid (CSF). The choroid plexus epithelium, where the blood-cerebrospinal fluid barrier (BCSFB) is located, is set up in a way that prevents molecules and cells from entering the cerebrospinal fluid (CSF). [15–17] At the blood-CSF barrier, the choroid plexus, and arachnoid membrane collaborate. [18] The blood-CSF barrier is formed by the arachnoid membrane, which is typically impermeable to hydrophilic substances and has a primarily passive role. The cerebrospinal fluid (CSF) is actively regulated by the choroid plexus, which also creates cerebrospinal fluid. [18]

C. **Blood-tumour barrier**- When the target is a Central nervous system (CNS) tumour, intracranial drug delivery becomes even more difficult. The presence of the blood-brain barrier (BBB) in the Central nerve system (CNS) tumour microvasculature has clinical implications. [19] In Central nerve system (CNS) malignancies where the blood-brain barrier (BBB) is extensively disrupted, a range of physiological obstacles common to all solid tumours prevents medication delivery via the circulatory system. Drug delivery to neoplastic cells in a solid tumour is compromised by the heterogeneous distribution of microvasculature across the tumour interstitial, leading to

spatially uneven drug delivery. However, as a tumour enlarges, the vascular surface area decreases, which inhibits the exchange of blood-borne chemicals between vessels. In addition, due to the high interstitial tumour pressure and the accompanying peri-tumoral oedema, the intra-capillary distance increases, increasing both the diffusional requirement for drug delivery to neoplastic cells as well as the hydrostatic pressure in the healthy brain parenchyma next to the tumour. This leads to exceedingly low extra-tumoral interstitial drug concentrations since the cerebral microvasculature in these tumour-adjacent normal brain regions maybe even less permeable to medicines than normal brain endothelium. [20] The blood-brain barrier (BBB) can also be damaged by brain tumours, but this damage is limited and non-homogeneous. [21]

Mechanism of transfer of drug via blood-brain barrier (BBB)-

A. **Transmembrane diffusion-** Most drug pass through the blood-brain barrier through transmembrane diffusion. Drug binding to the cytomembrane is necessary for this non-saturable process. This mechanism is favored by small molecular mass & high lipid solubility. A medicine that is absorbed by the blood-brain barrier (BBB) membranes must then partition into the hydrated medium of the brain interstitial fluid to work. A lipid-soluble chemical may therefore be trapped by the capillary bed and obstruct its path to the cells behind the blood-brain barrier (BBB). The rate of transport through the blood-brain barrier (BBB) and the number of drugs presented in the brain both influence the percentage of administered drugs entering the brain. The largest chemical known to penetrate the blood-brain barrier (BBB) by transmembrane diffusion is cytokine-induced neutrophil chemoattractant-1 (CINC-1), which has a molecular weight of 7800 Dalton. [3]

B. **Saturable transport system**- A saturable transport system is used by some medications or compounds with drug-like effects to traverse the blood-brain barrier (BBB). Levo Dopa (L-DOPA) and caffeine are two examples. A transporter's endogenous ligand crosses the blood-brain barrier (BBB) at a rate that is around 10 times faster than would be anticipated if it did so via transmembrane diffusion. Additionally, several carriers for regulatory molecules, including peptides and proteins, are preferentially absorbed by particular brain areas. Saturable systems frequently regulate the rate at which their ligands cross the blood-brain barrier (BBB). For molecules like glucose that depend on blood flow, the transport rate is a function of that blood flow. Several different agents can change how slowly moving items are carried. Leucine is an example of a peptide that controls the peptide transport system's rate of transport (PTS-1). [3] The transport of molecules across the brain barriers shown in figure-3.

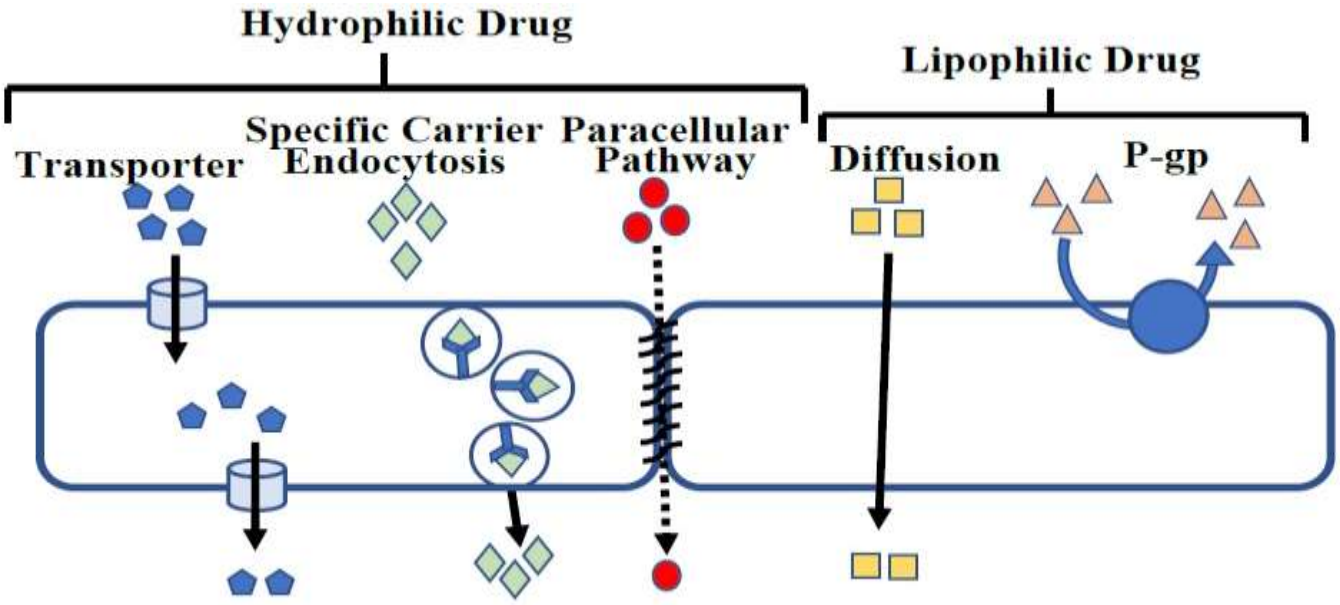
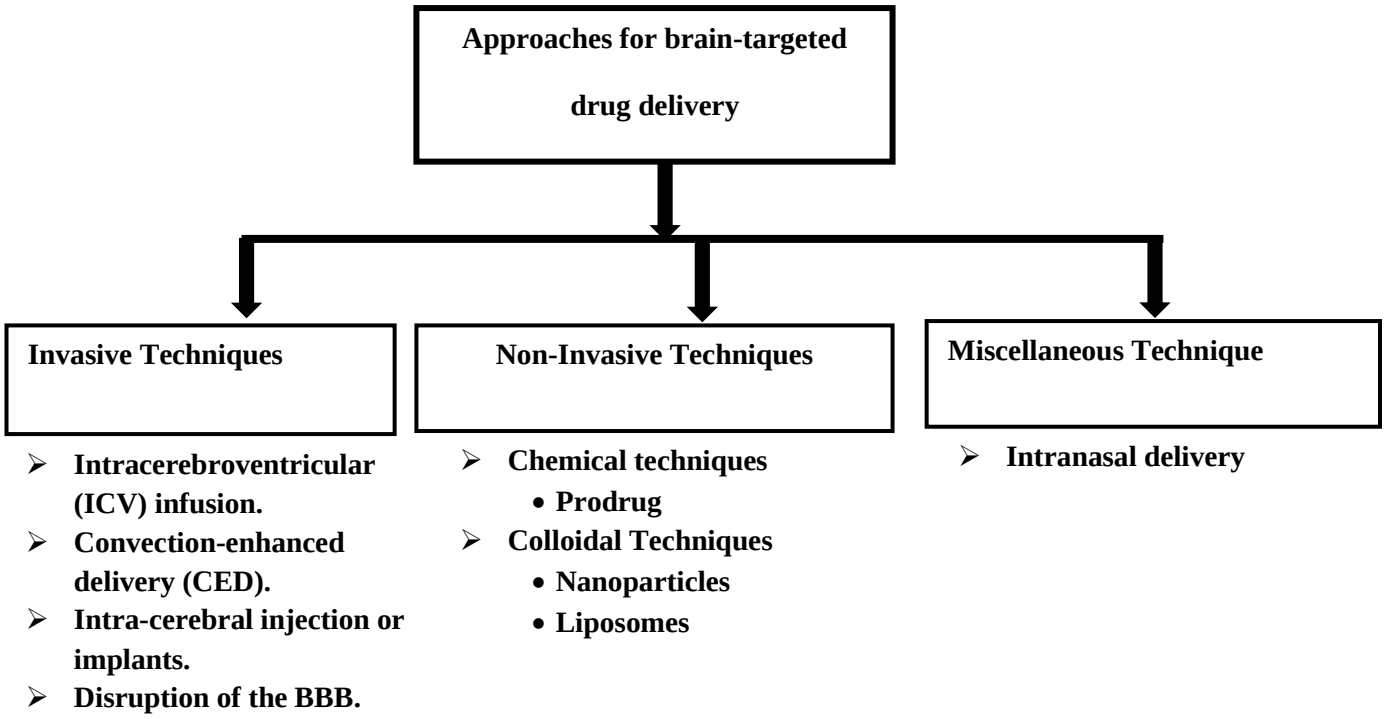


Figure 3: Schematic representation of the transport of molecules across BBB [9]

Challenges in the brain-targeted drug delivery-

The first is that many times, even when a compound crosses the barrier, it does not do so in such a way that the drug is in a therapeutically relevant concentration. The simplest explanation is that the drug was produced in such a way that only a small amount can pass through the barrier. Another possibility is that the drug binds to other proteins in the body, rendering it ineffective to be therapeutically active or to cross the barrier with the protein that has become attached. Another challenge is the occurrence of enzymes in brain tissue, which could render the drug inactive. [3]

Approaches for delivery of drugs targeted to the brain-



1. **Invasive techniques-** Drugs can be administered to the brain by first drilling a hole in the brain, after which an implant is placed intracerebrally (IC) or infusion is administered by Intra-Cerebro Ventricular (ICV) route. This route can allow for a wide range of compounds and formulations for ICV or IC administration. Both big and small compounds can be given, either alone or in different polymer compositions, to ensure continuous release. [3]

Various invasive techniques:

- Intra-cerebro-ventricular infusion
- Convection-enhanced delivery
- Intracerebral Implants
- Breakdown of the blood-brain barrier (BBB)

A. Intra-cerebro-ventricular infusion-A drug's concentration in the brain at 1-2 mm below the surface is said to be just 1-2% of the cerebrospinal fluid (CSF) concentration. Drugs could be easily delivered to the brain's surface via intraventricular drug infusion but not to the brain parenchyma. Pharmacologic effects can be observed following Intra-Cerebro Ventricular (ICV) delivery if the drug's target receptors are close to the ependymal surface of the brain. [3]

Limitations- There is relatively little drug diffusion in the parenchyma of the brain. A target must be close to the ventricles for this type of medication administration to be effective. Antibiotics like glycopeptide and aminoglycoside, for instance, are used to treat meningitis.

B. Convection-enhanced delivery (CED)- The basic idea behind convection-enhanced delivery (CED) is the stereo-tactically guided insertion of a small-calibre catheter into the brain parenchyma. Through this catheter, infusate is actively injected into the brain parenchyma and enters the interstitial space. The catheters are withdrawn at the bedside after the infusion, which lasts several days. After as little as 2 hours of continuous infusion, convection-enhanced delivery (CED) has been demonstrated in laboratory studies to deliver high molecular weight proteins 2 cm from the injection site in the brain parenchyma. [3]

Limitations- Some areas of the brain, particularly infiltrated tissues surrounding a cavity, are difficult to completely saturate with infusate. The placement of catheters is critical for proper drug delivery.

C. Intracerebral implants- Direct drug administration into the brain parenchymal space is possible by:

- Intrathecal injection administered directly.
- Release control matrices.
- Chemicals microencapsulated.

In general, diffusion is the mechanism. useful in the treatment of many Central nervous systems (CNS) conditions like Parkinson's disease and brain cancers. [3]

Limitations-There is an exponential decrease in the distribution with distance by diffusion. To achieve efficacy and avoid the problem associated with drug diffusion in the brain parenchyma, the injection site must be precisely mapped.

D. Disruption of the BBB- This method, which is frequently employed for Central nerve system (CNS) medication delivery, requires disrupting the blood-brain barrier. The blood-brain barrier (BBB) may be damaged by X-ray exposure and solvent injections like ethanol and dimethyl sulfoxide. The blood-brain barrier (BBB) may also be impacted by pathological circumstances including hypertension, hypoxia, or ischemia. Alcoholic and hypoglycaemic coma have different effects on blood-brain barrier (BBB) permeability which depend on the energy metabolism. These are two important techniques for disrupting the blood-brain barrier (BBB). [3]

Limitations of the invasive approach- These methods are all relatively expensive, call for hospitalization, and involve anaesthetics. After the successful breakdown of the BBB, these techniques may enhance tumour dissemination. Neurons may

be permanently injured if inappropriate blood components enter the brain.

2. Non-Invasive techniques- The brain's blood vessel network has been used for drug distribution in several non-invasive brain drug delivery methods. Non-invasive methods rely on medication manipulations, which can involve changes [3] like:

A. Chemical methods

a. Prodrug

B. Colloidal Techniques

a. Nanoparticles

b. Liposomes

A. Chemical techniques-

a. Prodrug- Prodrug that can penetrate the blood-brain barrier (BBB) and is lipid-soluble. The prodrug is digested and changed into the parent drug inside the brain. Prodrugs are substances that lack pharmacological activity. The goal of chemical modification is frequently to enhance physical characteristics like solubility or membrane permeability. A drug that has been covalently joined to an inert chemical component is referred to as a prodrug. When the connected molecule in the prodrug is split by hydrolytic or enzymatic activities, the active drug is created. Prodrugs should have to attach chemical moieties that improve the drug's lipoidal character. Examples: levodopa, GABA, Niflumic acid, and valproate. [3]

Limitations of the prodrug-

- The approach is unfavourable to pharmacokinetics.
- The increased molecular weight of the drug follows lipidation.

B. Colloidal techniques-

When certain amphiphilic building blocks are in contact with water, they form a vesicular system of highly ordered assemblies of one or more concentric lipid bilayers. Drug carriers may be made to deteriorate gradually, react to stimuli, and target specific sites. Controlling drug loss and degradation, avoiding negative side effects, and improving drug accessibility at the site of the disease are the ultimate objectives. Some of the advantages of a vesicular drug delivery system [3] include:

- Extends the time the medication is available in the bloodstream and lessens toxicity if selective absorption is possible because the medication is delivered right to the infection site.
- Enhances bioavailability, particularly for poorly soluble medicines.
- It is possible to integrate drugs that are both hydrophilic and lipophilic.
- Acts as a sustained-release mechanism and delays the clearance of medicines that are quickly metabolized.

a. Nanoparticles- Nanoparticles are solid particles or particulate dispersions with sizes ranging from 10 to 1000nm. A nanoparticle matrix is used to either dissolve, trap, encapsulate, or bind the medication. [22] Both active and passive medication targeting uses nanoparticles. These devices can only encapsulate modest amounts of material due to their small size. Nanoparticle systems in Central nerve system (CNS) targeted medication therapy offer improved therapeutic and diagnostic agent penetration compared to conventional therapies. Nanotechnology can be used to carry the medicine over the blood-brain barrier (BBB) to the targeted region, release it at a controlled rate, and prevent degradation processes. The targeted delivery of drug via nanoparticle shown in figure-4. These systems can also reduce toxicity to the peripheral organ. Examples of Nanoparticle medications include vaccines and cancer treatments for metastatic brain tumours. [23] Additionally, the application of nanoparticles for oral and ophthalmic administration was studied concurrently. [24]

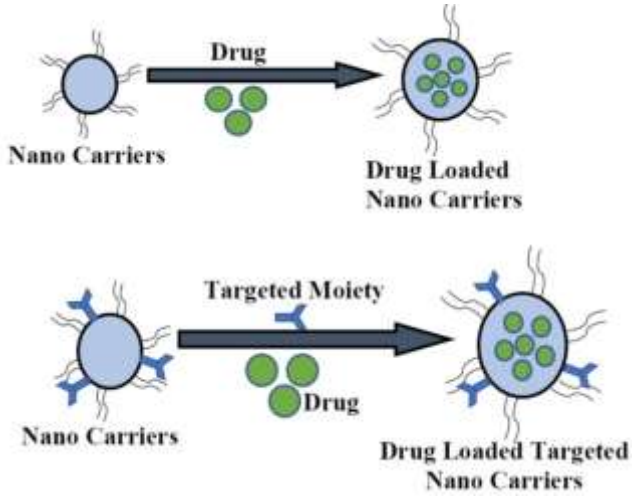


Figure 4: Drug-loaded nanoparticle for targeted drug delivery [1]

Advantages of nanoparticles- Some advantages like [25]

- It is simple to alter the surface characteristics and size of nanoparticles to accomplish active and passive targeting.
- The release of drugs can be regulated or prolonged to boost therapeutic effectiveness while lowering negative effects.
- They have a longer shelf life because they can be kept for up to a year.
- They have a larger carrier capacity, allowing pharmaceuticals to be included without producing a chemical reaction and maintaining pharmacological activity.
- They can incorporate both hydrophilic and hydrophobic drug molecules.
- The system can be given orally, nasally, parenterally, or intravenously, all of which have the potential to increase medication bioavailability.

Disadvantages of nanoparticles- Some disadvantages like [25]

- Manufacturing cost is high.
- These have a low efficiency of encapsulation.
- Water-soluble medications can rapidly leak out when there are blood components present.
- Nanoparticles can agglomerate due to their tiny size and huge surface area, which makes physical handling of both dry and liquid forms challenging.
- They may cause an allergic reaction as well as an immunological response.
- In the preparation process, harsh toxic solvents may be used.

Mechanisms of blood-brain barrier nanoparticle transport-

The blood-brain barrier can be crossed by nanoparticles using six different boosting mechanisms.

- Nanoparticle adhesion to the walls of blood vessels in the brain [26]
- Surfactants' fluidization of the blood-brain barrier (BBB) endothelium [27]
- Opening of endothelial tight junctions [28]
- Transcytosis across the endothelial cells in the brain [29]
- Brain endothelial cell blockage of the glycoprotein [30]
- Brain vascular endothelial cells endocytosis [31]

b. Liposomes- Liposomes are tiny, submicron-sized vesicles consisting of one or more phospholipid bilayers arranged in concentric layers and spaced apart by hydrate compartments. Additionally, it has been suggested that liposomes might improve drug transport across the blood-brain barrier (BBB). Even though liposomes have been demonstrated to improve the brain absorption of various medications after intravenous delivery. Adding ligands to the surfaces of liposomes stabilizes them sterically [32–34] Transferrin surface conjugated liposomes have recently been used to deliver the anticancer drug 5-fluorouracil (5-FU) to the brain. One of the most effective anticancer drugs, 5-FU, cannot reach a concentration that is effective in brain tumour cells when given systemically. Modified liposomes have also been utilized to enhance the delivery of genes to brain tumours. [35]

Advantages of liposomes [35,36] -

- Liposomes are suitable for administering hydrophobic, amphipathic, or hydrophilic medicines because they are biocompatible, biodegradable, non-toxic, and immunogenic.
- Keep the medicine inside the capsule away from the surroundings.
- Minimize the exposure of vulnerable tissue to harmful medicines, while increasing stability.

Disadvantages of liposomes [36] -

- The formulation cost is expensive.
- Leakage and fusion of encapsulated drugs or molecules may occur.
- Relatively short half-life.

3. Miscellaneous technique-

a. Intranasal drug delivery- The medicine is administered through the nasal cavity using this delivery method. Analgesics, sedatives, hormones, cardiovascular medications, vaccinations, and corticosteroid hormones are all administered systemically as well as to the central nervous system (CNS) through the nasal mucosa. [3]

Transport mechanism-The direct nasal-to-brain drug delivery mechanism is based on two mechanisms:

- Intracellular transport-mediated route
- Extracellular transport-mediated pathways

It takes hours for intra-nasally injected drugs to reach the olfactory bulb via the intracellular transport-mediated route. The extracellular transport pathway is a quick one. The first extracellular transport-based route allowed for intranasally delivered drugs to first cross the space between olfactory neurons in the olfactory epithelium before entering the olfactory bulb. The second extracellular transport-based route allows for intranasally delivered drugs to cross through the BBB by travelling down the trigeminal nerve. The medication diffuses into other parts of the brain when it reaches the olfactory bulb, possibly assisted by the perivascular pump. [3]

Advantages of intranasal drug delivery [3] -

- Fast drug absorption through highly vascularized mucosa.
- Drugs that not be absorbed orally may be administered by systemic circulation using a nasal drug delivery system.
- Long-term therapy was a convenient route as compared to the parenteral route.
- Absorption enhancers or other approaches can improve the bioavailability of larger drug components.
- It is Self-administered.
- A large nasal mucosal surface area for dosage absorption.

Disadvantages of intranasal drug delivery [3] -

- Some medications can irritate the nasal mucosa.
- The ingestion of drugs may be hampered by nasal congestion brought on by a cold or allergies.
- Drug distribution should become less effective as molecular weight rises.

New developments in the brain-targeted drug delivery system-

Table 1: Recent Advances in Brain-Targeted Drug Delivery

S. N.	Recent Advances	Explanation
1.	Dendrimers [37]	A dendrimer is a highly branched polymer molecule formed by a central core to which the branches are attached, the shell of the branches enclosing the core, and the surface formed by the termini of branches. Dendrimers conjugated with anti-cancer agents have been studied as drug delivery carriers to the brain for the treatment of tumours at the CNS level.
2.	Scaffolds [38]	Scaffolds are implantable and can be used to treat a variety of brain injuries and disease-related conditions. Woerly S et al. investigated the efficacy of poly (hydroxyl phenyl methacrylate) [PHPMA] and PHEMA scaffolds containing glucosamine or N-acetylglucosamine groups in a fimbria-fornix lesion cavity when implanted between the septum and the hippocampus. PHEMA scaffolds were found to have significantly less connective tissue infiltration than PHPMA scaffolds.

3.	Lipoplexes and Polyplexes [38]	To improve new DNA delivery into cells, the DNA must be protected from damage and its entry into the cell must be facilitated. Lipoplexes and polyplexes are used for this. A lipoplex is formed when the organized structure is complex with DNA. The majority of polyplexes are made up of cationic polymers and are formed through ionic interactions. One significant difference between lipoplexes and polyplexes is that polyplexes cannot release the associated DNA into the cytoplasm.
4.	Polyanhydrides [39]	Polyanhydrides are biodegradable polymers that primarily release the drug through simple hydrolysis. Polyanhydrides are intracerebral implants that are used for controlled drug delivery. Polyanhydrides are drugs embedded in a polymer matrix.
5.	Modified nanoparticles [40, 41]	Multifunctional nanoparticles. Magnetic nanoparticles for MRI.
6.	Receptor-mediated transport (RMT) [42]	Monoclonal antibody (MAb) molecular Trojan horses (MTH). Trojan horse liposomes for CNS gene therapy. In vivo brain imaging of gene expression.
7.	Transporter-independent mechanisms to circumvent the BBB [42, 43]	Convection-enhanced drug delivery (CED). Bradykinin receptor-mediated BBB opening. Ultrasound-mediated BBB opening.

Conclusion-

The lack of specialized and effective methods affects the administration of medications for the treatment of cerebral illnesses. Despite these difficulties, brain targeting techniques have advanced significantly. However, none have proven to be satisfactory. This review concludes that the drug can be efficiently delivered across the blood-brain barrier (BBB) according to the methods mentioned above. The difficulties posed by brain drug administration have been decisively overcome by recent developments in drug delivery through the blood-brain barrier (BBB). Thus, since these approaches are useful in brain targeting, there is still a need for the most reliable techniques or methods that are clinically significant as well as cost-effective.

Conflict of Interest-

There are no conflicts of interest surrounding the publishing of this paper, according to the author.

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References-

1. Mantry S, Bhagyalaxmi M, Kumar SA, "Targeted Drug Delivery System" International Journal of Innovative Pharmaceutical Sciences and Research, 2014; 2(10):2596-2635.

2. Rani K, Paliwal S, "A review on targeted drug delivery: Its entire focus on advanced therapeutics and diagnostics" Sch. J. App. Med. Sci, 2014; 2(1):328-331.

3. Varsha Z, Gite VZ, Ghume VK, Kachave RN, "Brain Targeted Drug Delivery System" World Journal of Pharmaceutical And Medical Research, 2020; 6(11):45-57.

4. Misra A, Ganesh S, Shahiwala A, Shah SP, "Drug delivery to the central nervous system: a review" J Pharm Pharm Sci. 2003; 6(2):252-273.

5. Schinkel AH, Wagenaar E, Mol CA, Van Deemter L, "P-glycoprotein in the blood-brain barrier of mice influences the brain penetration and pharmacological activity of many drugs" The Journal of clinical investigation, 1996; 97(11):2517-2524. https://doi.org/10.1172/JCI118699

6. Pardridge WM, "Blood-brain barrier drug targeting: the future of brain drug development" Molecular interventions, 2003; 3(2):90-105. https://doi.org/10.1124/mi.3.2.90

7. Shinde SC, Mahale NB, Chaudhari SR, Thorat RS, "Recent advances in brain targeted drug delivery system: A review" World J Pharm Res, 2015; 4(5):542-549.

8. Mehmood Y, Tariq A, Siddiqui FA, "Brain targeting drug delivery system: a review" International Journal of Basic Medical Sciences and Pharmacy (IJBMSP), 2015; 5(1):32-40.

9. Singh SB, "Novel approaches for brain drug delivery system-review" International Journal of Pharma Research & Review, 2013; 2(6):36-44.

10. Misra A, Ganesh S, Shahiwala A, Shah SP, "Drug delivery to the central nervous system: a review" J Pharm Pharm Sci, 2003; 6(2):252-273.

11. Witt KA, Gillespie TJ, Huber JD, Egleton RD, Davis TP, "Peptide drug modifications to enhance bioavailability and blood-brain barrier permeability" Peptides, 2001; 22(12):2329-43. https://doi.org/10.1016/S0196-9781(01)00537-X

12. Alavijeh MS, Chishty M, Qaiser MZ, Palmer AM, "Drug metabolism and pharmacokinetics, the blood-brain barrier, and central nervous system drug discovery" NeuroRx, 2005; 2(4):554-571. https://doi.org/10.1602/neurorx.2.4.554

13. Egleton RD, Davis TP, "Bioavailability and transport of peptides and peptide drugs into the brain" Peptides, 1997; 18(9):1431-9. https://doi.org/10.1016/S0196-9781(97)00242-8

14. Deeken JF, Loscher W, "The blood-brain barrier and cancer: transporters, treatment, and Trojan horses" Clinical cancer research, 2007; 13(6):1663-1674. https://doi.org/10.1158/1078-0432.CCR-06-2854

15. Pardridge WM, "Non-invasive drug delivery to the human brain using endogenous blood-brain barrier transport systems" Pharmaceutical science & technology today, 1999; 2(2):49-59. https://doi.org/10.1016/S1461-5347(98)00117-5

16. Singh AK, Singh A, Madhv NVS , Nasal cavity, a promising transmucosal platform for drug delivery and research approaches from nasal to brain targeting, Journal of drug delivery and therapeutics 2012; 2(3). https://doi.org/10.22270/jddt.v2i3.163

17. Kusuhara H, Sugiyama Y, "Efflux transport systems for drugs at the blood-brain barrier and blood-cerebrospinal fluid barrier (Part

1)" Drug discovery today, 2001; 6(3):150-156. https://doi.org/10.1016/S1359-6446(00)01632-9

18. Siegal T, Zylber-Katz E, "Strategies for increasing drug delivery to the brain" Clinical pharmacokinetics, 2002; 41(3):171-186. https://doi.org/10.2165/00003088-200241030-00002

19. Rasheed A, Theja I, Silparani G, Lavanya Y, Kumar CA, "CNS targeted drug delivery: current perspectives" JITPS, 2010; 1(1):9-18.

20. Gabathuler R, "Approaches to transport therapeutic drugs across the blood-brain barrier to treat brain diseases" Neurobiology of disease, 2010; 37(1):48-57. https://doi.org/10.1016/j.nbd.2009.07.028

21. Jones AR, Shusta EV, "Blood-brain barrier transport of therapeutics via receptor-mediation" Pharmaceutical Research, 2007; 24(9):1759-1771. https://doi.org/10.1007/s11095-007-9379-0

22. Mohanraj VJ, Chen Y, "Nanoparticles-a review" Tropical journal of pharmaceutical research, 2006; 5(1):561-573. https://doi.org/10.4314/tjpr.v5i1.14634

23. Chaudhary K, Parihar S, Sharma D, A Critical Review on Nanoscience Advancement: In Treatment of Viral Infection. Journal of Drug Delivery and Therapeutics 2021; 11(6):225-237 https://doi.org/10.22270/jddt.v11i6.5030

24. Des Rieux A, Fievez V, Garinot M, Schneider YJ, Preat V, "Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach" Journal of controlled release, 2006; 116(1):1-27. https://doi.org/10.1016/j.jconrel.2006.08.013

25. Singh D, Harikumar SL, Nirmala, "Nanoparticles: An Overview" Journal of Drug Delivery & Therapeutics, 2013; 3(2):169-175. https://doi.org/10.22270/jddt.v3i2.407

26. Kelly KA, Allport JR, Tsourkas A, Shinde-Patil VR, Josephson L, Weissleder R, "Detection of vascular adhesion molecule-1 expression using a novel multimodal nanoparticle" Circulation research, 2005; 96(3):327-336. https://doi.org/10.1161/01.RES.0000155722.17881.dd

27. Batrakova EV, Li S, Vinogradov SV, Alakhov VY, Miller DW, Kabanov AV, "Mechanism of pluronic effect on P-glycoprotein efflux system in blood-brain barrier: contributions of energy depletion and membrane fluidization" Journal of Pharmacology and Experimental Therapeutics, 2001; 299(2):483-493.

28. Brightman MW, Hori M, Rapoport SI, Reese TS, Westergaard E, "Osmotic opening of tight junctions in cerebral endothelium" Journal of Comparative Neurology, 1973; 152(4): 317-325. https://doi.org/10.1002/cne.901520402

29. Descamps L, Dehouck MP, Torpier G, Cecchelli R, "Receptor-mediated transcytosis of transferrin through blood-brain barrier endothelial cells" American Journal of Physiology-Heart and Circulatory Physiology, 1996; 270(4):1149-58. https://doi.org/10.1152/ajpheart.1996.270.4.H1149

30. Nakagawa S, Deli MA, Kawaguchi H, Shimizudani T, Shimono T, Kittel A et al., "A new blood-brain barrier model using primary rat brain endothelial cells, pericytes and astrocytes" Neurochemistry international, 2009; 54(3-4):253-263. https://doi.org/10.1016/j.neuint.2008.12.002

31. Georgieva JV, Hoekstra D, Zuhorn IS, "Smuggling Drugs into the Brain: An Overview of Ligands Targeting Transcytosis for Drug Delivery across the Blood-Brain Barrier" Pharmaceutics, 2014; 6:557-583. https://doi.org/10.3390/pharmaceutics6040557

32. Gulyaev AE, Gelperina SE, Skidan IN, Antropov AS, Kivman GY, Kreuter J, "Significant transport of doxorubicin into the brain with polysorbate 80-coated nanoparticles" Pharmaceutical Research, 1999; 16(10):1564-1569. https://doi.org/10.1023/A:1018983904537

33. Krewson CE, Klarman ML, Saltzman WM, "Distribution of nerve growth factor following direct delivery to brain interstitium" Brain Res., 1995; 680:196-206. https://doi.org/10.1016/0006-8993(95)00261-N

34. Tosi G, Costantino L, Ruozi B, Forni F, Vandelli MA, "Polymeric nanoparticles for drug delivery to the central nervous system" Expert opinion on drug delivery, 2008; 5(2):155-174. https://doi.org/10.1517/17425247.5.2.155

35. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK, Hua S, "Advances and challenges of liposome assisted drug delivery" Frontiers in pharmacology, 2015; 6:286. https://doi.org/10.3389/fphar.2015.00286

36. Kant S, Kumar S, Prashar BA, "Complete Review on Liposomes" International research journal of pharmacy, 2012; 3(7):10.

37. Kabanov AV, Batrakova EV, Melik-Nubarov NS, Fedoseev NA, Dorodnich TY, Alakhov VY, Chekhonin VP, Nazarova IR, Kabanov VA, "A new class of drug carriers: micelles of poly (oxyethylene)-poly (oxypropylene) block copolymers as micro containers for drug targeting from blood in the brain" Journal of controlled release, 1992; 22(2):141-157. https://doi.org/10.1016/0168-3659(92)90199-2

38. Gupta AH, Kathpalia HT, "Recent advances in brain targeted drug delivery systems: a review" Int J Pharm Pharm Sci., 2014; 6(2):51-57.

39. Alam MI, Beg S, Samad A, Baboota S, Kohli K, Ali J, Ahuja A, Akbar M, "Strategy for effective brain drug delivery" European journal of pharmaceutical sciences, 2010; 40(5): 385-403. https://doi.org/10.1016/j.ejps.2010.05.003

40. Karanth H, Rayasa M, "Nanotechnology in brain targeting" Int. J. Pharm. Sci. Nanotechnology, 2008; 1:10-24. https://doi.org/10.37285/10.37285/ijpsn.2008.1.1.2

41. Lee Koo YE, Reddy GR, Bhojani M, Schneider R, Philbert MA, Rehemtulla A, et al., "Brain cancer diagnosis and therapy with nanoplatforms" Advanced drug delivery reviews, 2006; 58(14):1556-77. https://doi.org/10.1016/j.addr.2006.09.012

42. Michelle AE, William AB, "Neuroimmune Axes of the Blood-Brain Barriers and Blood-Brain Interfaces: Bases for Physiological Regulation, Disease States, and Pharmacological Interventions" Pharmacol Rev, 2018; 70(2):278-314. https://doi.org/10.1124/pr.117.014647

43. Lu CT, Zhao YZ, Wong HL, Cai J, Peng L, Tian XQ, "Current approaches to enhance CNS delivery of drugs across the brain barriers" International journal of nanomedicine, 2014; 9:2241-2257. https://doi.org/10.2147/IJN.S61288