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Brain Targeted Drug Delivery System: A Novel Approaches

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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.

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

INTRODUCTION

Drug delivery refers to approaches, formulations technologies and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. It may involve scientific site-targeting within the body or it might involve facilitating systemic pharmacokinetics, in any case it is typically concerned with both quantity and duration of drug presence. Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience. Current efforts in the area of drug delivery include the development of targeted delivery in which the drug is only active in the target area of the body. The goal of a targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased tissue. Targeted drug delivery system has been developed to optimize regenerative techniques. This helps maintain the required plasma and tissue drug levels in the body, thereby preventing any damage to the healthy tissue via the drug. Barriers in Brain Targeted Drug Delivery the failure of systemically delivered drugs to effectively treat many CNS diseases can be rationalized by considering a number of barriers that inhibit drug delivery to the CNS. There are physical barriers that separate the brain extracellular fluid from the blood

1**. Blood-Brain Barrier**
2. Blood-Cerebrospinal Fluid Barrier
3. Blood-Tumor Barrier

1) **Blood - Brain Barrier (BBB):** The blood – brain barrier (BBB) is a highly selective permeability barrier that separates the circulating blood from the brain extracellular fluid in the central nervous system. The blood brain barrier is formed by capillary endothelial cells, which are connected by tight junctions with an extremely high electrical resistivity of at least 0.1 µm. It is estimated that more than 98% of small molecular weight drugs and practically 100% of large molecular weight drugs (mainly peptides and proteins) developed for CNS pathologies do not readily cross the BBB. Endothelial cells restrict the diffusion of microscopic objects (e.g., bacteria) and large or hydrophilic molecules into the cerebrospinal fluid (CSF), while allowing the diffusion of small hydrophobic molecules (e.g., O2, CO2, hormones, etc.) [(1)]

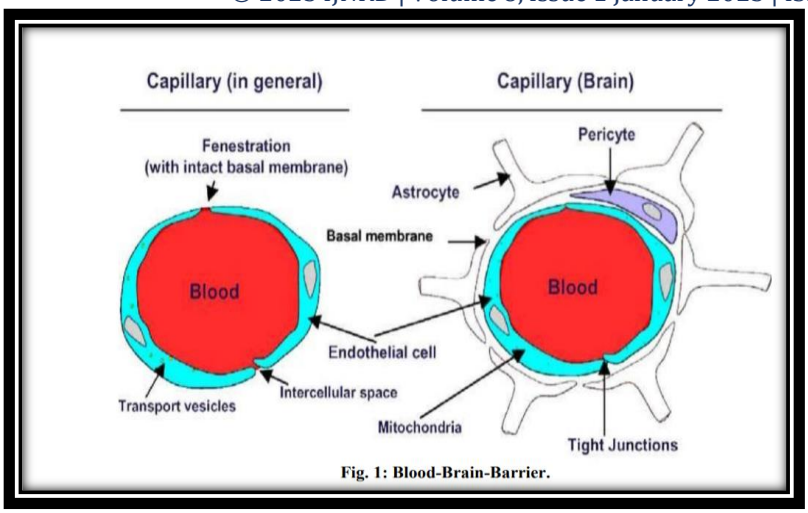


Fig. 1: Blood-Brain-Barrier.

2) **Blood - Cerebrospinal Fluid Barrier (BCSFB)**: The second barrier, loca ted at the choroids plexus, is represented by the blood-cerebrospinal fluid barrier that separates the blood from the cerebrospinal fluid (CSF) which, in turn, runs in the subarachnoid space surrounding the brain. On the external surface of the brain the epidermal cells fold over onto themselves to form a double layered structure, which lies between the dura and pia, this is called the archnoid membrane. Within the double layer is the subarachnoid space, which participates in CSF drainage. Passage of substances from the blood through the archnoid membrane is prevented by tight junction. [(2)]

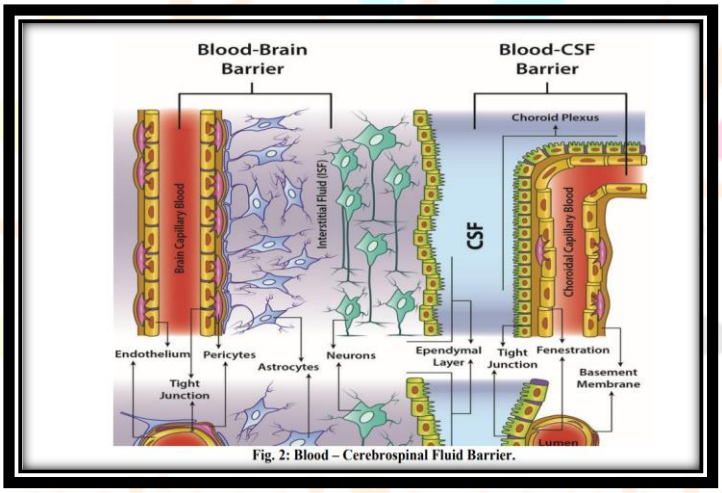


Fig. 2: Blood – Cerebrospinal Fluid Barrier.

3) Blood – Tumor Barrier: Intracranial drug delivery is even more challenging when the target is a CNS tumor. For example, even when primary and secondary systemic tumour's respond to chemotherapeutic agents delivered via the cardiovascular system, intracranial metastases often continue to grow. At the same time, intracapillary distance increases, leading to a greater diffusional requirement for drug delivery to neoplastic cells and due to high interstitial tumor pressure and the associated peritumoral edema leads to increase in hydrostatic pressure in the normal brain parenchyma adjacent to the tumor. As a result, the brain may be less permeable to drugs than normal brain endothelium. [(3)]

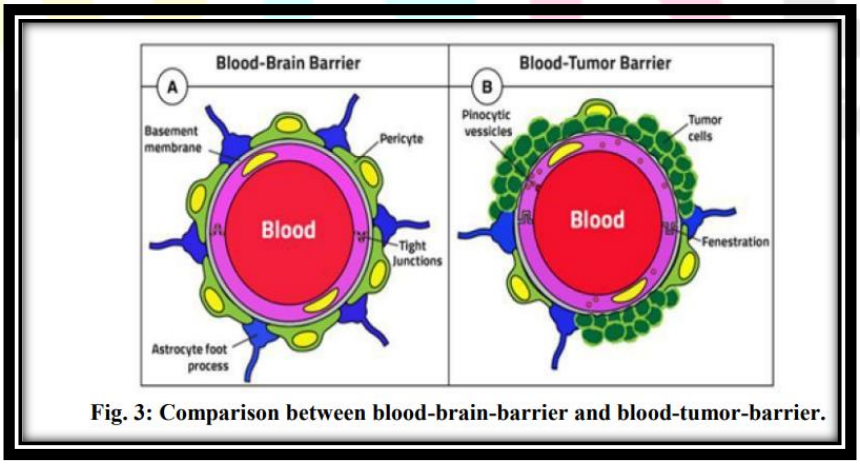
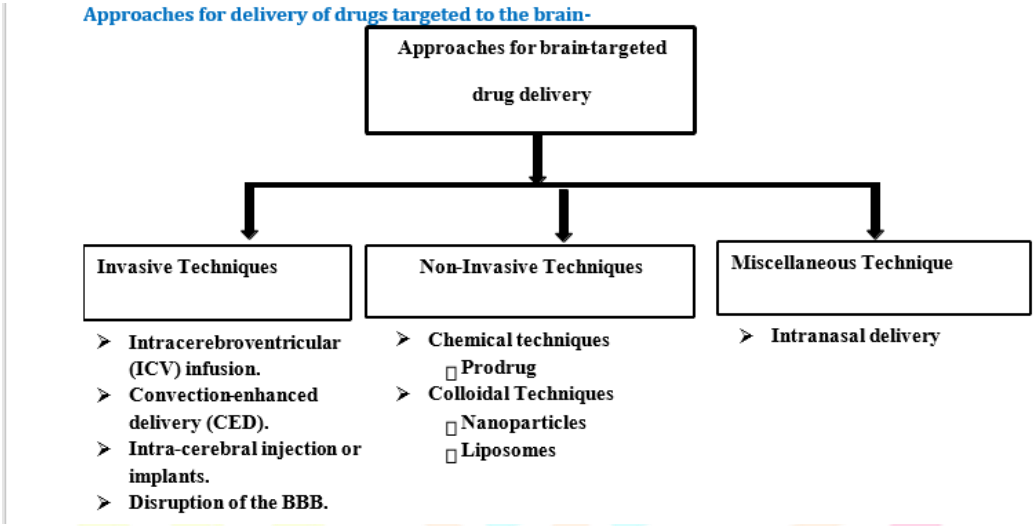


Fig. 3: Comparison between blood-brain-barrier and blood-tumor-barrier.

Approaches to CNS drug delivery:

Basically, two methods have been described in the literature to actively enhance drug delivery to the brain after systemic administration: either opening/disruption of the neuroprotective BBB by osmotic imbalance, ultrasound or vasoactive compounds (e.g., bradykinin or P-glycoprotein inhibitors), or physiological

strategies aiming to use endogenous transport mechanisms. While the first method has the disadvantage that those neurons may be damaged (semi)-permanently due to unwanted blood components entering the brain [4]. The physiological strategies have a largepotential as discussed in several review papers elsewhere. As a third alternative (using a combination of aspects of both methods), [5] positive charge has also been applied to compounds or drug carriers to quite effectively enhance the absorptive-mediated transport across the BBB however, a beneficial therapeutic window of this basically toxic transport mechanism has thus far not been established. To overcome the multitude of barriers restricting CNS drug delivery of potential therapeutic agents, numerous drug delivery strategies have been developed. These strategies generally fall into one or more of the following categories: invasive, non-invasive or miscellaneous techniques. [6]



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. [7] Various invasive techniques:

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

a) Intra-cerebral-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.

b) Convection-enhanced delivery (CED)- The basic idea behind convection-enhanced delivery (CED) is the stereotactically 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, convectionenhanced delivery (CED) has been demonstrated in laboratory studies to deliver high molecular weight proteins 2 cm from the injection site in the brain parenchyma. [8]

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.

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). [9]

2. Non-Invasive techniques- The brain's blood vessel network has been used for drug distribution in several noninvasive brain drug delivery methods. Non-invasive methods rely on medication manipulations, which can involve changes 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. [10]

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 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. [11] Both active and passive medication targeting uses nanoparticles.

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.

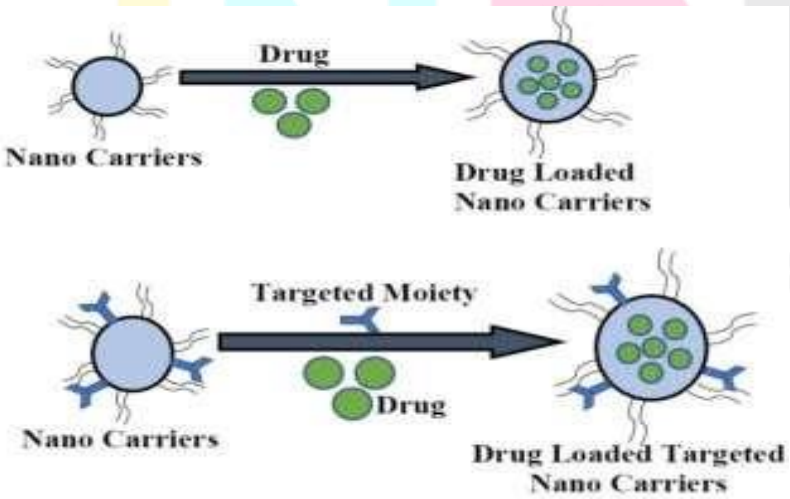


Fig. 4: Drug-loaded nanoparticle for targeted drug delivery [1]

Mechanism for transport

The mechanism for transport of lipoprotein to be endocytosis via the Low-Density Lipoprotein (LDL) receptor of the endothelial cells after adsorption of lipoproteins form blood plasma to the nanoparticles. suggested that the recognition and interaction with lipoprotein receptors on brain capillary endothelial cells is responsible for the brain uptake of the drug. [12]

Advantages of using nanoparticles for CNS targeted drug delivery

- Nanoparticles protect drugs against chemical and enzymatic degradation.
- Due to their small size nanoparticles penetrate into even small capillaries and are taken up within cells, allowing an efficient drug accumulation at the targeted sites in the body. Degradation.
- They are also able to reduce side effects of some active drugs.

Limitations of using nanoparticles for CNS targeted drug delivery

- Their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.
- In addition, small particles size and large surface area readily result in limited drug loading and burst release.

Example

Radiolabelled polyethylene glycol coated hexadecylcyanoacrylate nanospheres targeted and accumulated in a rat gliosarcoma. However, this method is not yet ready for clinical trials due to the accumulation of the nanospheres in surrounding healthy tissues.

B. Liposomes

Liposomes or lipid-based vesicles are microscopic (unilamellar or multilamellar) vesicles that are formed as a result of self-assembly of phospholipids in an aqueous media resulting in closed bilayered structures. Liposomes are potential carrier for controlled drug release of tumours therapeutic agents and antibiotic, for gene and antisense therapy through nucleic acid sequence delivery, immunization through antigen delivery and for antiParkinson's. [13]

Advantages

- Liposomes supply both a lipophilic environment and aqueous "milieu interne" in one system and are therefore suitable for delivery of hydrophobic, amphipathic and hydrophilic drugs and agents.
- Liposomes could encapsulate not only small molecules but also macromolecules like superoxide dismutase, haemoglobin, erythropoietin, interleukin2 and interferon-g.
- Liposomes reduced toxicity and increased stability of entrapped drug via encapsulation (eg. Amphotericin B, Taxol).

Limitations

- High production cost
- Leakage and fusion of encapsulated drug / molecules.
- Sometimes phospholipid undergoes oxidation and hydrolysis
- Short half-life
- Low solubility
- Less stability

C. Miscellaneous techniques Intranasal drug delivery

In nasal drug delivery system drug are deliver in nasal cavity. The nasal mucosa used for delivering the drugs for CNS disorders and systemic administration of analgesics, sedatives, hormones, cardiovascular drugs, and vaccines, corticosteroid hormones. [14]

Mechanism for transport

There are two mechanisms underlying the direct nose to brain drug delivery:

a. Intracellular transport mediated route
b. Extracellular transport mediated routes.

The intracellular transport mediated route is a relatively slow process, taking hours for intra nasally administered substances to reach the olfactory bulb. Extracellular transport mediated routes are rapid.

In the first extracellular transport-based route intranasal administered substances could first cross the gap between the olfactory neurons in the olfactory epithelium which are subsequently transported in to the olfactory bulb After reaching the olfactory bulb the drug enters in to other regions of brain by diffusion, which may also be facilitated by perivascular pump. [15]

Advantages of intranasal drug delivery

- Rapid drug absorption via highly vascularized mucosa.
- Convenient route when compared with parenteral route for long term therapy.
- Bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
- Self-administration

- Large nasal mucosal surface area for dose absorption.

Disadvantages of intranasal drug delivery

- Some drugs may cause irritation to the nasal mucosa
- Nasal congestion due to cold or allergies may interfere with absorption of drug.
- Drug delivery is expected to decrease with increasing molecular weight. **(16)**

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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