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Review Article

Brain Targeted Drug Delivery System: A Review

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Abstract:

Brain is the most sophisticated and important organ of our body. Together with spinal cord it control all actions, all functions voluntary or involuntary and plays a vital role in managing various organ systems of our body. It has its own protective barriers that protects the brain from various pathogens and toxins that may cause the harm. These barriers are namely Blood-Brain barrier and Blood-Cerebrospinal Fluid Barrier. The highly lipophilic nature of these barriers helps them in protecting the brain, allowing the passage of only highly lipophilic drugs to the brain through blood. However when there is an infection or injury in brain, the same barriers pose a hindrance in the delivery of drugs to the brain for treatment. Usually, drugs are usually hydrophilic in nature and since barriers of brain are lipophilic in nature, the finds it hard to cross these barriers and reach the brain. In order to overcome the problem in drug delivery to the brain as a target organ various drug delivery techniques were developed. Invasive and non-invasive approaches are two main approaches that are used to deliver drug to brain. In invasive approach the permeability of BBB is decreased or the drug is directly administered, whereas in non-invasive approach the drug molecule is altered to enhance its lipophilicity allowing its passage to the brain. This review aims to describe the various brain targeted drug delivery system..

Keywords: Brain, Blood-brain Barrier, Blood-Cerebrospinal Fluid Barrier, Invasive approach, Non-invasive approach.

Introduction

Brain is the master organ of our body. It is a very versatile organ of our body. Together with the spinal cord the brain constitutes Central Nervous System (CNS) where spinal cord governs over many functions like reflex, etc. and the brain takes control over many important functions like thinking, learning, speaking, etc. Brain also have some centres or zones which regulates the various involuntary functions, e.g. Chemoreceptor Trigger Zone (CTZ), in which CTZ controls the peristaltic movement of gastrointestinal tract. Being a delicate organ, the brain is also protected by several protective features as it is physically protected by hard cranium, beneath whom are present three layers of meninges. Between the meninges the CSF flows and provide nourishment and nutrients to the brain and remove the waste from the brain and its surroundings. Brain also have two physiological barriers which regulates the entry of molecules or compounds into the brain *via* blood. These barriers are Blood-Brain Barrier (BBB) and Blood-Cerebrospinal Fluid Barrier (BCSFB). Both are highly selective barriers of lipophilic nature. They allow only the highly lipid soluble molecules to pass through them, along with some less lipid soluble or hydrophilic molecules. It prevents the brain from entry of several pathogens, toxins like toxic metabolites of drugs, etc. *via* blood.[1]

However, in disease state conditions like Parkinson's disease, Alzheimer's disease, multiple sclerosis, traumatic brain injuries, etc., the delivery of drug to the brain becomes a problem as a the BBB and BCSFB only allows highly lipid soluble molecules to enter the brain but the drugs used in treatment of pathological or disease condition are usually less lipid soluble or hydrophilic in nature. This makes the treatment of such disease and disorders difficult. To overcome these difficulties in the treatment of such brain related disorders, scientists have been trying to develop methods/techniques which help us delivering the drug molecule directly/indirectly into the brain.[1]

The techniques developed usually include administering drug directly into the brain by several measures, changing the drugs nature to make it pass through the BBB and BCSFB. The techniques do also involve some methods involving delivery of drug to the brain *via* BBB deficit region of brain. With time needed techniques are being developed for brain targeted drug delivery to ensure safe and efficient/proper administration of drug to the brain, if possible without disrupting the BBB. [1]

The Anatomy of the Brain

The brain is the most versatile and sophisticated organ of our body. It controls all the body functions and is also responsible for various functions like learning, listening, hearing, thinking, etc. The brain constitutes the CNS along with the spinal cord. The brain is mainly consist of *neurones* and *neuroglia*. [1]

Neurones, also known as nerve cells, the basic unit of the Brain as they are solely responsible for all the functions of the brain. Neurones are also known as longest cells in our body. They are consist of a cell body and its processes, one axon and many dendrites. There are two types of neurones, *viz* Myelinated neurones and Non-myelinated neurones. Myelinated neurones are large

axons and axons of peripheral nerves are surrounded by a myelin sheath. This consists of a series of Schwann cells. Non-myelinated neurones have short axon and are found in postganglionic fibres and small fibres of CNS. The axons are embedded in Schwann cell plasma membranes. Neurones generate and transmit electric impulses called action potentials. Bundles of axons bounded together are called nerves. Nerves are of three types *viz*, afferent nerves, efferent nerves and mixed nerves. Afferent nerves or sensory nerves carry information from the body to the spinal cord. Efferent nerves or motor nerves transmit impulses from the brain, spinal cord and autonomic ganglia to the effector organs like muscles and glands. Outside the spinal cord, when sensory and motor nerves are enclosed within the same sheath of connective tissue, they are called *mixed nerves*.[1]

Neuroglia are cells present in the CNS other than the nerve cells. Neuroglia are of four types and all are non-excitable glial cells, which greatly outnumber the neurones of the CNS. Unlike nerve cells, which cannot divide, glial cells continue to replicate throughout life. These cells are Astrocytes, Oligodendrocytes, Ependymal cells and Microglia. [1]

Astrocytes are star-shaped cells with fine branching processes, and they lie in the mucopolysaccharide ground substance. At the free ends of some of the processes are small swelling called foot processes. Astrocytes are found in large number adjacent to blood vessels with their foot processes forming a sleeve round them. This layer of astrocytes foot processes and the capillary wall of blood vessel separates the blood from the neurones constituting the blood-brain barrier (BBB).[2]

Oligodendrocytes are cells smaller than the astrocytes and are found in cluster round nerve cell bodies in grey matter. They form and maintain myelin, having the same function as Schwann cells in the peripheral nerves. **Ependymal cells** form the epithelial lining of the ventricles of the brain and the central canal of the spinal cord. These cells also form the choroid plexus of the ventricles secrete cerebrospinal fluid. **Microglia** are said to be derived from the monocytes migrating from the blood into the nervous system before birth. They have phagocytic action and remove microbes and damaged tissues from the areas of inflammation and cell destruction.[1]

As shown in Fig.1, the adult brain consists of four major parts, (i) Brain stem, (ii) Cerebellum, (iii) Diencephalon, (iv) Cerebrum. The brain stem is continuous with the spinal cord and consist of the medulla oblongata, pins and midbrain. Posterior to the midbrain is the cerebellum. Superior to the brain stem is the diencephalon, which consists of thalamus, hypothalamus and epithalamus. Supported on the diencephalon and the brain stem is the cerebrum, the largest part of the brain. [1]

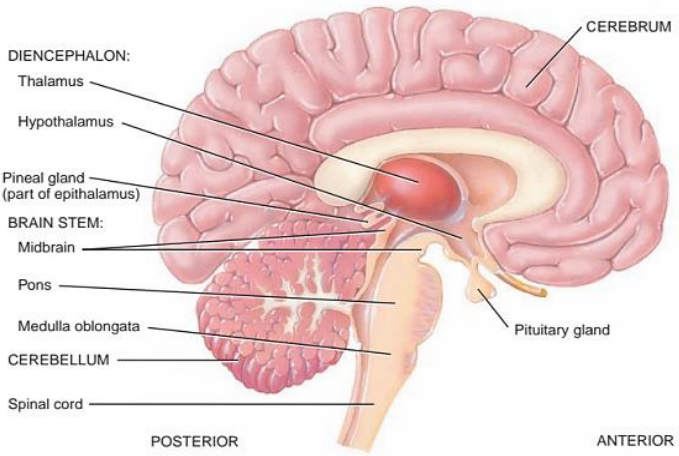

Fig 1: Brain – Medial view of sagittal section

Cerebrum, largest part of the brain, occupies the anterior and middle cranial fossae. It is divided into right and left cerebral hemispheres, each containing one of the lateral ventricles, by a deep cleft, the longitudinal cerebral fissure. Deep within the brain hemispheres are connected by a mass of white matter (nerve fibres) called the corpus callosum. The falx cerebri formed by dura mater separates the two hemispheres and penetrates to the depth of the corpus callosum. The superficial (peripheral) part of cerebrum is composed of grey matter, forming the cerebral cortex, and the deeper layers consists of white matter. The cerebral cortex have many furrows of varying depth. The exposed areas of the folds are the gyri (convolutions) and these are separated by sulci (fissures). [1]

Diencephalon is the part of brain that connects the cerebrum and the midbrain. It consists of several structures situated around the third ventricle, the main ones being the thalamus and hypothalamus. The pineal gland and the optic chiasma are situated there.

Brain stem consists of three parts, viz., Midbrain, Pons and Medulla oblongata.

Midbrain is situated around the cerebral aqueduct between the cerebrum and pons. It consists of nuclei and nerve fibres which connects the cerebrum with lower part of the brain and the spinal cord.

Pons is situated in from of the cerebellum, below the midbrain and above the medulla. It consists mainly of nerve fibres (white matter) forming a bridge between the two hemispheres of the cerebellum and of fibres passing between the higher levels of the brain and the spinal cord. Some nuclei within the pond act as relay stations and some of these are associated with cranial nerves. Others form the Pneumotaxic and Apneustic centres that operate in conjunction with the respiratory centre in medulla. [1]

The **Medulla oblongata**, or Medulla, extends from the pons and is continuous with the spinal cord. It lies just within the cranium above the foramen magnum. It contains many vital centres, consisting of group of cell bodies (nuclei) associated with autonomic

reflex activity, in its deeper structure. E.g., Cardiovascular centre, Respiratory centre, Chemoreceptor Trigger Zone (CTZ). [1]

Cerebellum is situated behind the pins and immediately below the posterior portion of the cerebrum occupying the posterior cranial fossa. It also has two hemispheres separated by a narrow median strip, the vermis. The peripheral part is made of Grey matter and the white matter lies deeply. Cerebellum is concerned with the coordination of voluntary muscular movement, posterior and balance. [1]

The Brain is physically protected by the set of bones called cranium and some layers of meninges present beneath it. Meninges are three layers of tissue which completely surround the brain and the spinal cord. It lies between the cranium and the brain, and between the vertebral foramina and the spinal cord. From outside inwards, the meninges are named as Dura mater, Arachnoid mater and Pia mater. [1]

Dura mater is a layer of meninges closest to the cranium. The cerebral dura mater consists of two layers of dense fibrous tissues. The outer layer takes place of the periosteum on the inner surface of the cranium and the layer provides a protective covering for the brain. There is potential space between the two layers except where the inner layer sweeps inward to form falx cerebri, falx cerebelli and tentorium cerebelli. Venous blood from the brain drains into the venous sinuses between the two layers of dura mater. Spinal dura mater forms a loose sheath round the spinal cord, extending from the foramen magnum to the 2nd sacral vertebra. **Arachnoid mater** is a layer of fibrous tissue that lies between the dura and pia mater. It is separated from the dura mater by the subdural space and from the pia mater by the subarachnoid space, cerebrospinal fluid. It passes over the convolutions of the brain and accompanies dura mater in the formation of falx cerebri, tentorium cerebelli and falx cerebelli. **Pia mater** is a delicate layer of connective tissues containing minute blood vessels. It adheres to the brain, completely covering the convolutions and dipping into each fissure.[1]

Physiological Barriers of the Brain

Like other organ systems the nervous system also requires blood for supply of O_2 and glucose for its function. In nervous system majority of the supplies are utilised to satisfy the need of the brain.

In an adult, the brain represents only 2% of total body weight, but consumes about 20% of the O_2 and glucose used, even at rest. It clearly depicts the massive requirement of oxygen and glucose by brain which shows the importance of uninterrupted blood flow to the brain.

Blood flows to the brain mainly via the internal carotid artery and vertebral artery. The internal jugular vein returns the blood from the head to the heart. As the blood directly reaches to brain from the heart, it contains several proteins, lipids, amino acids, etc. in it. The blood flowing in body also contains several drugs, their metabolites and pathogens (entered the body) which may cause serious casualties to the Brian, if able to enter in it. To prevent the diffusion of such substances into the brain or cerebrospinal fluid some physiological barriers, viz., Blood-Brain Barrier (BBB) and Blood-Cerebrospinal fluid Barrier (BCSFB). [3]

A. Blood-Brain Barrier

As shown in the Fig.2, the blood-brain barrier is a highly selective barrier formed around the blood capillaries in the brain. It is diffusion barrier essential for the normal function of the brain, which impedes the entrance of substances from the blood to the brain to maintain homeostasis. The blood-brain barrier protects the brain cells from potentially toxic substances, pathogens and chemical variations in the blood. Brain microvascular endothelial cells (ECs), pericytes, astrocytes, tight junctions (TJs), neurons and basal membrane construct physically tight brain capillaries in the BBB.

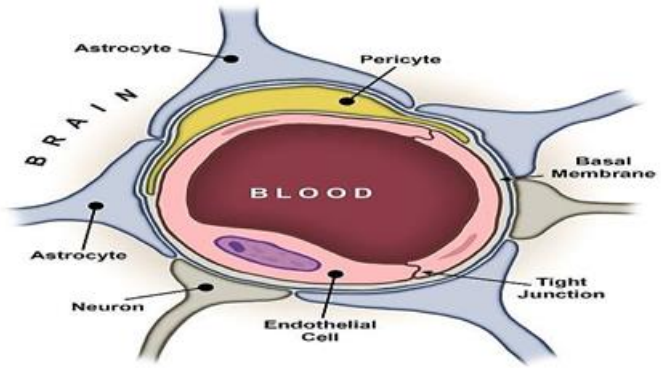

Fig 2: Blood-Brain Barrier (BBB)

The brain capillary endothelial cells do not have fenestrations, which limits the diffusion of small molecules and proteins. Inter-endothelial junctions link the ECs to a continuous barrier, severely restricting the penetration of water-soluble substances. Pericytes, astrocytes and basal membrane surround the ECs and finally form the impermeable BBB. Additionally, efflux transporters are located in brain capillary ECs, which are further obstacles against substances entering the brain. [3]

The permeability of the BBB is mainly controlled by inter-endothelial junctions that are protein complexes such as adherens junctions, tight junctions and gap junctions. Adherens junctions primarily regulate the permeability of the endothelial barrier.

Tight junctions play a vital role in sustaining the permeability barrier of epithelial and endothelial cells, which control tissue homeostasis. Gap junctions composed of 6 connexin molecules, direct electric and chemical communication between endothelial cells. Instead of having a static structure, the components of the BBB continuously adapt in response to various physiological changes in the brain. [3]

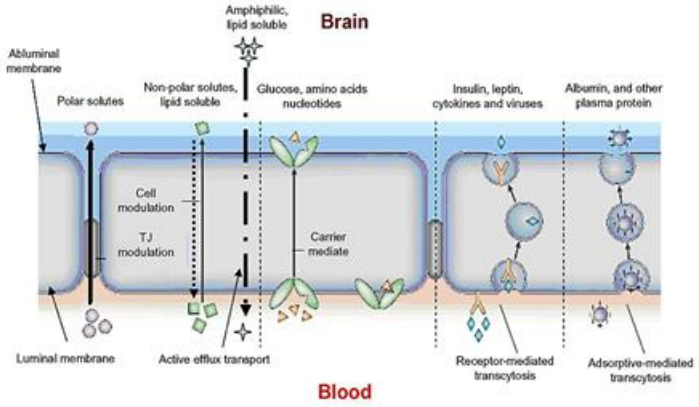

Fig 3: Different pathways for transport across the BBB[4]

As shown in Fig.3, molecules cross the BBB by a paracellular pathway or a transcellular pathway. For the paracellular pathway, ions and solutes utilize concentration gradients to pass the BBB by passive diffusion. The transcellular pathway includes different mechanisms such as a passive diffusion, receptor-mediated transport and transcytosis. The physicochemical factors that influence BBB permeability include molecular weight, charge, lipid solubility, surface activity and relative size of the molecule. Small lipophilic molecule such as CO_2 cross the BBB by passive diffusion through a transcellular pathway.[3] BBB permeability can also be influenced by physiological factors such as efflux transporters (e.g., P-glycoprotein (P-gp)), enzymatic activity, plasma protein binding and cerebral blood flow. Hydrophilic molecules such as proteins and peptides enter the brain through specific and saturable receptor-mediated transporter mechanisms such as glucose transporter-1 (GLUT-1), insulin transporter and transferrin transporter. These endogenous transporters are expressed at the luminal and abluminal endothelial membranes.[5]

There are also some specific sites in brain where the BBB does not exist, viz., Chemo Trigger Zone (CTZ), the Median Hypothalamic eminence.

B. Blood Cerebrospinal Fluid Barrier

Blood Cerebrospinal Fluid Barrier (BCSFB) is a barrier similar to BBB and is located in the choroid plexus, capillary lined by the choroidal epithelium having tight junctions.

Cerebrospinal Fluid (CSF) is a clear, colourless liquid that protects the brain and the spinal cord from chemical and physical injuries. It also carries O_2, glucose and other needed chemicals from the blood to neurones and neuroglia. It continuously circulates through the cavities in the brain and spinal cord and around the brain and the spinal cord in the subarachnoid space (between the arachnoid mater and pia mater).

The cerebrospinal fluid is produced in the choroid plexus, network of blood capillaries (microscopic blood vessels) in the walls of the lateral, third and fourth ventricles. The capillaries are covered by ependymal cells that form CSF from blood plasma by filtration and secretion. Thus, an extravascular space is created between the capillary epithelium and ependymal cells of choroid plexus. As the ependymal cells are joined by tight junctions, materials entering CSF from choroid plexus cannot leak between these cells; instead, they must pass through the ependymal cells. This creates a barrier similar to BBB, called the **Blood Cerebrospinal Fluid Barrier (BCSFB)**, as shown in Fig.4.[6]

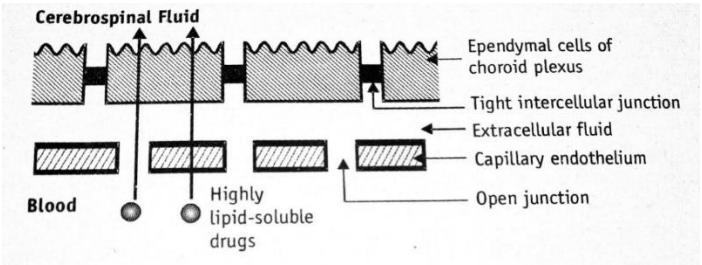

Fig 4: Blood Cerebrospinal Fluid Barrier (BCSFB)

It has permeability characteristics similar to that of the BBB and allow only highly lipid soluble substances to pass through it. In addition, efflux transporters like P-gp (P- glycoprotein) and anion transporter (OATP) present in brain and choroidal vessels extrude many drugs that enter brain by other processes and serve to augment the protective barrier against potentially harmful xenobiotics.[6]

The Blood Brain Barrier (BBB) and Blood Cerebrospinal Fluid Barrier (BCSFB), both prevents the passage of potentially harmful

substances into brain tissues. But another consequences of the BBB's and BCSFB's efficient protection is that it also prevents the passage of certain drugs that could be therapeutic for brain cancer or other CNS disorders.[6]

In case of the pathological disease condition of brain such as stroke, diabetes, seizures, hypertensive encephalopathy, acquired immunodeficiency syndrome, traumatic brain injuries, multiple sclerosis, Parkinson's disease and Alzheimer's disease; the delivery of drug to the brain with available therapeutic system is very difficult, as because of highly lipophilic nature of these barriers only an insufficient amount of drug reaches to the brain which makes it difficult to treat the disease. However, many advancements have been made in the methods/techniques of drug delivery to the brain.[6]

Methods of Drug Delivery to the Brain

There are various methods which are used to deliver the drug to the brain. These methods are broadly classified into two categories, viz., Invasive approach and Non-invasive approach, meanwhile there is also another method called as Miscellaneous approach.[7]

In **Invasive approach** the drug is either administered directly into the brain by different methods or by using permeability enhancers which alters the permeability of Blood-Brain Barrier by disrupting it and allow the drugs to pass through it.

In **Non-invasive approach** the blood-brain barrier is not disrupted instead the drug molecule is altered to increase its lipophilicity or such nano molecules are designed which are highly lipophilic in nature, can carry aqueous drug into them and can also pass through the Blood Brain Barrier.[7]

A. Invasive Approach

1. Intracerebral Ventricular Infusion
2. Intracerebral Implants
3. BBB Disruption

B. Non-invasive Approach

a. Chemical Techniques

1. Prodrug
2. Drug conjugates
3. Chemical Drug Delivery System
4. BBB Shuttle Peptides

b. Biological Technique

1. Monoclonal Antibodies Conjugates
2. Cationic Bovine Serum Antibodies
3. Receptor/Vector Mediated Drug Transport
4. Aprotinin/Chimeric Peptide Drug Transport

c. Colloidal Techniques

1. Micelles and Microemulsions
2. Liposomes
3. Nanoparticles

a) Miscellaneous Approach

1. Intranasal Delivery
2. Iontophoric Delivery

Invasive Approach

Drugs are either directly administered into the brain by infusion or by first drilling the holes in the head and then planting intervertebral implants which continuously release the drug to the brain. An important advantage of this approach is that a wide range of compounds and formulations can be considered for administration. It also allows both large and small molecules to be delivered, either alone or in various polymer formulations to achieve sustained release.[7]

Different invasive approaches are-

A. ICV (Intra-cerebro-ventricular) Infusion
B. Convection-enhanced delivery (CED)
C. Intracerebral implants
D. Disruption of BBB

A. Intra-cerebro-ventricular Infusion (ICVI)

Intracerebroventricular (ICV) infusion is an intrathecal delivery method which instils therapy into the cerebral ventricles *via* an ICV port implanted under the scalp. This route of administration is also referred as intraventricular administration. It is an invasion injection technique of delivering the substances directly into the cerebrospinal fluid (CSF) in cerebral ventricles in order to bypass the BBB. It has been usually used to provide treatment for paediatric and adult patients who suffer from a wide range of disease like infectious meningitis, intractable pain, and various types of cancers.[8]

ICVI can deliver therapies in the long term and at a constant rate that does not results in increased intracranial pressure. Once the device is no longer therapeutically needed, they can be explanted, although oncologists routinely recommend that in the absence of complications the device remain in place indefinitely. The intrathecal delivery method also includes single or repeated intrathecal lumber (IT-L) injections, in which agents are directly administered into the CSF by puncturing the membrane surrounding the spinal cord.[8]

- **Limitations**

1. The diffusion of the drug in the brain parenchyma is very low.
2. Unless the target is close to the ventricles it is not an efficient method of drug delivery.

Application

The administration of Glycopeptide and an Aminoglycoside antibiotic used in meningitis.

B. Convection-enhanced Delivery (CED)

CED was developed in the early 1990s by Edward Oldfield's group at the National Institute of Health. The technique was proposed as a method to deliver drugs that were either limited by the BBB or were too large to diffuse effectively.

CED is a technique that generates a pressure gradient at the tip of an infusion catheter to deliver therapeutics directly through the interstitial spaces of the central nervous system. It allows for the delivery past the blood-brain barrier in a targeted and safe manner that can achieve therapeutic drug concentration (shown in Fig.5).[9]

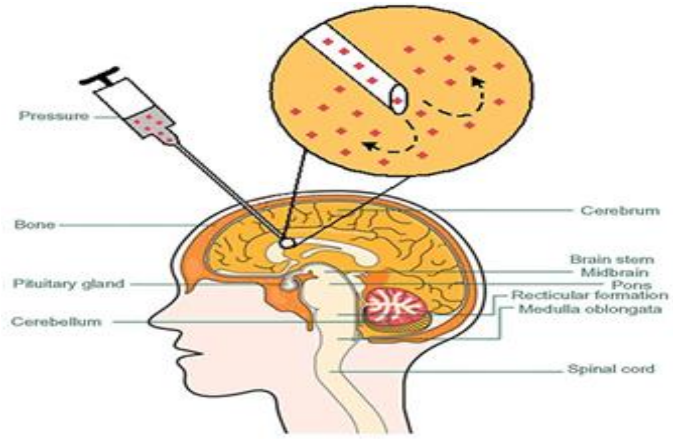

Figure 5: Convection-enhanced Delivery using a microfusion pump

CED allows passing the BBB, targeted delivery and perfusion of deep brain targets both near and downstream of the site of infusion. CED is applicable to a wide range of compounds as evidenced by a number of studies using chemotherapeutic agents, low molecular weight imaging tracers, proteins, viruses & virus shaped particles, liposomes and nanoparticles.[9]

In CED one or more catheters are stereotactically inserted through a burr hole into the interstitial spaces of the brain using image guidance. To create the pressure gradient and drive the flow, and infusion pump is connected to the catheter(s), and the drug is infused directly into the extracellular space of the brain, while displacing the extracellular fluid. The interstitial pathways into the brain allow for convective transport independent of molecular size.[9]

Future Improvements in Catheters

Newer Generation Catheters
Reflex preventing Catheters
Multiple-hole/ Hollow-fibre Catheter
Ultrafine Catheter
Bottom-tipped Catheter

Albumin and Gadolinium-diethylenetriaminepentaacetic acid - CED infused albumin tracers can be linked to gadolinium-diethylenetriaminepentaacetic acid (Gd-DPTA) which can be visualised with traditional imaging techniques.

- **Limitations**

1. *Backflow* or *Reflux*- It occurs along with catheters insertion tract if the catheter has mechanically disrupted the tissue enough to allow a void to form along the outer wall. In intrinsic backflow, the pressure associated with the infusion pushes against the tissues and separate them from the catheter. The shear force in the tissue balance the pressure field and retrograde axial flow stops.
2. *Air bubble*- They are not inherently a health hazard but can disrupt the flow of the infused agent causing unpredictable flow patterns and can also contribute to backflow.
3. *Pathologic condition*- Pathologic scenarios (i.e., active tumours) and post-operative tissue alterations present further challenges in the effective use of CED.

- **Applications**

CED is used to deliver a variety of drugs to brain in cases of diversity of disease, including Parkinson's disease and Alzheimer's disease. It is especially relevant in the treatment of malignant gliomas, as reoccurrence generally occurs within centimetres of the original tumour and CED can reach the peritumoral region and beyond.

C. Intracerebral Implants

Intracerebral implants are small patches which are inserted into the brain and placed into the interstitial spaces of brain where they release their medicament slowly into the brain. It entails the delivery of drug into the parenchymal spaces of brain. The drug distributes into the brain by diffusion mechanisms which makes the distribution of drug a concentration dependent process in this method.[10] Intracerebral injections are also utilised to administer drugs into the brain. In this the drugs can be administered by:
Direct injection *via* intrathecal catheter.
Control release matrices.
Microencapsulated chemicals.

- **Limitations**

1. The distribution of drug into the brain by diffusion decrease exponentially with the increase in distance from site of administration.
2. The site of injection has to be very precisely mapped to get efficacy and overcome the problem associated with the diffusion of the drug into the brain parenchyma.

- **Application**

This technique is useful in treatment of the various CNS disorders, e.g., Parkinson's disease, brain tumour, etc.

D. Disruption of the BBB

This is a popular invasive technique for CNS drug delivery. It involves the disruption of the Blood-Brain Barrier. As the Blood-Brain Barrier is disrupted, it loses its highly lipophilic nature characteristics for allowing only highly lipophilic molecules to pass through it and it starts to allow less lipophilic or hydrophilic molecules to pass through it.
The substances used to enhance the permeability of the Blood-Brain Barrier are called *Permeability enhancers*. They have the ability to transiently open the BBB and allow the high concentration of systemically administered chemotherapeutics to reach the brain. One of the rationale for these molecules to open the BBB is based on the transient disruption of the BBB by decreasing expression of tight junction proteins such as claudin-1, occludin and tricellulin.[11]
The Blood-Brain Barrier can be disrupted by several methods such as by using Permeability enhancers and by Osmotic disruption.

1. By using Permeability Enhancers

The BBB, like other cell membranes, is subject to solvent-mediated disruption with various chemicals. These chemicals decreases the permeability of the Blood-Brain Barrier and allow the drug to pass through the BBB from the systemic circulation in high concentration. Such chemicals are called *permeability* enhancers and are generally used as solvent media or adjuvant with the drug. Some examples of these enhancers are ethanol, dimethyl sulfoxide (DMSO), or detergents such as SDS, or Tween 80 also known as Polysorbate 80, polyethylene glycol hydroxy stearate.[11]
These chemicals are supposed to destabilize the membranes and causing BBB disruption which allows the drug molecule to access the brain tissues and show their therapeutic effects. Permeability enhancers are co-administered with the drug to the patients to achieve the significant. However in studies it is found that the co-administration of drug with permeability enhancers is insufficient to achieve the benefits of the enhancers in humans. Since the interaction of the enhancers with the Blood-Brain Barrier is transient, co-delivery of both enhancer and drug by one carrier could be important to allow the drug to cross the BBB, while the enhancers open the Blood-Brain Barrier.[11]

2. By using Osmotic disruption

Substances that increases the osmotic pressure of the systemic blood flow are administered into the internal carotid artery of the patients. It increases the osmotic pressure of the systemic blood flow to the brain. It results in osmotic shock to the endothelial cells of the brain blood capillaries which causes them to shrink. This results in disruption of the tight junctions and finally the blood-brain barrier is disrupted.[11]
As an agent to increase the osmotic pressure of the blood flow to brain, a hypertonic mannitol solution is administered into the internal carotid artery of the patients followed by subsequent administration of the drug. It increases the concentration of drug in brain and tumor tissues to reach the therapeutic concentration.[11]
The hypertonic mannitol solution injected into the internal carotid artery is solution of 25% Mannitol in saline.

- **Limitations of the Invasive Approach**

1. All the techniques are relatively expensive than the techniques used in non-invasive approach.
2. The invasive techniques require anaesthesia and hospitalization of the patient.

3. These techniques may enhance tumor dissemination after successful disruption of the BBB.
4. Neurones may be damaged permanently from unwanted blood components entering the brain.

Non-Invasive Approach

The BBB is not disrupted instead various methods/techniques are utilised which can deliver the drug to the brain without damaging/disrupting the BBB. Scientists have developed several methods to increase the lipophilicity or lipid solubility of the drug molecule to make it able to pass through the BBB, or designed such nano molecules which can cross the BBB and deliver the desired drug to the brain. This approach rely on the brain blood vessel network for drug distribution.
The techniques involved in this approach are:

A. Chemical Techniques

This technique involves development of drugs so that they can easily penetrate through the BBB. The physicochemical properties of drugs are altered so that their lipid solubility can be increased. As the BBB is highly lipophilic in nature, the highly lipid soluble drugs can easily permeate through them and reaches the brain. To increase the lipid solubility a drug is also linked together with some lipophilic molecules so that it can form a conjugate with high lipid solubility.

1. Prodrug

Prodrugs are the molecules which do not have any therapeutic effect on our body on their own but when they undergo certain structural changes, they become a new molecule, called drug, showing therapeutic effects on the body. Prodrugs are usually created for drug with poor lipid solubility which makes it harder for them to penetrate or cross through the biological membranes.[4]

In case of drug delivery to brain, the drugs which are unable to cross the BBB are made into a prodrug. These prodrugs possess characteristics like high lipid solubility and ability to cross the BBB. The prodrugs are metabolised by enzymes present in brain and convert into active drug showing its action (shown in Fig.6).[4] Making a prodrug improves the physicochemical, biopharmaceutical or pharmacokinetic properties of the drug. It enhances the availability of the drug beyond the BBB to the brain.

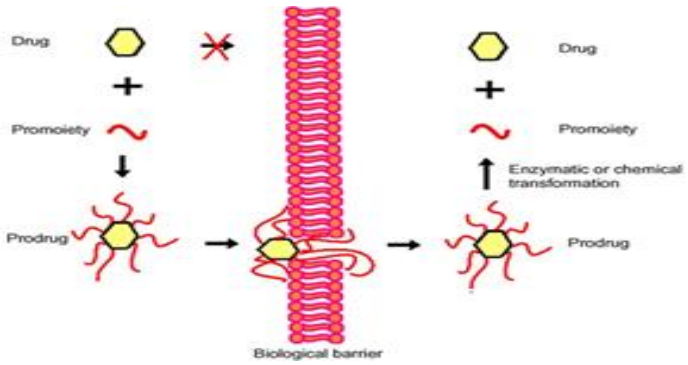

Figure 6: Prodrug Approach

Levodopa, a prodrug of *Dopamine,* is a prominent example of how making a prodrug enhances the availability of the drug to the brain. Dopamine is an aqueous drug used in case of Parkinson's disease but due to its aqueous nature it can't cross the BBB and has poor availability to the brain. However, its prodrug Levodopa can easily permeate through the BBB and reaches the brain where it is metabolised by an enzyme to form active drug compound, i.e., Dopamine. Similarly, prodrugs with better lipid solubility are prepared for aqueous drugs so that they can easily pass through the BBB in a significant number making them produce a proper therapeutic effect.[4]

2. Drug Conjugates

Drug conjugates are chemically modified drug molecules prepared by linking them together with a substance that will enhance their physicochemical properties, e.g., Lipid-drug conjugate. Lipid-drug conjugates (LDCs) are drug molecules that have been covalently modified with lipids. LDCs have played very important role in enhancing drug delivery to the brain.[10]
In LDCs the conjugates of drug are formed with,
With **Fatty acids** e.g., Decosahexaenoic acid (DHA), Squalenoic acid (SA), stearic acid and palmitic acid, etc. The drugs are conjugated with water or amide linkage by conjugation between lipid's carboxyl end with a hydroxyl or amine group of the drug,[10] with **Steroids**, e.g., Cholesterol, Cholic acid. The hydroxyl group at the ring of steroid nucleus is the primary site of linkage for the steroids, in most studies. It provides benefit of decreased side effects, targeted tumour delivery and efficient cellular uptake. Cancerous cells, like brain tumor cells, overexpress LDL receptors and requires a large amount of cholesterol for rapid growth. Cholic acid is used in the formation of ursodeoxycholic acid (UDCA) and lithocholic acid (LCA).[10]
with **Glycerides**- Triglycerides (TG) are glycerol molecules combined with three fatty acids via ester linkage. The fatty acids at second position of glycerol molecule is replaced with a drug molecule. It is to take the advantage of TG metabolism pathways known as the Triglyceride deacylation-acylation pathway. It helps in incorporating TGs into the lipoproteins followed by

accumulation in lymphatic system. The glyceride conjugate drugs take the advantage of the lymphatic transport pathway to improve adsorption and enhance the lymphatic targeting. Other examples of glyceride conjugated drugs include Mitomycin C (MMC), Methotrexate, Testosterone and Paclitaxel.[10]

with **Phospholipids**- There are two strategies to conjugate drug to a phospholipid linkage at the phosphate group or attachment on the second position of the glycerol backbone. A conjugate from these two strategies can form liposomes or enhance the incorporation of drug into phospholipid/lipid-based delivery system.[10]

The bonds involved in the formation of drug conjugate are usually ester bonds, amide bonds, hydrazone bonds, disulfide bonds and other bonds.

Ester bonds are very common to form LDCs. They increase the absorption of the drug conjugated and are also easily hydrolysed to release active drug. These are successfully used for formation of lipid conjugates of drugs like Paclitaxel, Zidovudine, Methotrexate, etc.[10]

Amide bonds are similar to ester bonds. They are formed by carbodiimide coupling, i.e. chemical reaction between carboxylic end of lipid and amine end of drug. These have slower rate of hydrolysis. They are used for synthesizing conjugates for drugs like Doxorubicin, Gemcitabine.

Hydrazone bonds are used to form pH sensitive LDCs. As a hydrazone shows no decomposition at neutral pH, but at lower pH it decomposes efficiently. It is successfully utilised to produce pH-sensitive Lipid Conjugated Doxorubicin.

Disulfide bonds form LDCs which are stable in extracellular oxidative environment, but they are cleaved after cellular uptake in response to the reductive intracellular environment. They are quite helpful in preparing conjugates for tumor treatment as the thiolytic environment of tumors hold advantages for LDCs with disulfide bond.[10]

As the formation of LDCs helps in increasing the lipid solubility of drug, it enhances the delivery of drug across the BBB. LDCs formed by the glyceride linkage with the drug, enhances the CNS delivery of the conjugated drug. Therapeutic agents such as GABA, L-Dopa, and Phenytoin, have been linked with glycerides or formulated as pseudoglycerides to improve CNS drug targeting and to increase the CNS drug activities. The brain penetration index of glyceride linked GABA showed a 127-fold increase compared to free GABA, establishing substantial evidence that glyceride prodrugs increase brain targeting. The sulfide linkage LDCs are usually used for enhancing the action of drugs against the tumors.[10]

3. Chemical Drug Delivery System

The chemical drug delivery system (CDS) term was first coined by Bodor. Unlike the prodrug approach CDS requires only a single activation step. However, more and more sophisticated prodrugs nowadays are activated in multiple steps. Three types of CDS have been most investigated, viz Enzymatic physiochemical CDS, Site-specific enzyme activated CDS and Receptor-based CDS.[11]

In CDS, a complex of drug is made with a lipophilic targetor moiety to enhance its lipid solubility or BBB permeability. The complex is formed in such a way that a single reaction leads to a chain of reactions ultimately releasing the drug into the brain. E.g. 1,4-dihydro-N-methylnicotinic acid (dihydrotrigonelline) is a commonly used lipophilic targetor moiety that can increase the brain distribution of a wide variety of drugs.[11]

4. BBB Shuttle Peptides

BBB shuttles are molecular vectors which carry drug or active compound to the brain. The BBB shuttle concept includes Trojan horse antibodies and any other molecule capable of transporting a cargo into the brain parenchyma without affecting the BBB integrity. The BBB shuttle concept was conceived by William M. Pardridge in the mid-1980s, inspired by chimeric proteins targeting cell receptors. The first successful attempt was done using cationised albumin, which lacked brain selectivity and then on IgG's directed against insulin and transferrin receptors. However, the success of these receptors was hampered by their high affinity, which hampered an efficient release into the brain parenchyma. This made the scientist to investigate a variety of protein shuttles; most of them were ligands of receptors on the brain endothelium and include the following: apolipoproteins (Apo) A and E, receptor-associated proteins (RAP), transferrin (Tf), lactotranferrin, melanotranferrin and leptin.[12]

BBB shuttles allow the transport of a wide range of cargoes, comprising small molecules, proteins, nanoparticles and genetic material cross the BBB. Substrate of natural carriers such as glucose and neutral amino acids have been applied to transport small molecules through their natural carriers on the BBB, while for nanoparticles and biomolecules receptor ligand proteins are used since vesicular mechanism tolerate a wide range of cargo size. Some famous BBB shuttle peptides are Angiopep-2 and GSH.[12]

Angiopep-2 was identified by sequence alignment of aprotinin with other human proteins having a Kunitz domain, which interacts with LRP1. This BBB shuttle was initially exploited to transport small molecules such as Doxorubicin, Etoposide, Paclitaxel and also peptides. Its conjugate with Paclitaxel (ANG1005 or GRN1005) showed good tolerance in phase I clinical studies, and reached phase II for the treatment of recurrent high-grade glioma in combination with Bevacizumab. Angiopep-2 has been used to transport a variety of nanocarriers loaded with small molecules, proteins or genetic material into the CN. These carriers include liposomes, nanotubes, dendrimers made of polyamidoamine and poly-L-lysine, and also nanoparticles made of PEG-polycaprolactam, PEG-poly (lactic-coglycolate) (PEG-PLGA), thermo-responsive hydrogels, upconversion nanocrystals and gold.[12]

GSH is a highly specialised BBB shuttle peptide that has been mainly applied to target PEGylated nanoliposomes loaded with

drugs, which are thereby protected from degradation and clearance. This formulation is known as G-Technology.[12]

B. Biological Techniques

In order to increase the lipid solubility of the drug molecule or making it able to cross the BBB the scientists have also tried to use biological molecules, which are produced inside our body and can easily cross through the BBB or can easily transfer any molecule across the BBB. Such techniques are called *biological techniques.* As endogenous molecules or proteins are used as a carrier for the drug molecule for delivery to the brain, it ensures an efficient delivery of drug to the target as BBB is not a barrier for them.

1. Monoclonal Antibodies Conjugates

The BBB prevents the penetration of majority of substances into the Brain, but it also selectively allows others to enter. These selectively permeable substances are endogenous substances such as Insulin, Iron, LDLs and other acting as substrate for carriers located at the BBB which facilitates their penetration into the CNS. Thus, the formulation of receptor-receptor-targeted monoclonal antibodies (MAbs) is being utilised to increase penetration across the BBB.[12]

Antibodies are endogenous proteins in the body which are produced in response to a foreign particle or antigen entered into the body and withstood other defences of the body. They have affinity only for the antigen against whom they are developed or prepared for and once they bind to the antigen, they break it down. Therefore, there are several antibodies present in our blood circulating throughout our whole body. However *Monoclonal Antibodies (MAbs)* are the antibodies which are deliberately prepared against a specific antigen, which is usually the substance to which we want MAbs to bind, in this case they are the receptors present on the BBB. [12]

Usually the substrate molecule can be used for me targeting its receptors, e.g. targeting insulin receptors can be done using insulin but it may lead to hypoglycaemia. Therefore, the MAbs against human insulin receptors were developed. Scientists have developed a human insulin receptor monoclonal antibody (HIRMAb) with high affinity binding to insulin receptor (IR). Scientists conducted a test to check the extent to which this MAb could act in drug delivery. Biotnyl [^{125}I]-Ab$^{1-40}$ (amyloid beta) was bond to the MAb and Streptavidine. While film autoradiography determined that A$^{1-40}$ does not cross the BBB, the drug-biological conjugates exhibited high brain uptake comparable to that of small molecules.[12]

HIRMAb fusion proteins were also synthesized. Iduronidase (IDUA) enzyme can be used for treatment of mucopolysaccharidosis type 1 (MPS1) though it does not cross the BBB. HIRMAb-IDUA enables enzyme replacement therapy by increasing BBB penetration.

AGT-181 is a fusion protein which had Brian uptake of 1% ID/brain and fusion protein activity in brain predicts that an infusion dose of 1mg/kg should restore enzyme activity to the brain. It is currently in clinical trials for the treatment of Hurler syndrome in children.[12]

OX26 Mab is a substitute of rat and human transferrin receptor (TfR). In mouse OX26 was found to have potential in drug delivery to brain. In humans OX26 was used to deliver agents across BBB by TfR targeting such as vasoactive intestinal peptide.

Bispecific antibodies (bsAbs) are novel molecules/antibodies with two different binding sites. These are underdevelopment as BBB permeation enhancers. The bsAb with TfR and BACE1 binding site are being prepared. The resulting bsAbs exhibit contrasting results due to their binding affinities to TfR. Low affinity binding to TfR results in increased BACE1 BBB penetration while high affinity resulted in poor penetration.[12]

Low density Lipoprotein receptor-related protein 1 (LRP1) is another target for Mab since it is responsible for transport of several ligands across the BBB.

ANG-1005, a conjugate between Paclitaxel and Angiopep-2 was synthesized. Angiopep-2 is a derived peptide with a ligand for LRP1. Conjugated Paclitaxel demonstrated significant improvement in BBB penetration vs conjugated Paclitaxel.[12]

- **Limitations**

1. As MAbs are targeted at specific carriers, they interfere with ligand transfer depending on the affinity of that Mab.
2. This makes the dose of administered agent increase.
3. Immune response to biological drugs have previously been reported.

2. Cationic Bovine Serum Antibodies (CBSA)

Cationic Bovine Serum Antibodies (CBSA) was investigated in isolated brain capillaries. It was evaluated with internal carotid, perfusion/capillary depletion technique *in vivo*, indicating a good accumulation profile in the brain.[12]

Both apparent brain homogenate and post vascular supernatant volume of distribution of CBSA were much higher than native bovine serum albumin (BSA) during a 10-minute constant rate brain perfusion in rats. CBSA appeared to have favourable pharmacokinetic properties with a longer serum half-life and a greater degree of selectivity to brain tissue as compared to other organs like liver, heart, lung.[13] In compare to Mab, CBSA are easier to prepare.

Such traits make CBSA a promising alternative brain targetor designed to couple with the liposomes. CBSA coupled pegylated liposomes were taken up into brain endothelium *via* an absorptive mediated endocytotic pathway and proved to be a suitable carrier for brain drug delivery under the confocal laser scanning fluorescence microscopy.[13]

3. Receptor-mediated Transport

The luminal surface of the BBB contains many receptors which helps in the transport of the proteins and peptides from the blood to the brain *via* BBB. These receptors usually transport the proteins like Insulin, Transferrin, etc. In this method of delivery specific antibodies against these receptors are prepared. Further the drug molecule desired to be transported across the BBB is attached to these antibodies and injected into the internal carotid artery. These antibodies have strong affinity for the receptors so allow the drug to reach to the BBB and then bind to the respective receptor. It allows the transport of drug across the BBB.

4. Chimeric-peptide Drug Delivery System

For the transport of several proteins, peptides across the BBB into the CSF, the brain capillary endothelium contains peptide receptors which mediate peptide transcytosis through the BBB. For example, Insulin is transported into the brain parenchyma through the insulin receptors present at the brain capillary endothelium. The insulin binds to its receptors present on the brain capillary and then transport into the brain, this makes this transport a receptor mediated transport.[14]

The receptor-mediated transport lead to the development of chimeric peptide hypothesis which propose that the drug delivery to the brain may be done by attachment of the drug to peptide or protein 'vector' which are transported into the brain from the blood by absorptive or receptor mediated transcytosis through the BBB. These molecules formed by the attachment of drugs to the peptide or protein 'vector' are called 'chimeric peptide'.

The action of chimeric peptide is observed in four steps. Initial step is the receptor-mediated endocytosis of the chimeric peptide at the luminal surface of the brain capillary endothelium, followed by a movement through endothelial space *via* a transcytotic compartment.[15] The next step is exocytosis into interstitial fluid. The third step is cleavage of the disulfide bond liberating the therapeutic compound from the transport vector. The final step is binding of the peptide therapeutics to its cognate receptors on the brain cells.

In chimeric peptides, the drug is usually attached to the peptide or protein 'vector' via a linker molecule which potentiates the bonding between the two molecules. Avidin-Biotin technology is usually used for this purpose.[16]

The variety of vectors used in chimeric peptide are cationised albumin, protamine, recombinant CD_4, anti-transferrin receptors, anti-compliment receptor antibody, etc. The linkers were developed from chemical cross-linking and Avidin-Biotin technology. In chemical cross-linking either cleavable or non-cleavable linking were made between the Biotin moiety and the therapeutic component. The cleavable linking involves the disulfide linkage between the two compounds whereas in non-cleavage linkage the bond is formed by amide linkage. In Avidin-Biotin technology either the vector or the drug is fused to Avidin while the other is fused to Biotin. As biotin has great affinity for the avidin, both molecules are attached together by a strong linkage.[16]

C. Colloidal Techniques

A colloid is a suspension of microscopically dispersed particles or droplets that typically have a diameter between 1 and 1000 nm. This technique involve the use of colloidal drug carriers to transport the drug across the BBB to the brain. These drug carriers cross the BBB by endocytosis and/or transcytosis. They have also shown successful results for the management of CNS condition such as brain tumor, HIV encephalopathy and Alzheimer's disease. The colloidal drug carriers used are Nanoparticles (NPs), micelles, liposomes, microemulsions and dendrimers. Particle size, surface affinity and stability in circulation are the important factors influencing the brain distribution of colloidal particles.

1. Micelles and microemulsions

Micelle are spherical molecules with inner hydrophobic core and outer hydrophilic surface. Their size is of colloidal range. Micelle and microemulsions have demonstrated great promise as intracellular drug delivery system. Theoretically, natural and synthetic polymer material can be used to prepare micelle and microemulsions.[17]

Currently polymeric micelles, which are mostly investigated have a hydrophobic polymer core, e.g. poly(propyleneglycol), poly(D,L-lactide) and polycaprolactone, and a shell of hydrophilic polymer blocks, e.g. PEG(polyethylenenglycol). Pluronic block copolymer micelles can inhibit drug efflux transporters and enhance drug transport to the CNS. Furthermore, pluronics inhibit the P-glycoprotein efflux transporters widely expressed on the BBB and do not demonstrate any toxicity to the brain.[17]

A microemulsion is defined as the system of water, oil and amphiphile, which is a single optically isotropic and thermodynamically stable liquid solution. The microemulsion concept was introduced in the 1940s by Hoar and Schulman, who generated a single-phase solution by titrating a milky emulsion with hexanol. The surfactant molecules which stabilise microemulsions are usually the same as those that form micelles. Miroemulsions have high loading capacity and good penetration ability, this makes this nanoscale system appealing.[17]

2. Liposomes

Liposomes are lyotropic liquid crystals composed of relatively biocompatible and biodegradable materials and consists of an aqueous core entrapped by one or more bilayers of natural and/or synthetic lipids, as shown in Fig.7.[17]

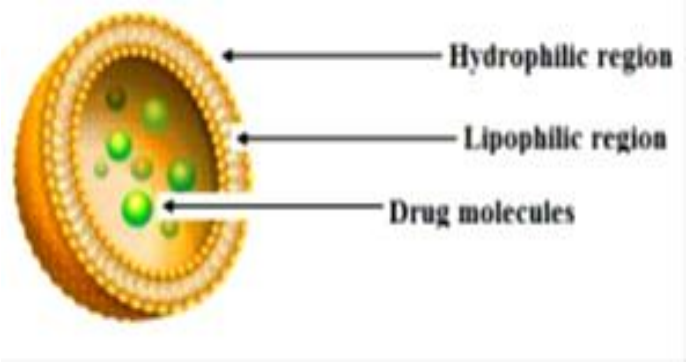

Fig 7: Structure of Liposome

Liposomes are tiny pouches made of lipids, or fat molecules surrounding a hydrophilic core. They are form of vesicles that are consists of either of many, few or just one phospholipid bilayers. The polar character of liposomal core enables polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilised within phospholipid bilayer according to their affinity towards phospholipids.[17]

3. Nanoparticles

Nanoparticles are mainly based on biodegradable polymers. They have been extensively exploited in targeted drug delivery as they offer excellent improvement by protecting encapsulated drug from biological and/or chemical degradation, and extracellular transport by P-gp efflux system. This increases CNS availability of the drug. Poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactide-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(methyl methacrylate), are the polymers known to be biodegradable, biocompatible and non-toxic.[18]

Nanoparticles are in solid state and are in either amorphous or crystalline form. They also include nanospheres and nanocapsules of size 10-200nm. They are capable to adsorb and/or encapsulate a drug, this protecting it against chemical and enzymatic degradation. In recent years, biodegradable polymeric nanoparticles have attracted a considerable attention as potential drug delivery device in view of their applications in their controlled release of drugs, in targeting particular organ/tissue, as a carrier of DNA in gene therapy, etc.[18]

The various nanomaterials used for this purpose are nanotubes, nanowires, nanocantilevers, nanoshells, nanospores, etc.

Studies have reported olanzapine-loaded PLGA nanoparticles to be effective for the treatment of psychotic illness, schizophrenia, *via* nose to brain drug delivery approach. They are also been extensively studied for their use in tumor imaging and diagnostics.[18]

Miscellaneous Approach

This approach different to the previous two mentioned do not interact with the BBB directly. Here the drug is administered at the points of body where there is no BBB in the way of drug to reach the brain, e.g. the nasal route

A. Intranasal Delivery

This is a miscellaneous method used to deliver drug to the brain. The junction at which olfactory nerves meet the brain there is no BBB, so it allows the drug to easily pass into the brain. Intranasal delivery is a method of drug delivery to the brain which bypasses the BBB. It provides a practical, non-invasive, rapid, and simple method to deliver the therapeutic agents to the CNS. This method does not require any modifications in the therapeutic agents and also do not require the drug to be coupled with any carrier to cross the BBB. A wide variety of therapeutic agents, including both small molecules and macromolecules can be successfully delivered, including to the CNS, using this method.[19]

There are two mechanisms involved in nasal delivery, a fast rate that depends on the lipophilicity of drug, and a slower rate that depends on the molecular weight of drug. Studies indicate that good bioavailability can be achieved for molecules up to 1000Da (without enhancer) molecular weight and good bioavailability can be extended to at least 6000Da molecular weight with enhancers.[19]

The olfactory epithelium in the nasal cavity act as a gateway for the substances entering the CNS and the peripheral circulation. The neural connection between the nasal mucosa and the brain provide a unique pathway for the non-invasive delivery of therapeutic agents to the CNS. The olfactory neural pathway provides both an intraneuronal and extraneuronal pathways into the brain. The intraneuronal pathway involves axonal transport requiring hours to days for drugs to reach different brain regions. The extraneuronal pathway probably relies on bulk flow transport through perineural channels, which deliver drugs directly to the brain parenchymal tissues and CNS. The extraneuronal pathway allows therapeutic agents to reach the CNS within minutes. The transport of drugs across the nasal membrane and into the bloodstream may involve either passive diffusion of drug molecules through the pores in the nasal mucosa or some form of non-passive transport.[20]

- **Advantage**

1. Non-invasive, rapid and comfortable.

2. Bypasses the BBB and targets the CNS, reducing systemic exposure and thus systemic side-effects.
3. No requirement of modification of therapeutic agent being delivered.
4. It is useful for a wide range of drug.
5. Rich vasculature and highly permeable structure of the nasal mucosa greatly enhance drug absorption.
6. The problem of degradation of peptide drug is minimised.
7. Easily accessible to blood capillaries.
8. First pass degradation is avoided.

➢ **Limitations**

1. Concentration available in different regions of the brain and spinal cord, varies with each agent.
2. With the increase in molecular weight of the drug, the delivery rate decrease.
3. Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa and may cause irritation in the mucosa.
4. Nasal congestion due to cold of allergies may interfere with the delivery of the drug.
5. Frequent use of method may result in mucosal damage.

B. Iontophoric Delivery

This is a novel approach. It is an electro-chemical method that enhances the transport of some solute molecule by creating a potential gradient through the BBB with an applied electric current or voltage.[18]

As shown in Fig.8, it involves the increased migration of ionic drug through the BBB by electrostatic repulsion at active electrode. Negative ions are delivered by cathode and positive ions by anode. As this method involves use of electric charges, this method is better for ionic drugs which found it hard to cross the BBB. However, the amount of charge needed to be applied varies with the size and the charge present on the drug molecules.[18]

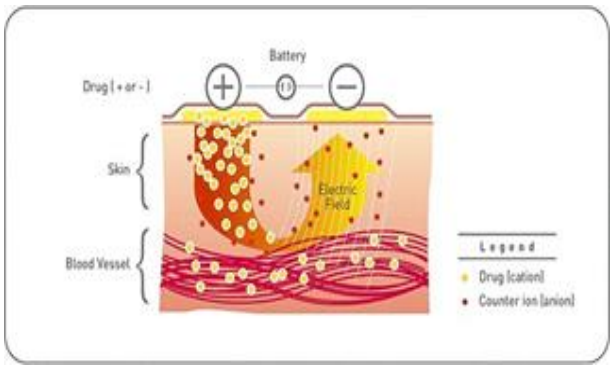

Fig 8: Active Iontopheresis

A typical iontophoresis device consists of battery, microprocessor controller, drug reservoir and electrodes, etc.[18]

➢ **Advantages**

1. Delivery rate can be controlled by variations of current density, pulse voltage, drug concentration and ionic strength of the drug.
2. Reduces side effects and variation among patients.

➢ **Limitations**

1. This method is not suitable for the delivery of non-ionic drugs to the brain.

Conclusion

The BBB act as a major obstacle in delivery of drug to the brain and prevent the entry of the drug to the brain. BBB is a barrier formed by tight junction between capillary epithelium and astrocytes. This allows entry of some specific molecules to the brain. In order to deliver the drug to the brain, the BBB was needed to be surpassed. To make this possible many approaches, basically three, were used. The primitive approach was the Invasive approach, in which the drug is administered to the brain by disrupting the BBB. In this approach many techniques were developed by time like ICVI, CED, use of permeability enhancers, etc. however, eventually some serious limitations of this approach came in light, like as the BBB was disrupted there were chances of flow of toxicants from the blood to the brain which may cause some serious damage. It leads to the discovery of an approach which do not disrupt the BBB, it was later called Non-invasive approach. Now-a-days, this approach is preferred over the other as this ensures that there will be no damage to the BBB. With time many researches were done in this approach and many new techniques were developed like, prodrugs, MAb conjugates, CBSA, Liposomes, Nanoparticles, etc. Other popular approach which indirectly deliver the drug to the brain is called miscellaneous approach. It includes nasal delivery and iontophoretic delivery. They both deliver the drug without approach the BBB. However, the non-invasive approach is preferred more than others to deliver the drug to the brain. Many researches are being done to invent new techniques to make this approach this much safer and efficient. Non-invasive approach with targeted drug delivery is more preferred as it makes the process more efficient. For the targeted drug delivery many micro molecules and devices are developed which ensures the efficient drug delivery to the brain. These micro

molecules or devices are nanoparticles like nanotubes, nanochips, nanospheres, etc., microemulsions, dendrimers, liposomes, etc. Niosomes are also developed by researchers for the same purpose, however their unique design and efficiency is much better than other micromolecules. Niosomes are newer compare to other micromolecules.

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