Different Strategies, Approaches and Recent Advances in Transcellular Brain Drug Delivery

Miss. Mayuri J. Chandrawanshi[1], Mr. Surajmal G. Malpani[2], Mr. Vishweshwar M. Dharashive[3], Mr. Sameer S. Shafi[4], Miss. Shraddha T Nemane[5]

[1]*Assiatant professor, Shivlingeshwar College of Pharmacy, Almala, Latur, Maharashtra, India*

[2,3,4,5]*Shivlingeshwar College of Pharmacy, Almala, Latur, Maharashtra, India*

Abstract **- There are three types of barrier present in central nervous system such as Blood Brain Barrier, Blood Cerebro-Spinal Fluid Barrier, and Blood–Arachnoid Barrier. BBB is the very tough barrier for the transport of drugs to brain. For the treatment of various diseases related to CNS like brain cancer, Alzheimer disease, parkinson's disease, epilepsy, psychiatric disorders or neurodegenerative diseases, different types of drugs are available. But they have some lacuna for transport of drug though these barriers and reaching drug to the target site. This review is one of the attempts to amend the recent information on cellular structure of BBB as well as different procedures planned to cross it. Different strategies and approaches are utilized to improve brain targeted drug delivery system. Lipophilicity of drug can be increased by chemical modification, while colloidal carriers like Nanoparticles, Dendrimers, Lipososmes , Nanogels enhances properties and therapeutic effect of drug in brain. Using these strategies, tumour targeting nanoparticles are developed according to the EPR. This effect could be useful to brain diseases by considering the leaky BBB. Information on structure and function of brain, recent strategies to deliver drugs into brain for treatment of CNS diseases are involved in this article.**

Index Terms **- BBB, Nanotechnology, targeted drug delivery, CNS disorders.**

I.INTRODUCTION

The nervous system monitors and coordinates internal organ function as well as responds to changes in the outside environment. The nervous system is accountable for transfer, acceptance, and interpreting information from all parts of the body. Central nervous system is the segment of the nervous system. The main function of the CNS is to progression the information received from the peripheral nervous system. Important neuro-physiological characteristics of the CNS are neurons, synaptic transmission, and neurotransmitters. CNS includes some behavioural aspects like sensation and perception, motor system, cerebral lateralization, and language. CNS is consisting of the two very important organs i.e. brain and the spinal cord.

Brain is the heart of central nervous system. It is located in the head, generally close to the sensory organs responsible for senses such as vision. Brain exerts a centralised control over other organs of body. Brain is responsible for generating muscle activity as well as driving the secretion of chemicals i.e. known as hormones. There consists of cerebrum, cerebellum, and diencephalon. Cerebrum occupies around 85 % of organ's weight and it is the largest part of brain. It is packed inside the skull. Cerebrum consists of two hemispherical sessions which are further divided in to four lobes i.e. frontal lobe, parietal lobe, temporal lobes, and occipital lobes. Frontal lobe is responsible for speech, thought, problem solving, Judgement and motor function. Parietal lobe manages the handwriting, body sensory information like touch, temperature, pain. Temporal lobes are concerned with memory and hearing while occipital lobe deals with brain's visual processing system. Cerebellum is the second main part of brain which is located under the back of cerebrum and plays an important role in coordinating movement, posture, and balance. Third part of brain is the diencephalon. It is located in the central part of the brain. There is an apricot consist of two major sections i.e. thalamus and hypothalamus. Thalamus acts as relay station for incoming nerve impulses from around the body after that, they are forwarded to suitable brain section for processing. Hypothalamus controls hormone secretions from the pituitary gland. It is very essential for keeping bodily processes like temperature, hunger and thirst balanced.

Brain stem controls reflexes and basic life function such as heart rate, breathing and blood pressure. [1] [2]

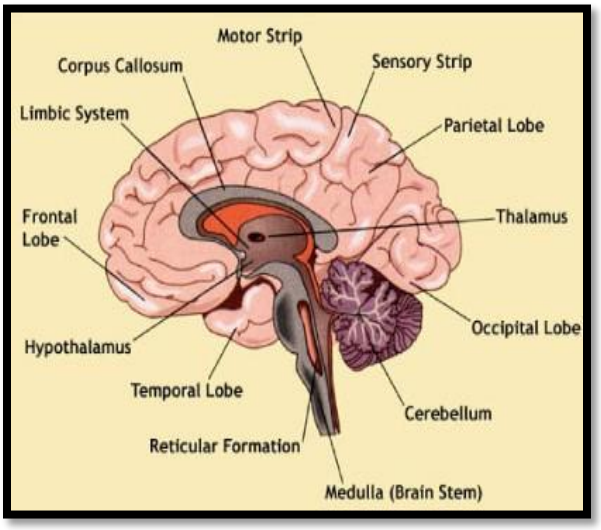

Fig. No. 1 Structure of brain

Various factors affect distribution of drug in brain. The distribution of a drug within the brain shows local concentration of drug that is available to bind to its target & bring an effect. Structural properties brain as well as drug affects the distribution drug within the brain. The brain-specific properties i.e structural properties of the brain are very significant for drug distribution within the brain. Blood is supplied to different part of brain through arteries and capillaries network. At brain capillaries level, compounds are exchanged between the blood and the brain tissue. Brains contain several potential binding sites for both endogenous and exogenous compounds. There are three types of barrier present in the brain i.e. BBB, BCSFB and Blood arachnoids barrier. [1] [2]

II. TYPES OF BARRIERS

Blood Brain Barrier: -In the brain, brain capillaries are separated from brain by means of blood brain barrier. This barrier separates the blood in the brain capillaries from brain tissues, including the brain ECF & brain cells. Blood brain barrier i.e. BBB is the protective, highly selective semi-permeable membrane which is made up of endothelial cells. These endothelial cells are joined to each other by continuous tight intercellular junctions comprising called as Blood Brain Barrier. BBB keeps the brain atmosphere secure and stable by preventing some toxins, pathogens, and other injurious substances from entering the brain through the bloodstream. At the same time, it allows oxygen and vital nutrients to pass through. On the base of endothelial membrane, there are the special cells are present called as pericytes and astrocytes. This cell support endothelial cells and forms a solid envelope around the brain capillaries. As a result, intercellular passage is blocked and for drug to gain access from capillary circulation into brain, it has to pass through the cells rather than between cells. Through this system molecules are allowed to pass by the passive diffusion and selective transport of several nutrients, ions, organic anions and macromolecules such as glucose, water as well as amino acids which play vital role in neural function.

Functions of blood brain barrier.

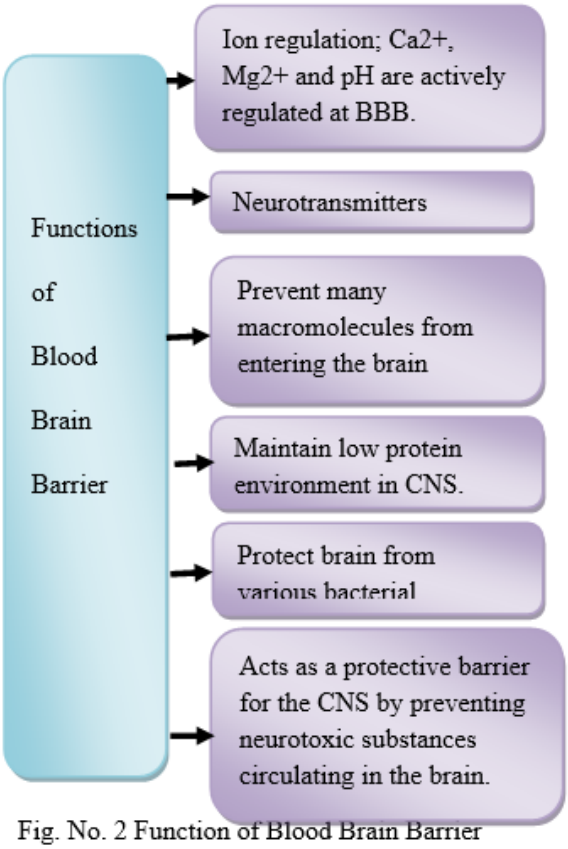

Fig. No. 2 Function of Blood Brain Barrier

The BCSFB: -

BCSFB stands for Blood Cerebro-spinal Fluid Barrier. It separates the blood in the brain capillaries from the CSF in the brain ventricles. Exchange of compound is regulated in order to maintain a secure atmosphere for normal brain function. This BCSFB consists of the epithelial cells of the choroid plexus situated in the

brain ventricles. These cells are strongly connected to each other by means of tight junctions. While the brain capillaries of the BCSFB have dissimilar to the BBB, contain pores and highly permeable.

The blood–arachnoid barrier: -
Blood–arachnoid barrier is the separation between the blood in the blood vessels of the dura mater and CSF in the sub-arachnoid space. The blood–arachnoid barrier segregates the brain capillaries in the dura mater from the CSF in the sub-arachnoid space. The barrier is produced by a film of arachnoid cells which are connected by tight junctions. [1] [2] [3]
Different properties of a drug affecting its distribution within the brain are

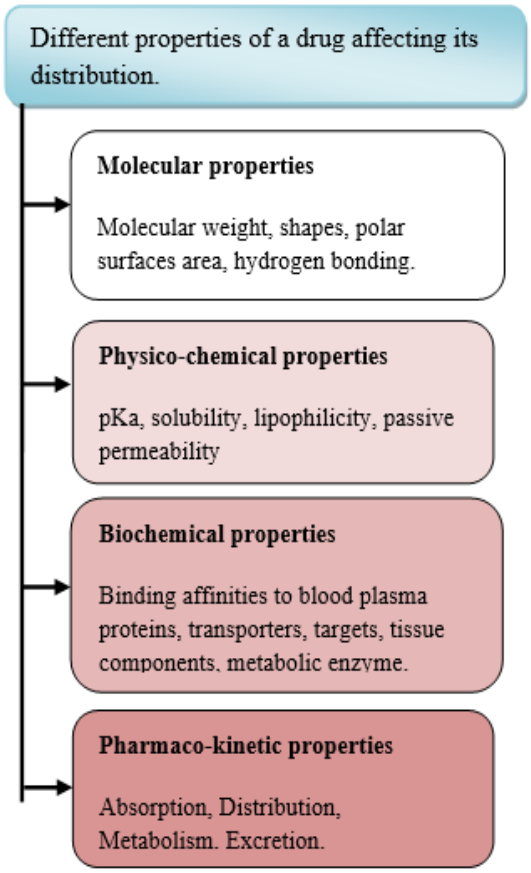

Fig. No. 3 Different properties of a drug affecting its distribution.

Diseases related to blood brain barrier

- Meningitis.
- Brain abscess.
- Epilepsy.
- Multiple sclerosis,
- Neuromylitis optica,
- Sleeping sickness,
- Alzheimers's disease,
- Parkinson's disease
- Dementia
- Myasthenia gravis,
- Memory loss, etc [3]

Approaches to bypass BBB

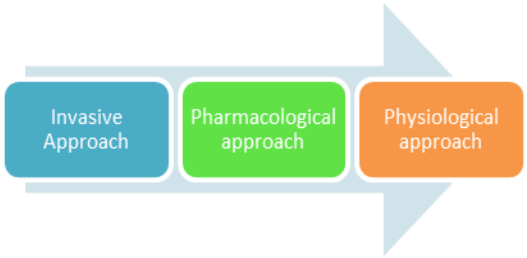

Fig. No. 4 Approaches to bypass BBB

III. APPROACHES AND STRATEGIES FOR CENTRAL NERVOUS SYSTEM DRUG DELIVERY

In CNS drug delivery, various drugs are used to show therapeutic effect in different CNS pathologies. But their applications are restricted due to their pharmacokinetics. Several strategies are applied to cross or to by-pass the BBB that can be grouped as invasive, non-invasive techniques and miscellaneous techniques.

Invasive Techniques
Some invasive strategies are applied for brain targeting. Temporary physiological distruption in the endothelial integrity of the brain is one of the invasive strategies for delivering drug to brain. It involves techniques like Intra-cerebral implants, Intra-cerebro ventricular infusion, BBB Modification /distribution. [4]

Intra-cerebral implants
Chemotherapeutic agent's administration through injections, placement of biodegradable, chemotherapeutic impregnated, wafers into tumour resection cavity, transmit through the diffusion to drive the drug into in filtrated brain. [4]

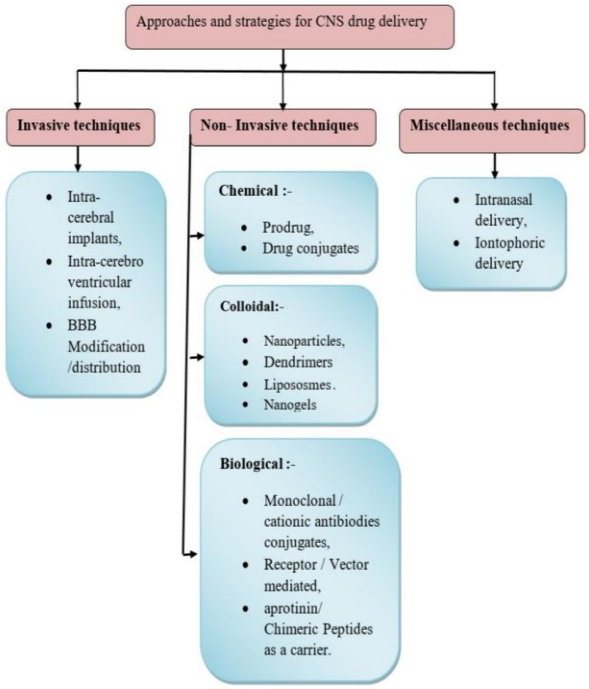

Fig. No. 5 Approaches and strategies for CNS drug delivery

Intra-cerebro ventricular infusion

It is one of the strategies used for bypassing the Blood Brain Barrier. This method involves drug administration through injections or intra-ventricular infusion of drug directly into the cerebrospinal fluid. Drug can be permitted intra-ventricularly with an ommaya reservoir, a plastic reservoir implanted subcutaneously in the scalp which is connected to the ventricles. Solutions of drug can be injected subcutaneously into the implanted reservoir and drug is delivered to ventricles by manual compression of the reservoir through the scalp.

E.g. glycoproteins and aminoglycoside antibiotics used in treatment of meningitis. [4] [5]

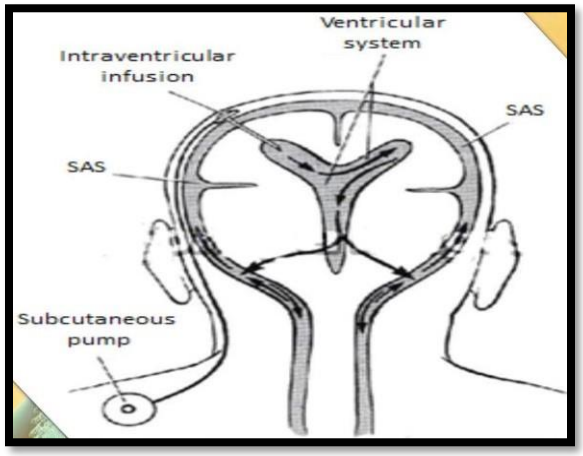

Fig. No. 6 Intra-cerebro ventricular infusion

BBB Modification /distribution

Disruption of BBB can be open access of the brain to components in the body by making the endothelial cells of brain capillaries leaky. Disruption of BBB can be cause by osmotic disruption, MRI- guided focused ultrasound BBB disruption techniques, application of bradykinin analogue. Osmotic disruption is done by osmotic shock. It causes endothelial cells to shrink, thereby disrupting the tight junction. MRI used BBB distribution techniques involves ultrasound for disturbing BBB. In bradykinin analogous, opening the tight junction to arise by activation of bradykinin B2 receptor during calcium- mediated mechanism. Different strategies involved in BBB disruption are Convection-enhanced delivery, Osmotic blood-brain barrier disruption strategy, Biochemical blood-brain barrier disruption strategy, Ultrasound-mediated blood-brain barrier disruption strategy etc.

This approach is designed with the thought to break down the barrier by injecting mannitol solution into arteries in the neck. Its effect is shown for 20-30 minutes, during this period drug freely diffuses, that would not generally cross the BBB. This technique allowed the release of chemotherapeutic agents in patients with cerebral lymphoma, malignant glioma and disseminated CNS germ cell tumours.

But this method shows undesirable side effect like Physiological stress, transient increase in intracranial pressure, and unwanted delivery of anticancer agents to normal brain tissues in humans.

Limitation of invasive techniques

- It is very costly process, requires anaesthesia as well as hospitalization. It is non friendly process to patients.
- These techniques may improve tumour dissemination after successful disruption of BBB.
- In this technique, there might be chances of permanently damaging of neurons from unwanted blood component entering the brain.[6] [7]

Pharmacological approach

Pharmacological approach is one of the mostly used approaches for by passing BBB. It is based on some molecules like alcohols, nicotine, benzodiazepines which are freely entering the brain. Some molecules have ability to cross the BBB and it is totally

depending upon molecular size and lipophilic property. Molecules having molecular size less than 500 Dalton can pass the BBB passively. This approach involves modification through medicinal chemistry and molecules active against CNS target to facilitate it to enter the Blood Brain Barrier.

Limitation: - For crossing BBB modification is necessary. It may result in loss of the desired CNS activity. Transport can be improved by increasing Lipophilicity of the molecules and can be result in making it a substrate for the efflux pump P-glycoprotein. [7] [8]

Physiological approach

Various approaches are used for increasing brain delivery of therapeutics. Between all these approaches physiological approaches is most accepted method by the researchers because of advantage of transcytosis capacity of specific receptor expressed at BBB. Low density lipoprotein is the receptor related protein most adapted for such use with engineered peptide compound platform which incorporate the angio-peptide in new most advanced method with promising data in the clinic.

E.g. Receptor mediated transcytosis. [8][9]

Non- Invasive techniques

Non- Invasive techniques involve pharmacological strategies capable of modifying drugs to assist transport across the BBB. Drug modification is done for improving lipid solubility and it is the most important factors for bypassing the drug through passive diffusion into the BBB. In this process, the water-soluble molecules are chemically transformed to lipid soluble molecule and it is made able of crossing the BBB. This chemical transformation of drug is carried out by adding lipid functional group to polar ends of drugs molecules. Non-invasive techniques consist of drug amendment by medicinal chemistry approaches and drug encapsulation by means of nanotechnological carrier. Drug transportation by using colloidal drug carriers is a most promising approach. Several colloidal carriers include in these techniques are emulsion, liposomes. Niosomes, nanoparticles etc. it also includes coating of surfactants like polyxypropylene, polyethylene glycol, polyoxymethylene. [9] [10][11]

Prodrug

A prodrug is one of the compounds, after the administrations it is metabolized and converted into a pharmacologically active drug. In prodrug, the chemical change is usually designed to improve some deficient physiologicochemical property such as solubility and membrane permeability. Instead of direct administration of drug, prodrugs are developed with improved absorption, distribution, metabolism, and excretion.

E.g. levodopa, GABA, niflumic acid, valporate etc. [11] [12]

Nanoparticles: -

Nanoparticles are particles occurred in nanometre range i.e., below 100 nm. Nano- sized drug delivery system is very important and widely used as it offers moderately drug nature – independent transport due to their capability to mask the physicochemical properties of the content. Nanotechnology-based drugs delivery acquires advantage of current administration methods and found in oral, topical, and injected formulation. Various polymer-based delivery system such as colloidal carriers, nanocarriers and nano vectors are developed in which their most important feature is their size that ranges from 10–1000nm. After reduced size of particles, a significant quantity of single or various compounds can be enclosed in them and reach the CNS. Recently not only pharmaceutical but also biotechnological companies have developed nanotechnology-based drug delivery systems. Crossing of dug through BBB is the final step in drug delivery process. Nano sized system has purpose to get better drugs bioavailability as well as pharmacokinetics, as a result improve the therapeutic index and safety profile. It also offers sustained release in addition to constant levels of drug in plasma over the time.

E.g. 1. Marketed drugs such as steroids and diphenhydramine show penetration through paracellular–transcellular transports are essential for expressing the quality of permeability in the BBB.

2. Albumin nanoparticles enhance BBB permeability; increase both solubility and half-life in circulation. Patients suffering from brain cancer over express albumin-binding proteins, such as SPARC and gp60, in their BBB and tumour cells, naturally mounting the uptake of albumin into the brain. [12] [13]

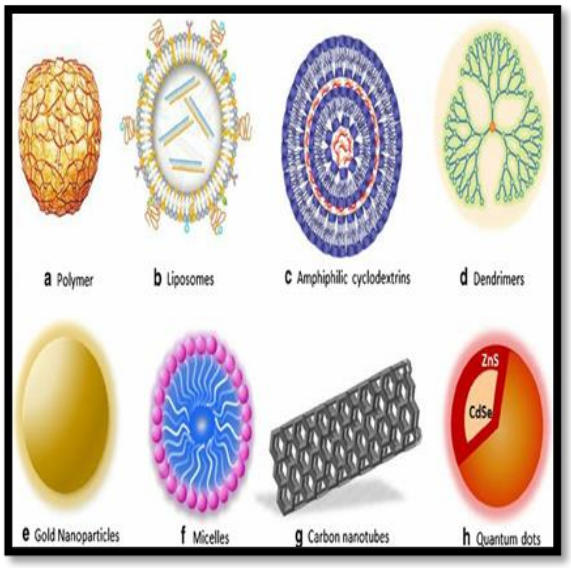

Fig. No. 7 Different types of nanoparticles

Dendrimers

Dendrimers are the branched; three dimensional molecules consist of three polymeric layers such as central core, branches, and terminal functional group. Dendrimers contain a single chemically addressable group known as core. It is also called as focal point. Branches are attached to the core and establish creation of dendrimers. Next part of dendrimers is the terminals functional group which is means for creating surfaces of nanoparticles. The branches of dendrimers and surface groups are increased with the enhancement of the number of dendrimer generation. Dendrimers have very low dispersion as well as high performance. Presence of several surface groups and hydrophobic core makes dendrimers acceptable for loading of high quantity of drugs and provide multi-purposes. Dendrimers are most compatible molecules containing controlled nano size structure for drug delivery. It assists the conveying of drugs to a variety of cell membranes or biological barriers via endocytosis through cellular internalization. A variety of types of dendrimers are used for the imaging and delivery of drugs which consist of polyamidoamine (PAMAM) dendrimers, polyhydroxylamine, and polypropylene amine. [13]

Nanogels

Nanogels are the aqueous dispersions of nanosized polymeric particles formed after physical or chemical cross-linking methods. It is extensively utilised as drug-delivery systems due to their excellent properties. Nanogels are webbing of nano-sized polymers such as polyethylene amine, PEG, polyacrylic acid and Pluronic. Hydrogel nanoparticles are well developed concept used for precise drug delivery systems because of its hydrogelic as well as nanosized features. It has high drug loading capacity around 40-60%. Modification of nanogel with transferrin and insulin enhances distribution through BBB. Nanogel not only enhances the absorption of oligonucleotides in the brain but also reduces their absorption in the liver and spleen. It is one of the most promising carriers for drug delivery to the CNS.

E.g. Nanogel containing Methotrexate is used in the treatment of anticancer. After the administration of nanogel through injection into the bloodstream and binding to lipoproteins. It binds to the endothelial cells of the brain capillaries and consequently diffuses into the endothelial cells by endocytosis. [13] [14]

Liposomes: -

Liposomes are the artificial vesicles made up of lipid bilayer. It contains different sizes ranging from 20–5000nm and number of lipid bilayers such as unilamellar or multilamellar vesicles. In this system, hydrophilic drug is provided by lipophilic environment by using cholesterol, phosphatidylacholine and facilitate the drug delivery across BBB. Drug which have lower distribution compared to free drugs are encapsulated in liposomes. Cholesterol, high-phase transition lipids are used in the formulation for stabilizing the lipid bilayer as well as provide a non-leaky transport system. Liposomes gives some advantages such as Provide selective passive targeting to tumour tissue, increased efficacy and therapeutic index, increased stability as well as reduces toxicity through encapsulation, progress pharmacokinetic effects, acts as best carrier for both controlled and sustained drug delivery, possibility of various route of administration and increases half-life of drug.

Liposomes shows some disadvantages like outflow of encapsulated drug during storage, uptake of liposome's by reticulo-endothelial system, batch to batch variations, difficult for both sterilization large scale manufacturing, chances of dose dumping due to

defective administration. When once liposomes are administered it cannot be removed. [14]

Receptor / vector mediated drug delivery

Receptor mediated drug delivery towards the brain utilize chimeric peptide technology. Conjugation of drug with antibodies is also called as Antibody-Drug Conjugates (ADCs). This is a recent division of very effective biological drugs which is developed by connecting a tiny particle of anticancer drug or any another therapeutic agent to an antibody. This binding may be either a permanent or tentative linker. The antibody targets a particular antigen merely set up on target cells.

E.g antibodies to transferrin receptor like OX- 26, 8D-3 Mab antibodies were able to undergo receptor transcytosis.[15]

Intranasal Drug Delivery

Drug administration through the nasal route is called as nasal drug delivery system. Nasal route for drug delivery is one of the best substitutes for invasive administration. It provides a direct entrée of drug to systemic circulation. Now a day, various drugs have been showed the better systemic bioavailability through nasal route than oral administration. Drugs are administered through nasal route and reaches to CNS by means of three different routes such as the olfactory pathway, trigeminal pathway, and systemic circulation pathway.

Both olfactory and trigeminal pathways avoid the BBB by delivering the therapeutic substance from the nasal cavity to the brain tissue via passive or active transport mechanisms. In the systemic circulation pathway, the therapeutic material diffuses throughout the mucus, bypass the nasal epithelium through passive as well as active transport and enter the venous blood stream to reach the CNS. Through this process overcome the BBB. The olfactory and trigeminal pathways are the direct means of drug transport from nose-to-brain. This development is much less invasive than the intra-parenchymal and intra-ventricular routes. These pathways have some limitation that, little quantity of drug that can flourish reaches the brain tissue as compare to the amount drug administered.

Advantages of Nasal drug delivery system

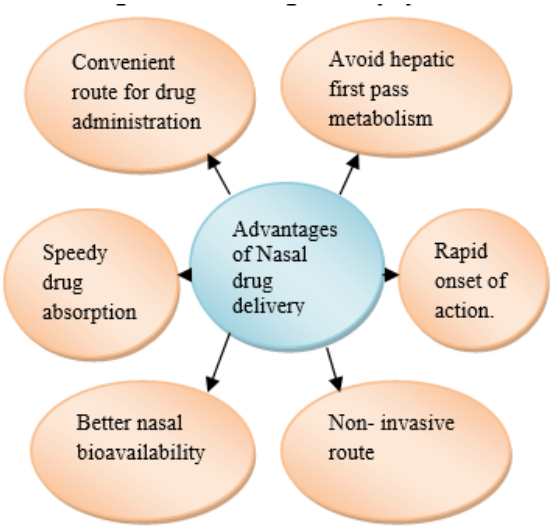

Fig. No. 8 Advantages of Nasal drug delivery system

Limitation: -

- Absorption enhancers are used to get better therapeutic effect of drug through nasal drug delivery system, but this may shows toxicity.
- Less absorption surface area as compared to GIT.
- Once administered drug cannot be removed.
- May cause nasal irritation.
- Chances of local side effects and damaging of cilia on the nasal mucosa.

Application of nasal drug delivery system

- Delivery of non-peptide pharmaceuticals such as progesterone, estradiol, propranol, nitroglycerin etc.
- Delivery of peptide-based pharmaceuticals like insulin, calcitonin, and pituitary hormones.
- Delivery of diagnostic drug.
- e.g. Secretin- used for diagnosis of pancreatic disorder.
- Phenolsulphulfonphthaline- used for diagnosis of kidney function.
- Nasal vaccination. [15] [16]
- Drug delivery to brain in the treatment of Alzheimer and Parkinson's diseases.

Iontophoric delivery

Iontophoresis is one of the recently used approaches of administering ionic medicinal compounds into the body throughout the skin with the application a local electric current. It is used to distribute ionized molecules across BBB by electric current externally.

It includes olfactory pathway for drug delivery to the CNS. There are various invasive methods as well as devices are presented for macromolecular drug delivery to brain. As compare to that invasive techniques' device for Iontophoresis permit for superior drug delivery into the brain under controlled strategy. [16] [17]

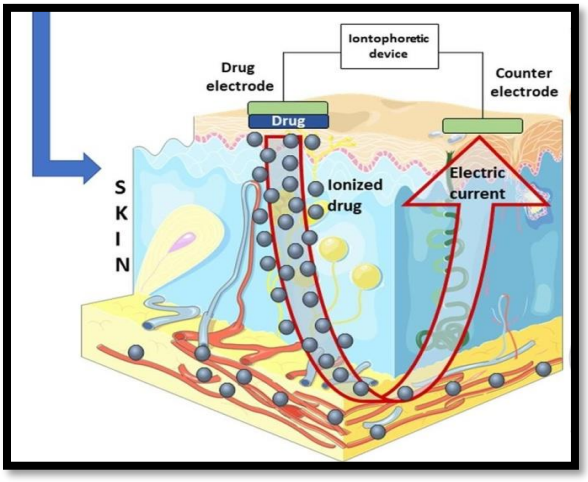

Fig. No. 8 Iontophoric delivery

IV. RECENT ADVANCES IN NANOTECHNOLOGY FOR BRAIN DRUG DELIVERY

- The research team of universities of Michigan has developed tools to diagnose & treat the most virulent forms of brain cancer.
- 20-200 nm diameter of probes encapsulated by biologically localised embeddeding in brain cancer targeting.
- Chimeric peptide technology.
- Lipobridge technology.
- Peptide radiopharmaceuticals.

V. LIST OF MARKETED FORMULATION AVAILABLE AS A BRAIN TARGETED DRUG DELIVERY SYSTEM.

Sr. No.	Brand name	API i.e. Active Pharmaceutical Ingredients.	Role
1	Ambisome	Amphotericin B	Liposomes for injections.
2	caelyx	PEGylated liposomal doxorubicin hydrochloride.	Brain tumour.
3	Aricept	Donepezil	Alzheimer disease.
4	Aurimmune	Colloidal gold IV nanoparticles	Solid tumour.
5	Auroshell	Gold coated silica nanoparticles IV	Solid tumour.

VI. CONCLUSION

Development of drug for the treatment of brain diseases is very challenging because delivery of drug molecules to brain prohibited by variety of physiological, metabolic, and biochemical obstacles. Various drugs are used for the treatment of neurological diseases, cancer, Epilepsy, Alzheimer's disease, Parkinson's disease, Myasthenia gravis etc. But it is very difficult for the drug to cross BBB and reach their cellular target in the brain. It has many other limitations, so that huge efforts are required to develop efficient targeting drug delivery system. Recently, several approaches are developed for preparing best drug delivery to treat CNS disorders. It is expected that inventive drug delivery system should assist brain disease diagnosis. By using these strategies and approaches, successful results are assumed and there will be a novel generation of drugs delivery system functioning properly. Systematic overview by using classical pharmacology and nanotechnology to treating different CNS disorders are well explained through this review article.

VII.ACKNOWLEDGEMENT

Authors are thankful to Shivlingeshwar College of Pharmacy, Almala, Latur, family and friends for support and motivation while writing this paper.

REFERENCES

[1] Marta A. Małkiewicz. et.al., Blood-brain barrier permeability and physical exercise, Journal of neuroinflammation, pp.1-16, 2019

[2] Hadi Maleki et.al. Transcellular brain drug delivery: A review on recent advancements, International journal of Pharmaceutics, pp 1- 52, 2020.

[3] Gary A Rosenberg et.al. Neurological diseases in relation to the blood–brain barrier, Journal of Cerebral Blood Flow & Metabolism vol 32, pp 1139–1151, 2012

[4] Luca Anna Bors, Franciska Erdo″et.al., Overcoming the Blood–Brain Barrier. Challenges and Tricks for CNS Drug Delivery, Scientia Pharmceitica,vol 87, 6. Pp. 1-28, 2019.
[5] Matthew Campbell, E. Keeffe et.al. modulating the paracellular pathway at the blood Brain Barrier: Current and future approaches for drug delivery to the CNS, Drug Discovery Today: Technologies, vol 20, pp 35-39, 2016
[6] Victor M. Pulgar et.al. transcytosis to cross the Blood Brain Barrier, new advancements and challenges, frontiers in Neuroscience, vol 12, pp 1- 9, 2019.
[7] Marta Tajes et.al. The blood-brain barrier: Structure, function and therapeutic approaches to cross it, Molecular Membrane Biology, vol 31(5), pp 152–167, 2014.
[8] Xiaowei Dong et.al., Current Strategies for Brain Drug Delivery, Theranostics, vol 8 (6), pp 1481-1493, 2018.
[9] David S. Hersh, Aniket S. Wadajkar, N B. Roberts, Jimena G. Perez et.al. Evolving Drug Delivery Strategies to Overcome the Blood Brain Barrier, Current Pharmaceutical Design, vol 22, pp 1177-1193, 2016.
[10] Cui-Tao Lu et.al. Current approaches to enhance CNS delivery of drugs across the brain barriers, International Journal of Nanomedicine, vol 9; pp 2241- 2257, 2014.
[11] RaviKant Upadhyay et.al. Drug Delivery Systems, CNS Protection, and the Blood Brain Barrier, BioMed Research International Volume, pp 1-37, 2014.
[12] Andreas M Grabrucker. et.al. Drug delivery across the blood–brain barrier: recent advances in the use of nanocarriers, nanomedicines, pp 1- 10, 2019
[13] MassimoMasserini et.al. Nanoparticles for Brain Drug Delivery, ISRN Biochemistry pp 1-18, 2013.
[14] Chiara Ferraris et.al. Overcoming the Blood–Brain Barrier: Successes and Challenges in Developing Nanoparticle-Mediated Drug Delivery Systems for the Treatment of Brain Tumours, International Journal of Nanomedicine, vol 15, pp 2999- 3021, 2020.
[15] Cinzia M. Bellettato et.al. Possible strategies to cross the blood–brain barrier, Italian Journal of Pediatrics 2018, 44(2):128-161
[16] Majid Saeedia et.al. Applications of nanotechnology in drug delivery to the central nervous system, Biomedicine & Pharmacotherapy, vol 1, pp 666–675, 2019
[17] Kabanov, H. Gendelman, et.al. Nanomedicine in the diagnosis and therapy of neurodegenerative disorders, Prog. Polym. Sci. Vol 32 (8), pp 1054–1082, 2007