A Review on Various Strategies of Brain Targeting Drug Delivery

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Abstract-

Brain- targeted drug delivery is one of the most challenging deliveries for the treatment of CNS related disorders like brain tumors and neurodegenerative disorders. The blood-brain barrier is made to allow for the selective movement of chemicals that are crucial for brain function. But it poses a significant obstacle to many potentially helpful medications. Several tiny medications can sufficiently cross the BBB. This review offers details about the present studies on methods and recent advancements to deliver proteins, peptides, and tiny compounds to the brain and anatomy of the brain. Nano carrier-based delivery of drugs is widely used to target the challenging areas of the brain. Nano carriers, not only protects the drug from environmental degradation but also it efficiently promotes the bioavailability and capability of sustained drug release by circumventing biological barriers. Nasal medication delivery has also gained considerable traction and appeal in the market today, Because of its numerous advantages for treating both acute and chronic illnesses. The Drug is absorbed more effectively into the systemic bloodstream because of the highly vascularized epithelium. Therefore nasal route is an alternative route that can easily circumvent the BBB and is more acceptable.

Keywords- Blood-brain barrier, Colloidal drug delivery, brain targeting through nasal route, Types of nanoparticles.

Introduction-

Drug delivery to the CNS is exceedingly complicated and difficult, in order to treat CNS- related disorders. The Brain is a complex and sensitive organ. The deterioration of brain function is caused by some neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Sclerosis, Encephalitis, Epilepsy and Strock. Etc. The brain is a uniquely protected organ that resides within the body. The bony constraints of the cranium protect the brain but make the systemic drug distribution problematic. There are Several techniques are available to promote the delivery of medicament including nanoparticles, nanoemulsion, dendrimers, molecular Trojan

horses, viral vectors, prodrugs, and nasal routes, are being investigated for this purpose and will be investigated in the future. It is feasible to traverse the BBB using an endogenous transporter, a receptor, or an efflux pump. The blood flow to the brain is vital, ranging between 750 and 1000 mL/min (about 15% of total cardiac output)[1]. There are three types of barriers present in the brain that restricts the access of drugs to the targeted site; these are blood-brain barrier (BBB), Blood CSF barrier and blood tumor barrier. The blood- brain barrier, comprises the endothelial cells, astrocytes and pericytes. The endothelial cells that line the cerebral microvessels play a crucial part in regulating a precisely controlled milieu for dependable neuronal signaling. The impermeable BBB is made up of ECs being encircled by pericytes, astrocytes and basal membrane. The further barrier to chemicals entering the brain is the presence of efflux transporters in brain capillary ECs. Inter endothelial junctions are protein complexes like adherence junctions, TJs and gap junctions[2].The adherence junction mainly controls the permeability of endothelial membrane. The permeability barrier of ECs and epithelial cells, which regulates tissue homeostasis, is maintained by TJs in a crucial manner[3]. Six connexin molecules make up gap junctions, which enable direct electrical and chemical communication between ECs[4]. Several transcellular transport mechanisms can be identified-

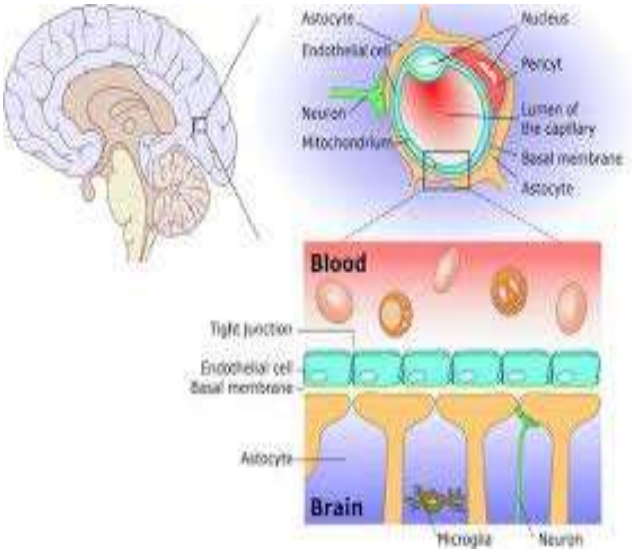


Figure: 1- Brain targeting

a. Most of the hydrophobic molecules are primarily delivered by diffusion mechanism, a concentration gradient drive it.
b. Paracellular transport, the transport of small water-soluble molecules, can only occur extracellular or by outside of cells.
c. Carrier- mediated transport is an energy-dependent transport of polar molecules like glucose amino acids and nucleoside therapeutics like vinca alkaloids and azidothymidine, etc.[5].

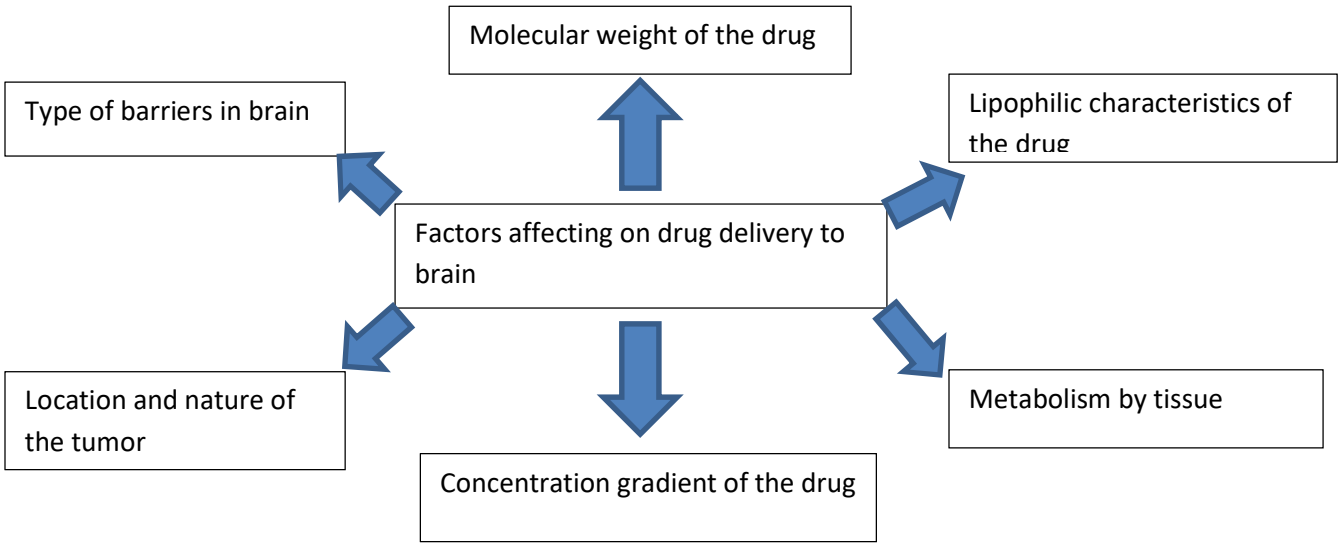
d. Receptor- mediated transcytosis for peptidic regulatory chemicals, food and signaling molecules.
e. Proton- pump efflux transporters[6].

B] Blood-Cerebrospinal fluid (CSF) barrier-

Brain containing CSF and circulating blood are separated by the blood-CSF barrier; this barrier does not provide a significant obstacle to the delivery of drugs because of its limited area than BBB (5000 folds smaller). The BCSFB is found in the epithelium of the choroid plexus, which is structured in such a way that molecules and cells cannot enter the CSF. Barriers separating the blood and CSF, the choroid plexus and arachnoid cooperate. Typically, the arachnoid membrane is resistant to hydrophilic substances.

C] Blood- Tumor Barrier-

The Blood-tumor barrier exists between blood tumor cells and micro vessels. The pathological disruption of BBB is depending on the location and variety of alterations brought on by a malignant tumor. It is very challenging to target the CNS tumor because of various factors which affect the transfer of drugs as follows-



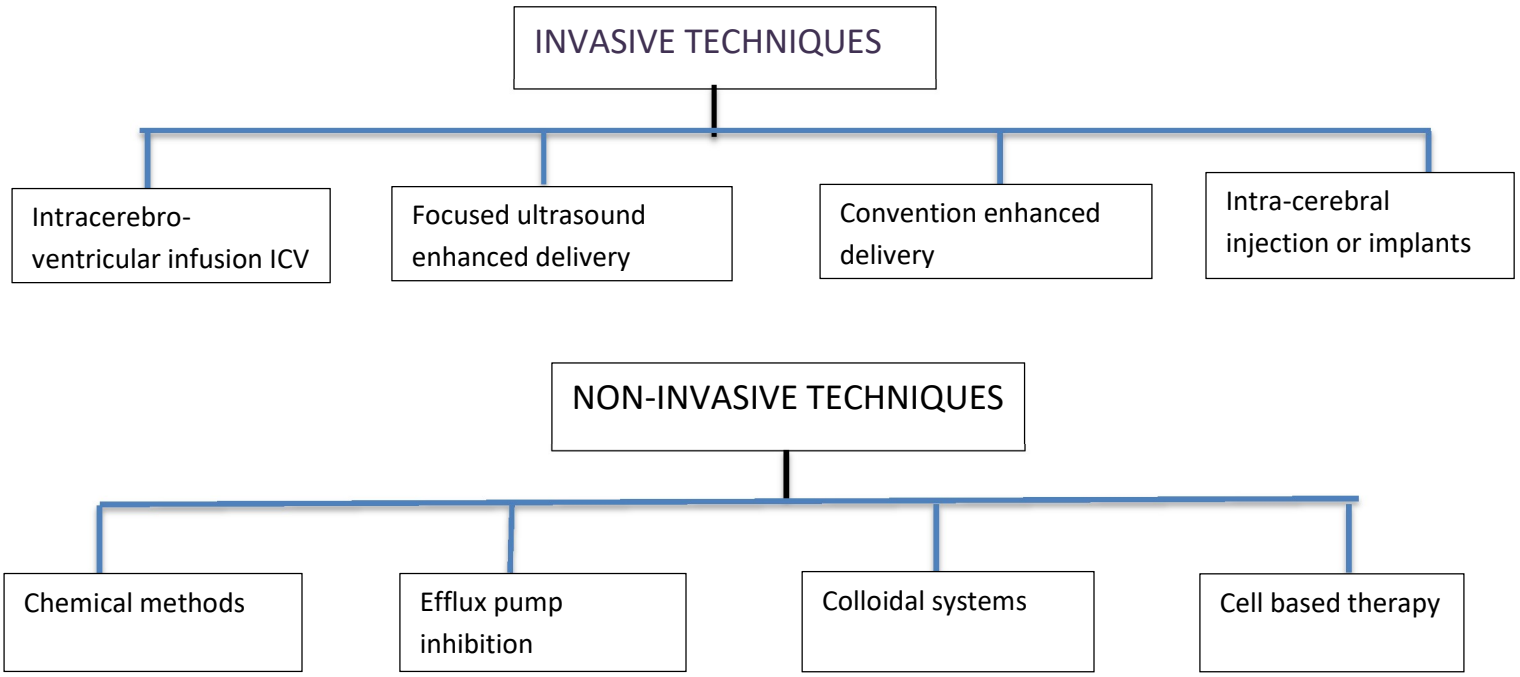
Recently, Nanocarriers have been used to deliver medicament to the targeted site; nanocarriers are the solid-lipid nanoparticles with size ranging from 1-1000nm. They are made up of either lipid or polymeric materials, and medicament is encapsulated, entrapped, attached or adsorbed to the surface of nanocarriers.

TECHNIQUES FOR CIRCUMVENTING THE BBB[7],[8]-

A] INVASIVE TECHNIQUES

B] NON-INVASIVE TECHNIQUES-

C] MISCELLANEOUS TECHNIQUES-



A] INVASIVE TECHNIQUES- In this technique, medicament is administered to the brain by an invasive approach. Drilling a hole in the brain and inserting an implant or infusing medication through it. This approach may accommodate the use of a diverse range of chemicals and formulations for ICV or IC delivery. To ensure continual release, both large and tiny chemicals can be provided, alone or in diverse polymer compositions.[9]

A] Intra-cerebroventricular infusion (ICV)-

The concentration of a medicine in the brain at 1-2 mm below the surface is estimated to be just 1-2% of the concentration of cerebrospinal fluid (CSF). Medicines could be easily infused intravenously into the brain's surface, but not into the cerebral parenchyma. If the drug's target receptors are close to the ependymal surface of the brain, pharmacologic effects can be seen following ICV administration.[10]

Limitations- Drug diffusion to the brain parenchyma is minimum. For effective targeting of drugs, the target must be close to the ventricles.

B] Focused ultrasound enhanced delivery-

This is also a feasible and effective method of delivery. In this method, the BBB gets opened reversibly and temporarily by utilizing ultrasonic waves. Micro bubbles (MBs) were used in ultrasound-based drug administration as a contrast agent[11,12,13]. MBs have diameters ranging from 1 to 10m and are constituted of semi-rigid lipid and albumin shells encapsulated in perfluorocarbon[14]. These MBs are used in conjunction with low- intensity Focal Ultrasound (FUS), and the combined technology is known as MB- assisted FUS. These bubbles were injected systemically and used the acoustic energy concept to press against endothelial cells and break down tight junctions, increasing BBB permeability and improving drug transport to the brain[15]. To disrupt the BBB for improved distribution, target the malignant cell, and promote penetration, this system may be used in combination with PEGylated NPs[16]. The best effects of doxorubicin on rat glioma were seen when the FUS approach was combined with liposomes[17]. This approach is used to deliver various antitumor agents like trastuzumab[18], temozolomide[19], methotrexate[20], stem cells[21]. The successful delivery of NPs encapsulating reporter gene along with MRI guided FUS to transfect the brain gives insight into the technology's future prospects for gene therapy[22].

C] Convention enhanced delivery-

CED overcomes the drawbacks associated with the intracerebral delivery mechanism. This diffusion technology uses an intracranial catheter to deliver large number of medications to the target tissues using a continuous infusion mechanism and pressure gradient[23,24].The principle behind this method relies on the stereotactically guided insertion of a small-calibre catheter into the brain parenchyma. Infusate is continually injected into the brain parenchyma and reaches the interstitial space through this catheter. After the continuous infusion, the catheters are removed at the patient’s bedside. In laboratory investigations, convection-enhanced delivery (CED) has been proven to deliver high molecular weight proteins 2 cm from the incision site in the brain parenchyma after as little as 2 hours of continuous infusion[24]. The effectiveness of CED for targeting brain tumors was increased when it was combined with liposomes. The CED process was further enhanced by using efflux-resistant infusion cannula to enhance infusion rate and employing MRI to guide liposomal delivery[25].

Limitations- Trained personnel is required for the administration
For effective drug delivery, catheter placement plays a vital role. It can be challenging to thoroughly saturate an area of the brain with infusate, especially when it comes to infiltrated tissues surrounding a cavity[26].

D] Intracerebral implants or injections-
Intrathecal injection directly supply enables direct medication administration into the brain parenchymal region. Chemicals that have been microencapsulated release control matrices. Diffusion is typically the mechanism that is effective in treating of various disorders of the central nervous system (CNS), including Parkinson's disease and brain cancer.

E] Disruption of the BBB-

This method is commonly used to deliver pharmaceutical actives to the CNS. X-ray exposure and solvent injections including, ethanol and dimethyl sulfoxide, can disrupt the blood-brain barrier (BBB). Pathological conditions such as hypertension, hypoxia, or ischemia can all have an effect on the blood-brain barrier (BBB). Blood-brain barrier (BBB) permeability is impacted differently by alcohol and hypoglycemia based on energy metabolism. These two methods are crucial for rupturing the blood-brain barrier (BBB)[24].

Drawbacks of invasive approaches-

- All of these procedures need hospitalization and entails anesthesia.
- Trained personnel required for administration.
- Several methods might promote tumor dissemination after the BBB has been successfully broken down.
- Inappropriate blood components reaching the brain can permanently damage neurons.
- Costly approaches.

B] Non- invasive techniques-

Many noninvasive brain drug delivery methods have used the brain's blood artery network to distribute drugs. Non-invasive techniques depend on drug modifications.

1) **Chemical method-**

a) Prodrug approach-

Prodrugs are pharmacologically inactive moieties that are converted into active forms at the targeted sites. Prodrug method is the chemical alteration of the active molecule to control its lipophilic nature, improve permeability, and increase water solubility. Targeted prodrugs contain a chemical entity in addition to parent medications that are intended to interact with the enzymes or transport systems at the targeted site to transform into active moiety. A prodrug is a medication that has been chemically covalently attached to an inert substance. Once they were joined through hydrolytic or enzymatic actions that divide the prodrug's molecules, the active medication is produced. Chemical moiety-attaching prodrugs should be required to enhance the lipophilic characteristics and efficiency of the drug. Examples include valproate, levodopa, GABA, and niflumic acid.[24,26]prodrugs are widely used for treating neurological disorders. For example, Parkinson's disorder can be treated with dopamine but, dopamine itself has some limitations; it has low bioavailability due its inability to cross BBB. Levodopa is a precursor of dopamine. L-dopa is carried over the blood-brain barrier by a L-amino acid transporter, where it is then converted to dopamine.[27]

2) **Efflux pump inhibition-**

The presence of an efflux pump in the BBB is another barrier to effective drug transport to the brain. Poor drug availability at the targeted brain tissues is caused by efflux by the active P-glycoprotein (P-gp), which is located on the apical membrane of the endothelial cells of the BBB. P-gp is more frequently associated with cationic and lipophilic medicines[28]. The MRP (multidrug resistant proteins) family of proteins, is found on endothelial cells and is in addition to P-gp involved in the efflux of cationic compounds.

The multi-drug resistance of cancer to chemotherapy drugs is caused by MRP. The primary purpose of P-gp and MRP is to secure the brain against the entry of hazardous chemicals, which prevent the entry of pharmaceuticals into the brain. Targeted distribution to the brain might benefit from concurrent P-gp and MRP inhibition .Pazopanib is a possible treatment for P-gp efflux. Pazopanib's brain absorption was markedly improved by administration with elacridar, a P-gp inhibitor.[29]

3) Colloidal systems-

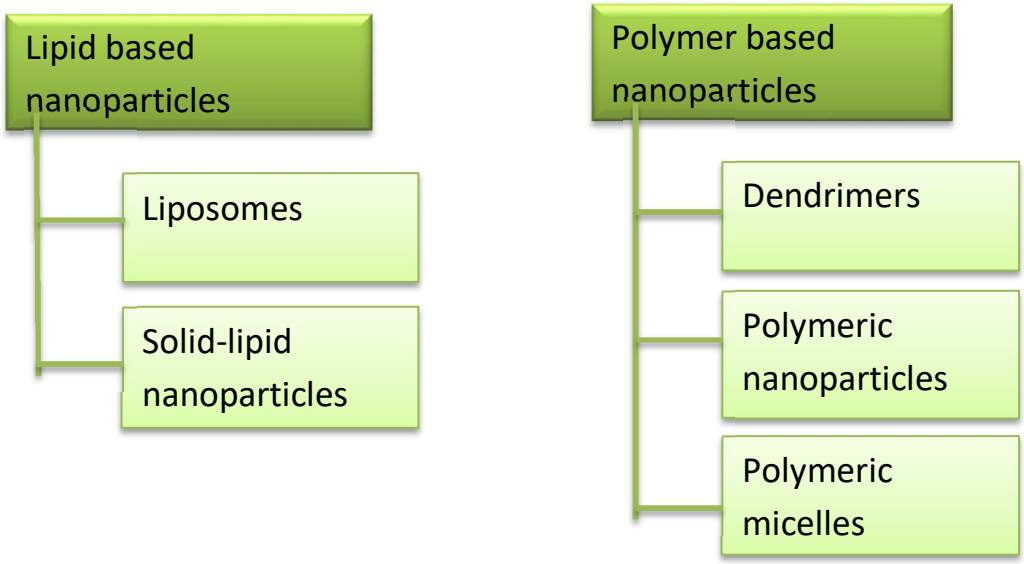
When specific amphiphilic building blocks come into contact with water, they create a vesicular system of highly ordered assemblies of one or more concentric lipid bilayers. Drug carriers might be programmed to decay progressively, respond to stimuli, and target particular areas. The ultimate goals are to reduce drug deterioration and loss, prevent adverse effects, and increase drug accessibility at the site of the disease. There are several attributes of colloidal systems make them more desirable for medical applications[30]-

- Drugs that are lipophilic and hydrophilic can both be encapsulated.
- Functions as a sustained-release mechanism.
- Postponing the clearance from the body.
- Increase in solubility and bioavailability of poorly soluble drugs.
- Having a range of delivery options (including oral, inhalational, and parenteral).

a) Nano-particles-

The sizes of nanoparticles, which range from 10 to 1000nm, are solid particles or particulate dispersions. Using a nanoparticle matrix, we can dissolve, capture, encapsulate, or bind the drug.[31]Nano-particle systems can be used in different drug delivery systems to improve the efficiency and bioavailability of drugs. NPs a are promising drug- targeting methods for the treatment of illnesses of the central nervous system and can increase a drug's ability to pass through the BBB.[32,33]

Nanoparticles for medicinal use-



Lipid-based nanoparticles-

a) Liposomes- liposomes are the first generation of the nanoparticulate system. liposomes, are made up of one or more vesicular amphiphilic lipid bilayers (lamellae) that contain and define interior aqueous compartments[34]. hydrophilic drugs should be entrapped in lipid bilayer and lipophilic drug should be entrapped in the hydrophilic core. Cholesterol is a crucial part of cell membranes. Glycerophospholipids, phosphatidylcholine, and sphingomyelin are other typical liposome components[35].

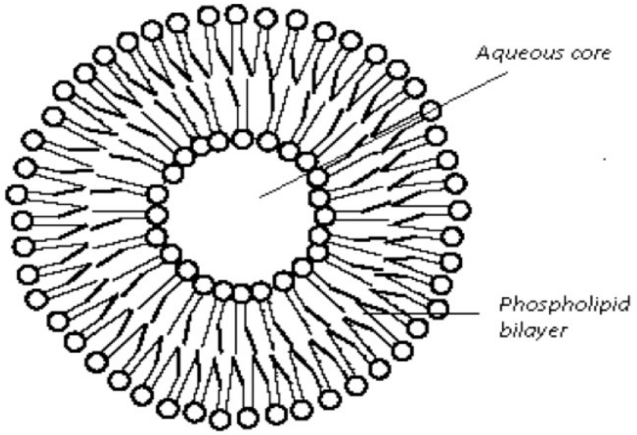


Figure: 2-Liposome[36]

b) Solid-lipid nanoparticles(SLN)-Solid- lipid nanocarriers (SLN) are lipid-based nanocarriers has with a solid hydrophobic lipid core inside of which the drug can be dissolved. They are created using biocompatible lipids like waxes, fatty acids, or triglycerides. Wang et al. described the synthesis of 3,5-dioctanoyl-5-fluoro-2-deoxyuridine (DO-FUdR) to get around the drug's poor accessibility. After the inclusion of DO-FUdR in SLN, the findings showed that DOFUdR- SLN had a brain-targeting efficiency in vivo of roughly two times that of free FUdR. SLN can enhance drug's ability to traverse the BBB because of their typically small size (in between 40-200nm) and therefore it's a promising approach for treatment for neurodegenerative disorders.[37,38]

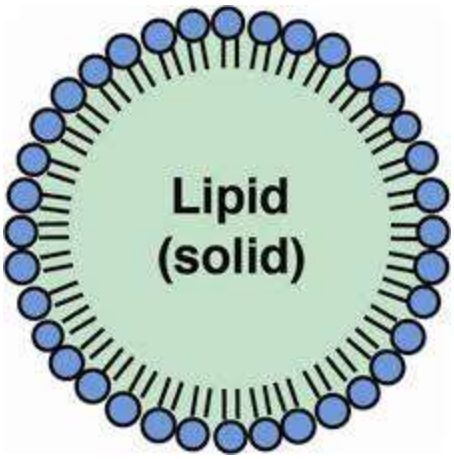


Figure:3- Solid- lipid nanoparticles (SLN) [

Polymer based nanoparticles-

a) Dendrimers-

Dendrimers are typically symmetric around the core; dendrimers frequently acquire a three-dimensional spheroidal form in water when sufficiently expanded. Typically, they are made from substances such as sugars, nucleotides, and amino acids that are either natural or manufactured. They have a central core with at least two chemical functions that are similar, and from these groups, repeating molecules can be formed, having at least one branching junction. A sequence of radially concentric layers with higher crowding are produced by the repetition of chains and branches. Because of this, the structure is densely packed in the periphery and weakly packed in the core, leaving gaps that are crucial to dendrimers' capacity to entrap drugs.[39]

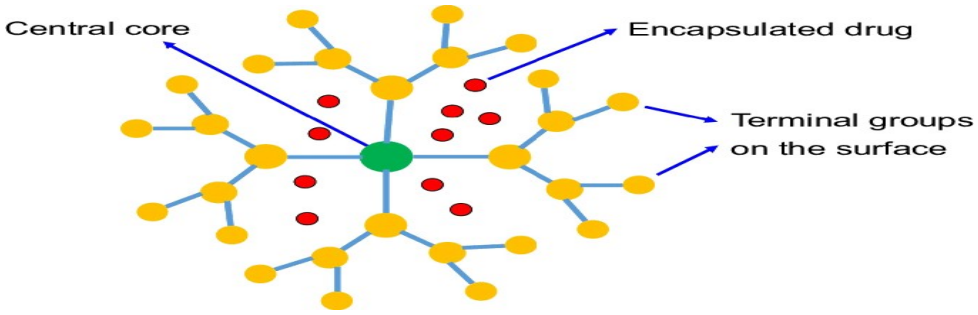


Figure:3- Dendrimers[40]

b) Polymeric nanoparticles-

The diameters of polymeric NPs, which usually range between 60 and 200 nm, are made up of a core polymer matrix in which pharmaceuticals can be incorporated.[41,42,43] Drug distribution has been done using a variety of materials. Polymeric NPs are made up of biopolymers, after administration, they can degrade inside the body and forms non- toxic metabolites. Polyglycolides and polylactides (PLA) are the most often used ones (PGA). PLGA, polyanhydrides, polycyanoacrylates, and polycaprolactone are examples of these materials. Natural polymers like chitosan can be used in addition to the development of numerous synthetic and semi-synthetic polymers.

c) Polymeric micelles-

Amphiphilic copolymers that aggregate in aqueous conditions to form spheroidal structures with a hydrophilic shell and a hydrophobic core and with a high degree of stability are known as polymeric micelles.[44] This self-assembly of amphiphilic monomers, which happens above their critical micelle concentration (CMC), is entropically preferred and leads to the creation of micelles with a core-shell structure.[45]Polymeric micelles can also be made responsive to external stimuli, such as pH, light, temperature, ultrasound, etc. Pluronic type, a block copolymer based on ethylene oxide and propylene oxide, is one of the most widely used polymers. It has been mentioned that these NPs might be used to carry drugs to the brain. For instance, a specific target peptide for Pluronic Nano carriers coupled to chitosan.

The brain of mice that had received an intravenous injection of the rabies virus glycoprotein (RVG29) showed in vivo brain accumulation of either a protein loaded into the carrier or a quantum dot fluorophore conjugated to the carrier.[46] The micellar medication has been demonstrated to have a stronger central analgesic effect in other investigations.[47]

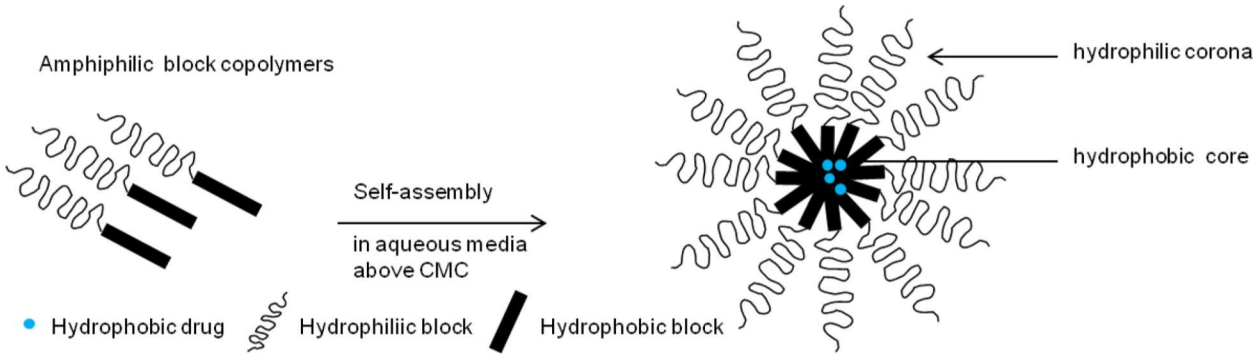


Figure: 5- Polymeric Micelles[48]

4] Cell based therapy-

For the successful administration of several medications to treat neurological diseases and brain malignancies, cell-based treatment has grown in popularity. This treatment uses macrophages and a variety of stem cell types as delivery systems for the brain.[49] Macrophages move from the blood to the brain through Transport systems that are paracellular and transcellular.[50,51] They can penetrate the brain as Trojan horses thanks to their innate capacity for phagocytosis. Macrophages are drawn to the brain and infiltrate there when there is an inflammation or brain tumor. Macrophages are potential targets for the targeted administration of NPs and diagnostic and imaging agents to brain tumor and neurodegenerative disorders. Nanovesicles called exosomes carry numerous medicines and biological substances. The exosomes' lipidic and protein composition makes it easier for them to fuse with the recipient cells and deliver therapeutic agents.[52,53]

C] MISCELLANEOUS TECHNIQUES-

Brain delivery through nasal route-

Brain delivery through the nasal cavity is a logical way for curing neurodegenerative disorders as well as local diseases related to nasal cavity. When a medication is administered nasally, the mucus layer and epithelial barrier must be passed before it can enter the system and affect the Brain or systemic circulation. In Ayurveda nasal therapy is known as ‘Nasya Karma’. The limitations of other drug delivery to brain are overcome by nasal drug delivery system. It is an alternative way for administration of the vaccines, biomolecules, sedatives, hormones, analgesics, etc. Drugs are delivered to the central nervous system via the intranasal pathway by penetrating the BBB through the trigeminal and olfactory nerves.[54] To be absorbed through the nasal cavity, medicine must first pass through the mucus layer. Large and charged medications have difficulty passing through this layer, but tiny and uncharged pharmaceuticals can do so with ease. Mucin, the primary protein in mucus, has a tendency to bind to solutes during formulation and hinder diffusion. There are many various ways to absorb substances; a few are described below:

a) Transcellular pathway
b) Paracellular pathway

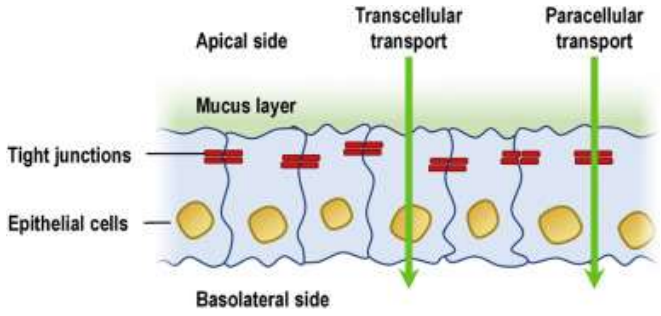


Fig: - Transmucosal drug delivery pathways

There are various polymers are utilized for formulation and development of intranasal formulations including intranasal sprays, nasal drops, nasal gels and liposomes. Different polymers have their different mechanisms and properties. Alginate (ALG), gellan gum (GG), and pectin (PEC) are some examples of anionic polysaccharides that are ion-sensitive polymers.[55,56,57]They are cross-linked by some monovalent (Na+) and/or divalent (Mg2+ and Ca2+) cations present in different physiological fluids, such as saliva, tears, nasal secretions, and bile. A sol-gel transition and the creation of a robust gel are the results of the cross-linking mechanism.[58,59]

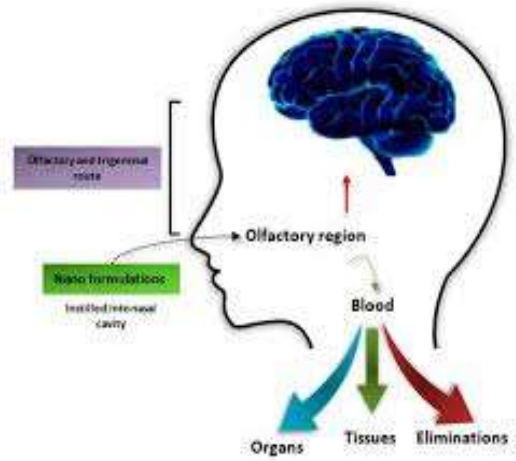
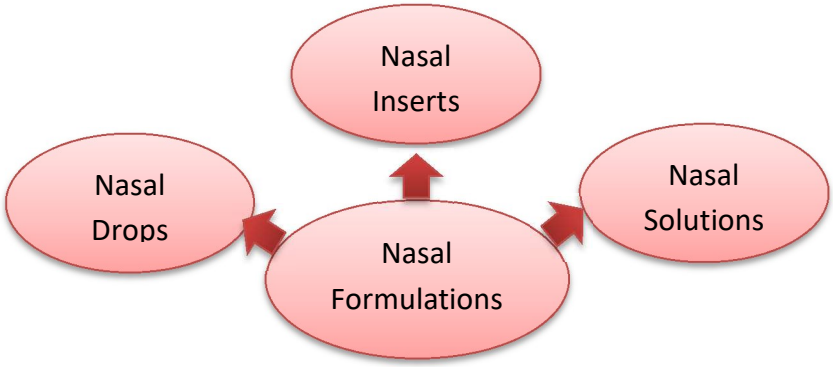


Fig- Nasal route of treatment[60]

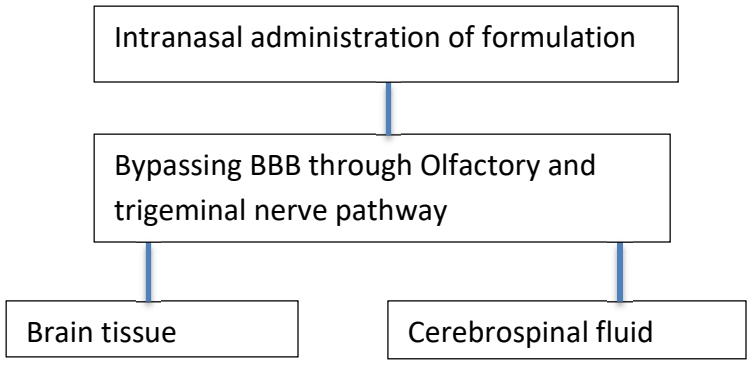


Advantages-

- Nasal administration is a good way to give medications that breakdown in the GI tract.
- This route bypasses the hepatic metabolism.
- It is a non-invasive approach since it offers a substitute for the parenteral administration of proteins and peptides.
- Nasal routes circumvent the blood-brain barrier (BBB), so they are now widely utilized for treating CNS disorders like depression, migraine, epilepsy, Parkinsonism, Alzheimer's, and other similar conditions.
- The highly vascularized epithelium of the nasal cavity allows for quick medication absorption into the bloodstream.
- Better patient acceptance due to the ability to self-administer.
- Due to highly vascularized epithelium, drugs are absorbed more efficiently.

Disadvantages-

- Less surface area available for absorption.
- This method cannot be used to deliver high molecular weight medications.
- Less surface area for absorption than the gastrointestinal tract (GIT).
- The volume administered should range from 25 to 200 mL.
- Significant interspecies diversity can be seen along this route.



RECENT ADVANCES IN BRAIN TARGETTED DRUG DELIVERY SYSTEM-

1. Polyanhydrides
2. Lipoplexes and Polyplexes
3. Scaffolds
4. Carbon dots

1. **Polyanhydrides**- Biodegradable polymers known as polyanhydrides primarily release the medication through hydrolysis. In essence intracerebral implants called polyanhydrides are helpful for delivering drugs under controlled conditions. The Drug is incorporated into polymer matrix in polyanhydrides.[61]

   Brain tumor therapy with polyanhydrides-

   brain cancer About 80% of adult primary brain tumors are glioblastoma multiforme (GBM), which are typically found in the cerebral hemispheres. Since many anti-cancer medications have large molecular structures, ionic charges, or are hydrophilic, they cannot cross the BBB and they must be administered at intolerably high systemic levels to reach therapeutic levels in the Brain.

   One of the easiest methods is to use polyanhydrides for direct localized delivery.

   In 1996, the FDA granted its approval for Gliadel® wafers. One of the most effective polyanhydrides delivery devices is available commercially. They are composed of Poly (Carboxy phenoxy) Propane: Sebacic Acid in a 20:80 ratio. These dime-sized wafers administer BCNU (carmustine), which is used to treat GBM. After removing the tumor, the wafers are inserted directly in the resection cavity. Up to eight Gliadel® wafers may be implanted for treatment along the walls of the tumor cavity following tumor debulking. It was discovered that Gliadel® wafers deliver medication for roughly 5 days.[62]

2. **Lipoplexes and Polyplexes-**

   Lipoplexes and polyplexes are lipid and polymer based phenomena. Both are utilized to protect the DNA from unfavorable deterioration and damage during the transfection process. Lipids may cover plasmid DNA, for example, in micells and liposomes. A lipoplex is what is produced when the ordered structure and DNA combine. There are three types of lipids-

   a) Anionic lipids
   b) Neutral lipids
   c) Cationic lipids

   For the production of lipoplexes for synthetic vectors, initially neutral and anionic lipids were utilized. They can be modified to be tissue-specific and have very low toxicity levels, making lipoplexes compatible with bodily fluids. Consequently, the focus shifted

to the cationic variants. The positive charge on cationic lipids gives them the capacity to bind naturally with the negatively charged DNA. Also, because of their positive charge, they interact with the cell membrane, causing the lipoplex to be endocytosed and the DNA to be released into the cytoplasm. The cationic lipids also guard against cellular DNA deterioration. Dioleoylphosphoethanolamine (DOPE) and dioleyloxy trimethylammonium chloride (DOTMA) are examples of cationic lipids [14]. Sawant et al. created TATp (TAT plasmid) lipoplexes using the cationic lipid N-[1-(2,3-Dioleoyloxy) propyl]-N, N, N-trimethylammonium methyl-sulfate (DOTAP). When treated with mouse fibroblasts, the lipoplexes showed greater in vitro transfection efficiency [15(15)].[63]

Polyplexes are complexes of polymers and DNA. Ionic interactions produce the majority of polyplexes, which are made up of cationic polymers. Polyplexes are unable to release the corresponding DNA into the cytoplasm, which is a significant distinction between their modes of action and those of lipoplexes. Co-transfection with endosome-lytic agents, which lyse the endosome, is required for release, and the polyplexes must enter the cell. This isn't always the case, some polymers, like chitosan, trimethyl chitosan, and polyethylenimine (PEI), have unique mechanisms for disrupting endosomes.[64]

3] Scaffolds-

Scaffolds are implantable medical devices that can be used to deliver medications for the treatment of neurological diseases like Parkinson's and Alzheimer's disease, as well as a various of conditions related to brain injury and disease. Therapeutic agent delivery through scaffolds may aid to preventing neuronal damage while retaining their functionality.

The brain faces similar challenges when designing scaffolds, despite the fact that scaffolds have a wide range of potential applications for neural tissue creation. The applications are as follows-

- Reducing cell death and inflammation during scaffold implantation by using biocompatible materials.
- These can avoid the surgeries after administration it releases medicament for a longer duration of time.
- This technique is not much invasive as other technologies, it maintains the BBB integrity.

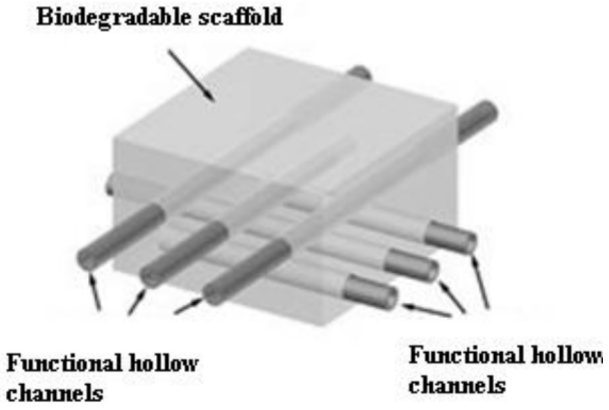


Fig. scaffold[65]

4] Carbon dots (CDs)-

A broad group of carbon-based nanomaterials known as CDs includes carbon nanodots, polymer dots, graphene quantum dots (GQDs), and carbon nitride dots, among others (CNDs). Top-down and bottom-up strategies are used to synthesize CDs, with a range of reaction conditions and precursors. Microwave irradiation is used most frequently to create CDs because of its quick response time and even heating.[66,67] In contrast, ultrasonication is a more delicate technique than microwave radiation or hydrothermal/solvothermal techniques, however there are examples of both as well techniques are not common. Using citric acid and o-phenylenediamine (OPD) as precursors, Zhou et al. discovered a novel form of excitation-independent yellow-emissive CDs (Y-CDs).[68,69]CDs have similar optical characteristics with a few small changes. Excitation-dependent emission, which is often present in carbon nanodots but has previously been confined; Originally restricted to the blue-green spectrum of light, it has since been expanded to the orange-red and even the near-IR (NIR) spectrum.[70,71]

Conclusion-

It is possible to cross the blood-brain barrier by using an endogenous transporter, a receptor, or an efflux pump. The presence of BBB makes it difficult for most currently present and future medications with the potential to be effective in treat these CNS- related disorders, still recent advances in drug delivery across the BBB have shown promise for overcoming the challenges of brain drug delivery. We have highlighted the many therapeutic drugs that are encapsulated in nanostructured carriers that have been devised and researched for a several neurological illnesses. The drug can be given across the BBB effectively through nanotechnology, nasal methods, disruption of the BBB, prodrugs, etc. Colloidal or nano-carrier drug delivery can enhance the targeting efficiency. Nowadays, a variety of NPs with various properties and applications are accessible for biomedical usage, making it easier to transfer neuroactive molecules, including medicines, growth factors, and genes, as well as cells, to the brain.

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