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AN OVERVIEW ON BRAIN TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

The most adaptable and complicated organ in the human body is the brain. It is protected by the skull bones, a semi-permeable membrane barrier that is highly selective i.e., blood-brain barrier (BBB), and CSF (cerebrospinal fluid). BBB separates the flowing blood from the brain without isolating the brain from other elements of the human body. The blood-brain barrier and also blood-cerebrospinal fluid barrier prevents the entry of lipophilic neurotoxins into the brain. Besides this they only allow selective materials into the brain which maintains homeostasis in the brain, thereby protecting the CNS. There are several techniques to incorporate the drug in the blood brain barrier for the essential treatments of brain and allied diseases which are broadly classified into three basic groups like intensive techniques, non-intensive techniques and miscellaneous techniques and they are further classified with several techniques. Beside this there are some latest approaches like dendrimers, scaffolds, modified nanoparticles also play major role in brain targeted drug delivery. In a nutshell it can said that in modern day there are lots of approaches which are helpful for the researcher to explore the system of drug delivery to the brain.

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INTRODUCTION

The targeted delivery of the drugs provides a definite amount of drug for an elongated time period to its targeted area that gives therapeutic activity to the greatest extent. The human brain is a very sophisticated organ, protected by two important systems blood-brain barriers while other is the blood CSF barrier. These systems safeguard the brain against harmful substances. Unfavorably, these systems challenge the mechanism of delivering drugs to CNS for curing central nervous system-related diseases, because it prevents the allowance of invasive chemicals into the brain frustrating therapeutic involvements. Advancement in the delivery system of drugs towards the brain is lagging over other areas due to the limitations of the blood-brain barrier. This paper encircles comprehensive analysis about targeted drug delivery towards the brain, its merits, and demerits, various diseases associated with the central nervous system which should be cured by targeted drug transportation, target challenges traditional and latest approach to brain targeting to overcome the problems regarding brain targeting which help the researchers to get an overview regarding the approaches on brain targeted drug delivery system by which the application of the aspects can be done to overcome the limitations of brain targeting. [1]

Targeted or site-specific drug delivery system

By restrained and fixed drug release kinetics, it provides a specified amount of drug to the specific targeted area in such a way that it gives its therapeutic effect to the largest extent, preventing deterioration or inactivation during transmission to the aimed sites and protecting the body from unfavorable reactions due to unsuitable disposition. [1][2]

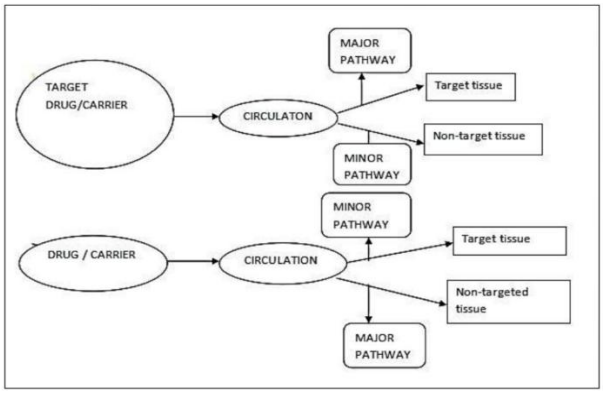

Fig 1. Simplified representation of targeted versus normal drug delivery pathway.

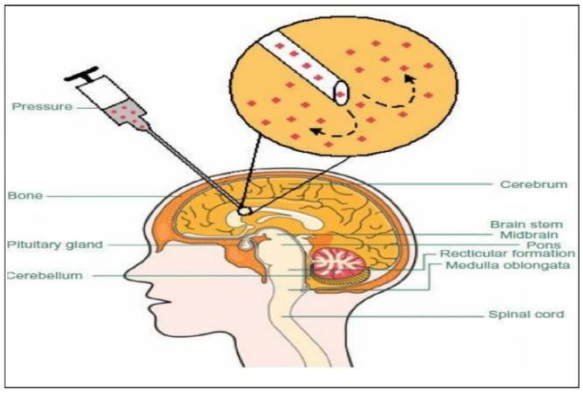

Fig 2. Simplified diagram demonstrating of brain targeted drug delivery route.

Brain targeted drug delivery system

Brain targeted drug delivery system is a process in which the particular drug should be given to the specific targeted site of the brain where it is needed which is shown through the particular figure given below. [3]

Advantages [4][5][6]

There are several advantages of brain targeted drug delivery system. Those are the following:

- Decreases toxicity and unwanted secondary effects.
- Decreases dose of the drug by targeting organ.
- Circumvent first-pass metabolism (deterioration of drug).
- Enhances the rate at which a portion of the drug enters the systemic circulation.
- Reduces changes in concentration
- Enhances the allowance of high molecular compounds (like proteins, peptides).
- Possibility of simplifying Drug administration protocol.
- Reduces fluctuations in plasma concentration.
- The therapeutic activity of the drug is also enhanced.
- The extent of wasting drugs is reduced.

Disadvantages [6][7][8]

- Besides some advantages there are some disadvantages also in this drug delivery system which are the following:
- Increases fast clearance from the target.
- Tough to target cancerous cells.
- Improved procedures necessity.
- Qualified people are needed.
- Toxicity may be caused because of drug deposition at the targeted site.
- Difficult to sustain dosage form stability, e.g., resealed erythrocyte should be stored at 40°C.
- Needs highly developed technical knowledge for the formulation.
- Loading of drugs is usually low, e.g., in the case of micelles. Does it's to predict the dosage rule?
- The release of drugs, redistribution, and diffusion is difficult.
- Unsusceptible reaction against intravenously administered carrier system.

Treated diseases [9][10]

There are many diseases of the central nervous system which can be cured by true BTDDS. Some examples of the disorders are as follows:

- Inflammation of Meninges
- Cerebral abscess
- Seizure disorder
- MS (Multiple Sclerosis)
- NMO (Neuromyelitis Optica)
- African sleeping sickness
- PML (Progressive Multifocal Leukoencephalopathy)
- Senile dementia (Alzheimer's disease)

Challenges [11]

The inability of drugs, delivered to the systemic circulation, to give effective therapeutic effect to cure many central nervous system diseases can be justified by taking into consideration several obstacles that hinder the delivery of drugs to the CNS. The obstacles are as follows:

Blood-brain barrier (BBB) [12]

BBB, like other barriers, is a remarkable anatomical adaptation, consisting of endothelial cells tightly joined by BBB tight junctions, made up of proteins and other substances which prevent blood substances to enter into the brain. Another component, surrounding the endothelial cells is the pericytes and atrocities, which nourishes the neurons, by allowing molecules like glucose to enter the neurons and prevent any unwanted molecules of compounds to enter into the brain. Thin-walled micro diameter vessels makeup to 95% of the whole exterior area of the blood-brain barrier, and depict the principal pathway by which chemicals reach the brain. In capillaries of the brain, intercellular partition pinocytosis and apertures are practically hypothetical; exchanges must occur trans-cellular. Molecules that can easily pass through the endothelial cells, can cross blood-brain barrier through passive transport, must be lipophilic solutes.

The favorable criteria taken into consideration for a compound to cross through the blood-brain barrier are following:

- The compound should not be ionized.
- The value of log P should nearly be equal to 2.
- The compound should have a molecular weight lower than 400 Da.
- Progressing Number of hydrogen bonds should not exceed 8 to 10.
- Only 2% of smaller molecular weight drug is calculated.

Blood cerebrospinal fluid barrier [11][12]

BCSFB, another barrier in between the blood and the brain, forms a boundary between blood and CSF. But this barrier is not taken into consideration as the main pathway for uptake of drugs because the surface area of BCSFB is 5000 folds lesser than that of the blood-brain barrier. Cerebrospinal fluid interchange substances with the interstitial fluid present in the brain. The passing of components, present in the blood, to the cerebrospinal fluid, is also controlled by BCSFB Physiologically, the BCSFB is originated at the epithelium of the arterial choroid (plexus), which is oriented in such a way that it does not allow molecules and other unwanted substances into the cerebrospinal fluid. The plexus and arachnoids matter function simultaneously at the blood-brain barrier. The membrane of arachnoids is predominantly impervious to hydrophilic matter, and it also has an important role in the origination of the blood-brain barrier, is chiefly submissive. The plexus produces the cerebrospinal fluid and actively controls the concentration of substances in the cerebrospinal fluid.

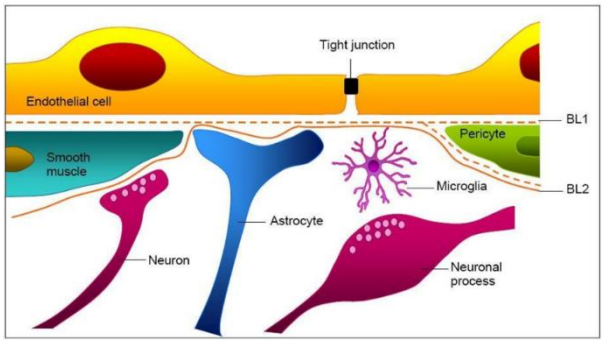

Fig 3. Blood-Brain Barrier.

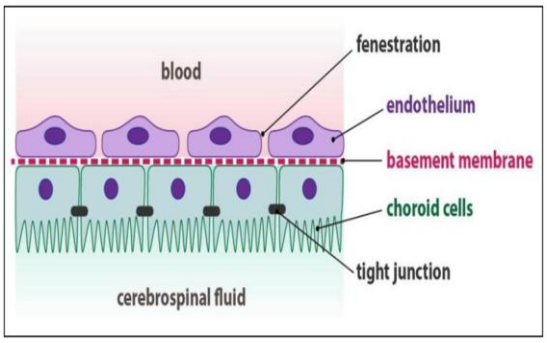

Fig 4. Simplified Representation of Blood-Cerebrospinal Fluid Barrier.

Common approaches

Two basic principles by which a component may enter into the brain [13]

- Passive diffusion through the lipid BBB: Small-sized components (maximum limit less than 700 Daltons) & possessing high oil-in-water (o/w) partition coefficient.
- Active transport of significant nutrients: for example, glucose and amino acids. But here the undesirable fallacious nutrient can be moved across the barrier.

Traditional approaches [14][15]

Currently, some traditional approaches are being used flourishingly to pass the drug through the blood-brain barrier and for curing various diseases. These are as follows:

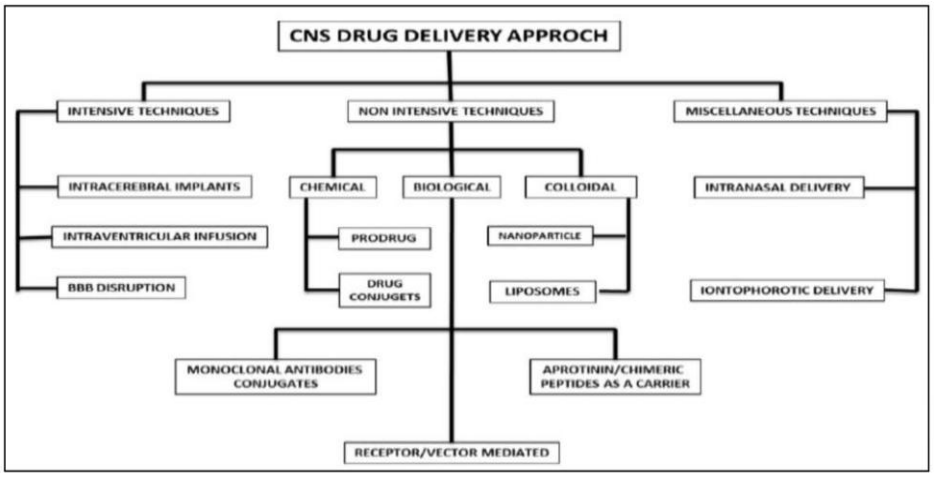

Fig.5. Simplified Representation of Central Nervous System Drug Delivery Procedures.

Intensive techniques [15]

It consists of three perspectives:

- Intracerebral implants.
- Intra-cerebro-ventricular infusion.
- Blood-brain barrier disruption.

Intracerebral implants [16][17]

This involves Drug Delivery straight to the space between the brain and parenchyma. The drugs can be taken by direct injection using an intrathecal catheter, Control release matrices, and microencapsulated chemicals. The primary mechanism is diffusion. It is beneficial for the therapy of various central nervous system diseases. E.g., Parkinson's disease, Gliomas, etc.

Drawbacks

In the brain, scattering by diffusion reduces exponentially with distance. The injecting site is to be very exactly plotted so that maximum affectivity is achieved and the problem related to the drug diffusion in the brain parenchyma is solved.

Intra-cerebro-ventricular infusion [17][18]

It has been surveyed that the ratio of the concentration of drug in the brain to that of cerebrospinal fluid is 3:25 at just 12 millimeters from the surface. Drugs can be easily dispersed throughout the brain surface using intra-ventricular drug infusion but the transportation of the drug towards brain parenchyma is not proper. Pharmacological effects can be noticed after intra-cerebroventricular administration if the targeted receptors of the drug are spotted around the ependymal surface of the brain. For example, GPAs and aminoglycoside antibiotics are used in the inflammation of meanings.

Disruption of blood-brain barrier [18]

This technique is utilized mainly for drug delivery in the central nervous system and includes disruption of the blood-brain barrier. Introduction to X - irradiation and infusion of solvents, e.g., C_2O_5, $(CH_3)_2SO$, may result in the alteration of the blood-brain barrier. By instigating pathological states such as successive tension, inadequate oxygen supply, or ischemia, the blood-brain barrier may also be altered. Various physiological effects on the blood-brain barrier are controlled by the process of energy metabolism. Some of the disruption procedures are:

Osmotic disruption [19]

The osmotic shock makes the endothelial cells contract, does altering the tight junctions. Administrating hypotonic mannitol solution within a carotid artery, simultaneously administrating drug, can enhance the concentration of drug in brain and cancerous tissue to perceive therapeutic concentration.

MRI-guided focused ultrasound blood brain barrier disruption technique [20]

It is seen that the disruption of the blood-brain barrier is possible through ultrasound. Pre-determined microbubbles of ultrasound contrast agent having a diameter of 2-6 micrometer, is injected into the bloodstream before introduction to ultrasound. This procedure causes an increment in the distribution of Herceptin in brain tissue by 50% in a mice model.

Drawbacks of intensive approach [21][22]

Every approach is expensive, demands anesthesia and therapy. These procedures may increase tumor dissemination after successfully disrupting the blood-brain barrier. Undesired blood constituents that enter the brain may harm the neurons.

Non-intensive techniques [23]

Several non-intensive brain drug delivery procedures have been explored, that employ the brain blood vessel nexus for drug conveyance. Noninvasive procedures usually based on drug handling that may include some modifications as:

Chemical techniques [24][25][26]

The chemical techniques which can be implemented in the delivery system are as follows:

Prodrug

Prodrug is lipophilic and can pass the blood-brain barrier. It is metabolized within the brain and transformed into the root drug. These drugs are a pharmacologically inert mixture of two or more elements. The chemical change is typically outlined to enhance some Physico-chemical characteristics, for example, solubility and membrane penetrability. A prodrug is a combination of a drug and inactive chemical component, using a covalent linkage. The active drug is comprised when the attached chemical component in the prodrug is split by hydrolytic enzymatic methods. In prodrug, the chemical component increases the lipoidal characteristics of the drug. E.g. -L-DOPA, Gamma aminobutyric acid, Niflumic acid, VPA.

The disadvantages of the prodrug

- Many attempts to produce a prodrug have failed due to their adverse effects on the pharmacokinetic property of a drug.
- The use of Lipid soluble prodrugs results in the enhancement of the entry of hydrophilic molecules into the brain. But this requires reverse lipidation and transformation of prodrug into the active agent using any chemical or enzyme present within the brain.

Drug Conjugates

Drug conjugates, or carrier-mediated transport (CMT), games and easier mechanism for some small molecules, glucose, amino acid, hormones, and other polar molecules passively transmit through the blood-brain barrier with the help of various carrier substrate present in the blood-brain barrier. Although some hydrophilic substances, such as catecholamine and levodopa were proclaimed to pass through the blood-brain barrier at pharmacologically relevant speed using carrier-mediated transport. To date, the application of carrier-mediated transport has failed to treat glioma. E.g., The usage of the redox system, based on dihydropyridines, as drug carriers (which are used to enhance pharmacokinetic properties of the drug) to the Brain.

Biological techniques [27][28][29][30]

The biological techniques are described as follows:

Monoclonal / cationic antibody conjugates

The significant method of the monoclonal antibody conjugate is CMT or receptor-mediated transport (RMT), where the monoclonal antibody is conventionally used as a carrier but not in a wide range because the method is still under survey for more improvements.

Receptor or vector mediated

This system is manifested on the blood-brain barrier and thus controls the physiological transport of big internal molecules to the brain needed for its function. The endothelial cells situated in the blood-brain barrier have certain distinct receptor-mediated transport mechanisms and various peptide-specific receptors that can be utilized for the transportation of drugs or other therapeutic substances to the brain. E.g., lactoferrin receptor, low-density lipoprotein receptor-related protein receptor, Neonatal Fc receptor, transferrin receptor, and insulin receptor are chiefly marked. There is a drawback which is the process of receptor-mediated transport is still not properly clear.

Chimeric peptide as a carrier

A new approach for delivering peptide to the blood-brain barrier via the brain capillary wall is discovered. It is a combination of chimeric peptides that are produced from the covalent coupling of non-transportable peptides to a transportable peptide that experiences receptor-mediated transcellular transport at the blood-brain barrier. E.g., Beta-endorphin was combined to cationized albumin (pI ≥9) by covalent coupling using disulfide linkage. It owes a highly basic charge, goes through fast absorptive- mediated transport from blood to the brain. The [3H] labeled beta-endorphin-cationized albumin chimera was quickly accepted by remote brain capillaries outside and by rat brain inside. On the contrary, the taking up of native [3H] beta-endorphin through the blood-brain barrier was insignificant. The drawback is this technique can only be applicable for the transportation of peptides.

Colloidal techniques [31][32]

The system of delivering drugs in colloidal form is vesicular dosage form where particles are in a very small size range. This system forms several concentric lipid bilayers when definite amphipathic building blocks face the water. Here the drug carrier can be designed in such a way that it gradually impaired, give response to stimuli, and release the drug at the specific site of action. The fundamental objective is to not only develop the therapeutic efficiency but also controlling the degradation and release of drugs, reducing undesirable toxic effects, extended shelf life, and having controlled drug loading and release characteristics. This system has some merits like:

- The side effect of the drug is minimized as there is the long presence of drug into the systemic circulation. The long presence
- Enhance the bioavailability, especially of drugs with poor solubility.
- Amphiphilic drugs can be absorbed.
- It helps in the sustained release of drugs, thus reducing the removal of drugs that undergoes rapid metabolism.

Nanoparticles [33][34][35]

These are definite colloidal particles, which are formed of polymers having a size range of 1-1000 nm. This includes both nano capsules having core-shell anatomy (a reservoir system), and nanospheres (a matrix system). Nanoparticles are utilized as carrier systems for those drugs which are dissolved, captured, enclosed in a capsule, and absorbed to the surface. This NPs system is beneficial in the case of CNS TDDS because it helps in more desired diffusion of drugs and less risk as compared to traditional therapies. By utilizing this technology, the delivery of drugs is possible to the targeted site by passing through the blood-brain barrier. It also prevents the drug from rapid degradation as well as promotes sustained release. This technology can also reduce toxic effects on peripheral organs.

Transport mechanism [33][34][36][37]

There is some Low-Density Lipoprotein (LDL) receptor on the endothelial cells. The lipoprotein is transported through the endocytosis process to the targeted region with the help of the receptors mentioned, after lipoproteins adsorption from blood plasma to the nanoparticles. It is proposed that the identification and communication with the lipoprotein receptors of capillary endothelial cells that are present in the brain cause the uptake of the drug by the brain.

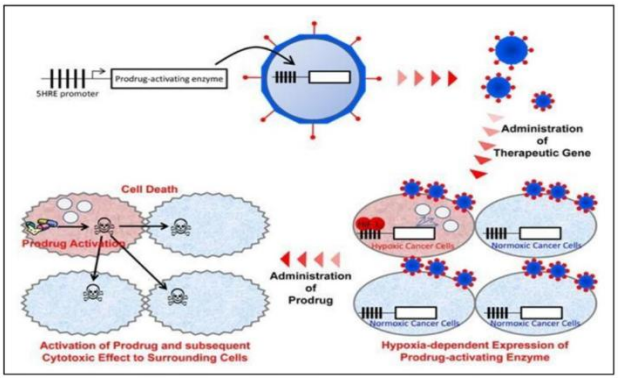

Fig.6. Simplified Representation of Functioning of Prodrug.

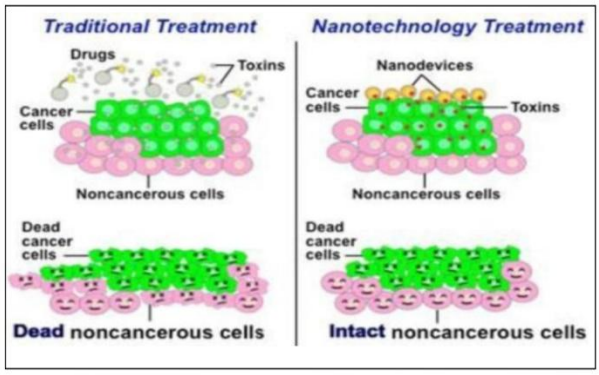

Fig.7. Nanoparticle technology in CNS Targeted Drug Delivery System.

Merits of utilizing nanotechnology for CNS TDDS [35][36][37][38]

- NPS keeps the drugs safe against deterioration caused by any chemical or enzymatic means.
- Since the nanoparticles have a very small size, they can easily go into minute capillaries and are absorbed within the cells, enhancing drug deposition at the specific site of infection in the body.
- If biodegradable substances are used for preparing nanoparticles it helps the drug for sustained release at the specific site after injection for some days or maybe weeks.
- Nanotechnology can also minimize the toxic effects of some dynamic drugs.

Drawbacks of nanotechnology in CNS TDDS [39][40][41]

- Nanoparticles are very small in size, so the surface area is large and can result in accumulation of the particles, thus making it difficult to handle the nanoparticles in liquid form & dry form.
- The small particle size, as well as the large surface area, can also lead to limited drug loading and drug release suddenly and noisily.

Example [42][43]

Hexadecyl cyanoacrylate nanosphere coated by radiolabeled polyethylene glycol is aimed and aggregated in a rat gliosarcoma. However, this process is not in a fit state for clinical try-outs because of the aggregation of the nanospheres in the neighboring healthy tissues.

Liposomes [34][35][37][43][44]

Liposomes are composite structures that are made up of phospholipids and may contain a small number of other molecules in the hydrous medium which results in a lipid bilayer anatomy. Wire liposomes both lipophilic and hydrophilic drugs can be introduced to the brain. Lipophilic molecules can be ensnared within the bilayer membrane and hydrophilic drugs can be ensnared in the middle hydrous core of the vesicles. Liposomes are the best suitable carrier for sustained drug release of and antibiotics for a tumor, for gene and antisense therapy via nucleic acid sequence delivery, sensitization by delivering antigen, and for medication intended to be used for treating and relieving the symptoms of Parkinson's disease.

Merits [44][45][46]

- Since liposomes provide both lipophilic and hydrophilic environments, does therapeutic agents like amphiphilic drugs can be delivered in this form.
- Other than small molecules, macromolecules can also be entrapped into capsules by the liposomes. For example, superoxide dismutase, hemoglobin, erythropoietin, interleukin- 2, and interferon-g.
- The toxic effects can be minimized and the stability of the enclosed drug can also be enhanced by the process of encapsulation. (Example: Amphotericin B, Taxol)
- Liposomes almost prevent the delicate tissues to interact with the drugs with high toxicity.
- Enhance the pharmacokinetic property and pharmacodynamic property of the drugs.

Demerits [48][49][50]

- Raw materials required for manufacturing are quite expensive.
- Drug leakage and entrapment of the drug during storing of the liposomes.
- Oxidation or hydrolysis of phospholipids may occur.
- Modest solubility.
- Reduced biological activity, i.e., short half-life.

Other various methods [51][52]

The other techniques are as following:

Intranasal drug delivery

In this method, the drugs are introduced through the nasal cavity. The mucosa of the nose is used for the delivery of the drugs used for the treatment of CNS diseases and the intake of analgesics, sedatives, hormones, cardiovascular drugs, or vaccines into the systemic circulation.

Mechanism of transport [35][36][53]

There are two mechanisms through which drug passes to the brain through the nasal cavity. They are as follows:

Intracellular transported mediated route (ITMR) [54][55]

ITMR is quite a slow process comma may take hours for administrating matter intranasal to approach the olfactory bulb. ETMR is comparatively a faster process.

Extracellular transported mediated route (ETMR) [56][57]

In the 1st ETMR process, the intranasally administered matter first passes through the gap between the olfactory neurons in the olfactory epithelium followed by transportation of the matter to the olfactory bulb. In the 2nd ETMR process, the intranasally administered drug may convey along the trigeminal nerve to detour to the blood-brain barrier. The drug then approaches the olfactory bulb followed by transportation of the drug towards other regions of the brain by the process of diffusion. A perivascular pump may be involved to assist this process.

Merits [58]

- The presence of a large number of vessels leads to the enhancement of the drug absorption rate.
- Sometimes it becomes difficult to administer the drug orally. This problem can be nullified by the intranasal drug delivery system through which the direct drug administration towards systemic circulation will get easily accessible.
- Comparatively the nasal route is more appropriate than the parenteral route for a longer period of treatment.
- The bioavailability of large molecules of drug can be enhanced with the help of absorption enhancer or by other techniques.
- The patient can administer the drug on his/ her own.
- The large surface area of the nasal mucosa is also an advantage of efficient drug absorption.

Demerits [59][60]

- Few drugs may cause irritation problems to the mucosal layer of the nasal cavity.
- Nose clogging due to cold or allergies may hinder efficient drug absorption.
- The efficiency of drug delivery and the molecular weight of drugs are inversely proportional to each other.

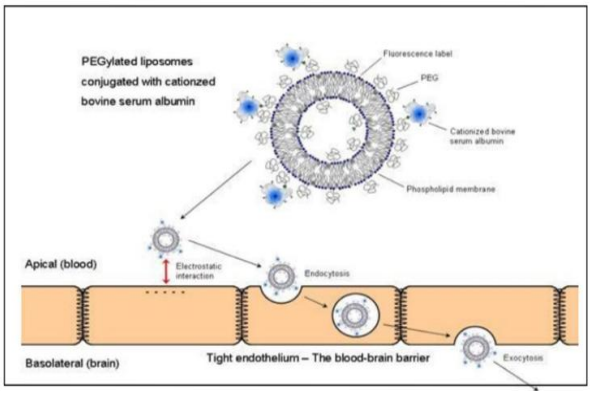

Fig.8. Diagrammatic Representation of Drug Delivery Via Liposome's to The Brain.

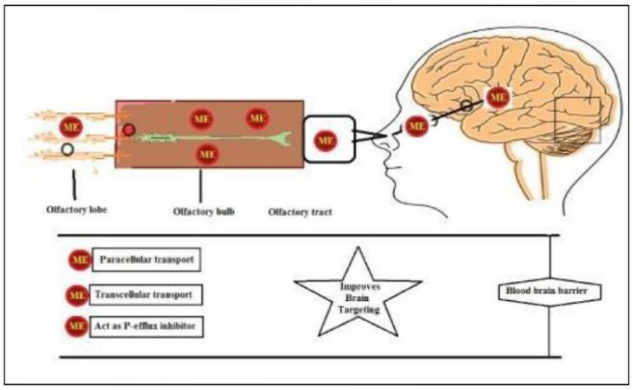

Fig.9. Diagrammatic representation of intranasal drug delivery towards the brain.

Latest expansion of target specific drug delivery system in brain [37][38][39][44][45][46]

Dendrimer

These are polymers having branches. It is normally uniform all over the core, and when adequately expanded, it takes the shape of a spheroidal three-dimensional anatomy in water.

Scaffolds

These act as a cell carrier for implantation and can be utilized to medicate diseases and brain injuries. Also, this can be used as the noble system for drug delivery for the medication of the diseases such as Parkinson's disease and Alzheimer's disease. But the brain offers similar hindrances while designing scaffolds.

Lipoplexes and polyplexes

Gene therapy has come out to be a favorable method for treating genetic diseases. Lipoplexes and polyplexes help in improvement regarding the delivery of new DNA into cells by avoiding its damage. It facilitates the new DNA to enter into the cell.

Poly anhydrides

Many anti-cancer drugs have high molecular weight, having a high affinity towards water, or have ionic charges. Thus, it becomes difficult for them to pass through the blood-brain barrier. So, unendurably developed systemic ways are needed to get the therapeutic doses towards the central nervous system. So, the utilization of poly anhydrases for direct localized delivery is also an easy method.

Modified nanoparticles

The nanoparticles are modified for better efficiency of drug delivery into the specific site of the brain which may have advantages like

- No toxic effects.
- Control in drug loading and drug-releasing.

CONCLUSION

The above discussion can be summarized as the drug delivery with developed clinical effectiveness and low toxic effects are beneficial. But there is still a possibility for improvement. Further studies relating to target-specific drug delivery systems in the brain can show that a new aspect for preventing many complex diseases effectively in the Healthcare system. Many diseases regarding the central nervous system like meningitis may be effectively treated by specific development techniques. Despite many hindrances, progressive measures have been taken for the drug delivery towards the brain. We can hope that it will give a positive result in near future. Thus, the above-discussed techniques are very useful in target-specific drug delivery systems in the brain with more efficiency and less toxicity.

Future Scope

This work describes regarding the several techniques of targeted delivery towards brain. Near future for the practical application an overview will be obtained from this work which help the scholars to get information regarding the challenges and their solution.

Conflicts of interest

The authors declare that they have no conflict of interests.

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ABBREVIATION

BTTDS - Brain targeted drug delivery system
BBB -Blood Brain Barrier
BCSFB - Blood cerebra spinal fluid barrier
CNS - Central nervous system
TDDS - Targeted drug delivery system
CMT - Carrier mediated transport

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