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TARGETING THE BRAIN: VARIOUS APPROACHES AND SCIENCE INVOLVED

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The brain targeting drug delivery system is the technique and process to deliver the drug into brain or central nerves system (CNS). The main problem arise during brain targeting in case of several brain related diseases and disorders such as CNS malignancy, brain abscess, multiple sclerosis, schizophrenia etc. selective and limiting permeation nature of barriers i.e. blood brain barrier (BBB) and blood cerebrospinal fluid barrier (BCSF), these two barriers only allow highly lipophilic molecule enters into brain and is one of the greatest clinical impediment of treatment of brain and CNS diseases and disorders. To treated this type of diseases and disorders drugs are targeted into brain and drug must be cross these two barriers they're by different types of approaches are used to delivered drug molecules.

Aim of research. *The main aim of this review paper is to compile all the approaches, strategies and techniques used for brain targeted drug delivery in a single paper/ article.*

Material and method. *To prepare this manuscript, various keywords were searched in different engines such as Google, Yahoo and Bing etc. The available information in public domain was collected and classified according to brain drug delivery system. This review deals with approaches and current strategies used to enhance the brain targeted drug delivery system. The approaches for brain targeting – invasive, non- invasive and miscellaneous techniques, by using these approaches enhance the drugs delivery and drugs are easily across BBB and BCSF.*

Result. *The different type of approaches and strategies used to enhance the drug delivery into brain and CNS. All these techniques described in this paper are applied for overcoming the problems that arises during treatment of brain related diseases. This review paper has a list of different types of models (In-vitro and In-vivo) used in study of brain and CNS drug delivery.*

Conclusions. *Drug delivery to brain for treating a various diseases and disorders are very difficult and challenging because the delivery of drug molecules must be pass through the BBB and BCSF. Overcome this difficulties and challenges certain approaches and technique such as invasive, non-invasive, intranasal delivery of drug, ocular delivery of drug and focused ultrasound technique are used to brain targeting. They are help to penetrate the drug molecule through BBB and CSF very easily and enhance the efficacy of treatment. This review article covered current approaches and strategies of brain targeting drug delivery in past five to ten years. These approaches and strategies are used to the brain delivery of drug, proteins, peptides, amino acids, etc.*

Keywords: *blood brain barrier (BBB); blood cerebrospinal fluid barriers (BCSF) of central nerves system; brain targeted drug delivery*

1. Introduction

The brain targeted drug delivery system is the process of passing active drug molecules across the blood brain barrier (BBB) and blood cerebrospinal fluid (CSF) [1], for the purpose of targeting brain disease and disorders like CNS disorder, CNS malignancy and various brain disorders as Parkinson's, Alzheimer's, brain abscess, epilepsy, multiple sclerosis, sleeping sickness (late-stage neurological trypanosomiasis) [1–3].

Blood brain barrier acts as a big stumbling block in the allocation of drugs in to the CNS. BBB plays vital role in the selectivity of many drugs, furthermore, it is well known that the hydrophilic drugs possess low affinity towards the BBB as compare to hydrophobic drugs [4]. Brain targeting drug must cross the BBB or bypass the barrier, which will affect brain in well-organized manner [5]. The BBB and BCSFB do not only defend the CNS against communicable agents and toxic agents, but also make a consequence to the systemic drug delivery into the CNS [6, 7]. BBB and BCSFB also control transfer of molecules among the blood, brain parenchyma and CSF. They help in transporting water and lipid soluble substances from blood circulation into CNS [5].

1.1. Blood brain barrier

The BBB is an almost resistant, highly demanded and energetic specialize barrier system of capillary endothelial cells that defends the brain against organisms and unwanted and harmful substances [8, 4]. It consists of capillary endothelial cell which are connected with each other by continuous tight intercellular junction [6].

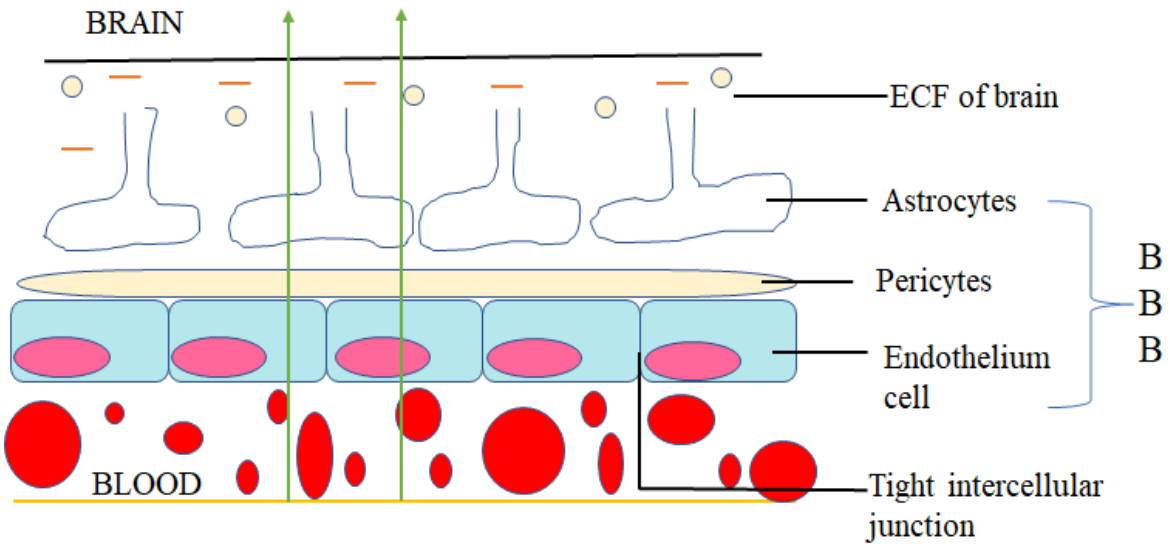

Fig. 1. Blood brain barrier

A solute cross to brain via only two pathways. Passive diffusion through the lipoidal barrier: - That is confined to small molecules with a molecular weight about 450 Daltons, and having extreme o/w partition coefficient [9].

Active transport: for essential nutrients such as sugars and amino acids [9].

1.2. Blood -cerebrospinal fluid barrier (BCSF)

BCSFB acts as barrier to drugs entering the CNS. The cerebrospinal fluid is formed mainly by the choroid plexus of the lateral, 3rd and 4th ventricles and is similar to the ECF of brain. Same as blood brain barrier, only highly lipid soluble drug can cross the blood-CSF barrier [7, 10, 11].

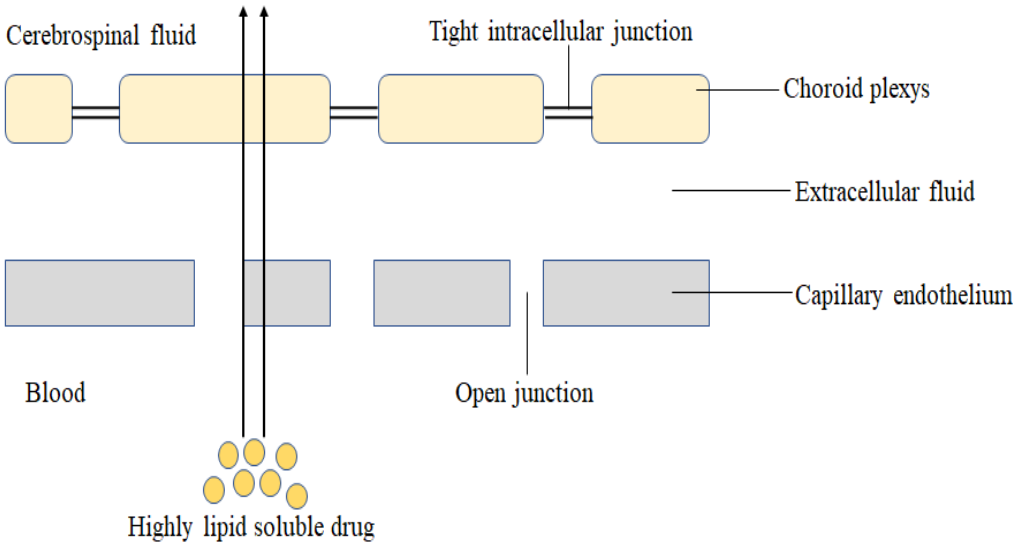

Fig. 2. Blood cerebrospinal fluid barrier

Factor affecting drug transport across BBB [12, 13]:

– concentration gradient of drug;
– molecular weight of drug;
– lipophilicity of the drug components;
– cerebral blood movement;
– cellular enzymatic solidity;
– pathological station.

Physiological factors affecting drug delivery to CNS [14]

– passive diffusion;
– carrier-mediated (active) transport;
– amino acid transporters;
– glucose transporters;
– monocarboxylic acid transporter;
– peptide transport systems;
– vesicular transport;
– transferrin;
– insulin.

2. Approaches for brain targeted drug delivery system

Essentially, two methods have been designated to actively improve drug delivered to the brain after systemic administration: either an introductory of the neuroprotective BBB by osmotic imbalance and ultrasound or

vasoactive of compounds (e.g., bradykinin or P-glycoprotein inhibitors) [10]. The approaches for brain targeting have been divided into invasive and non-invasive categories. The invasive approaches include momentary increase of BBB permeability, while non-invasive approach involves modification of drug molecule via physiological, chemical or colloidal carrier system approach [15].

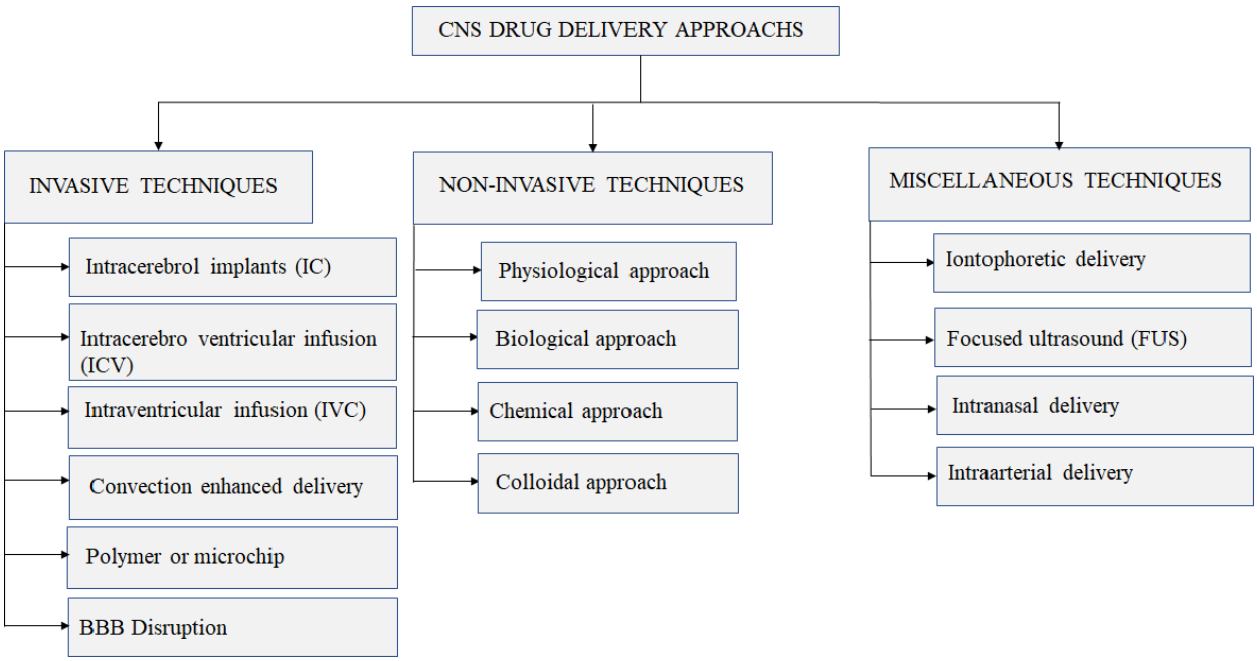

Fig. 3. Approaches for brain targeted drug delivery

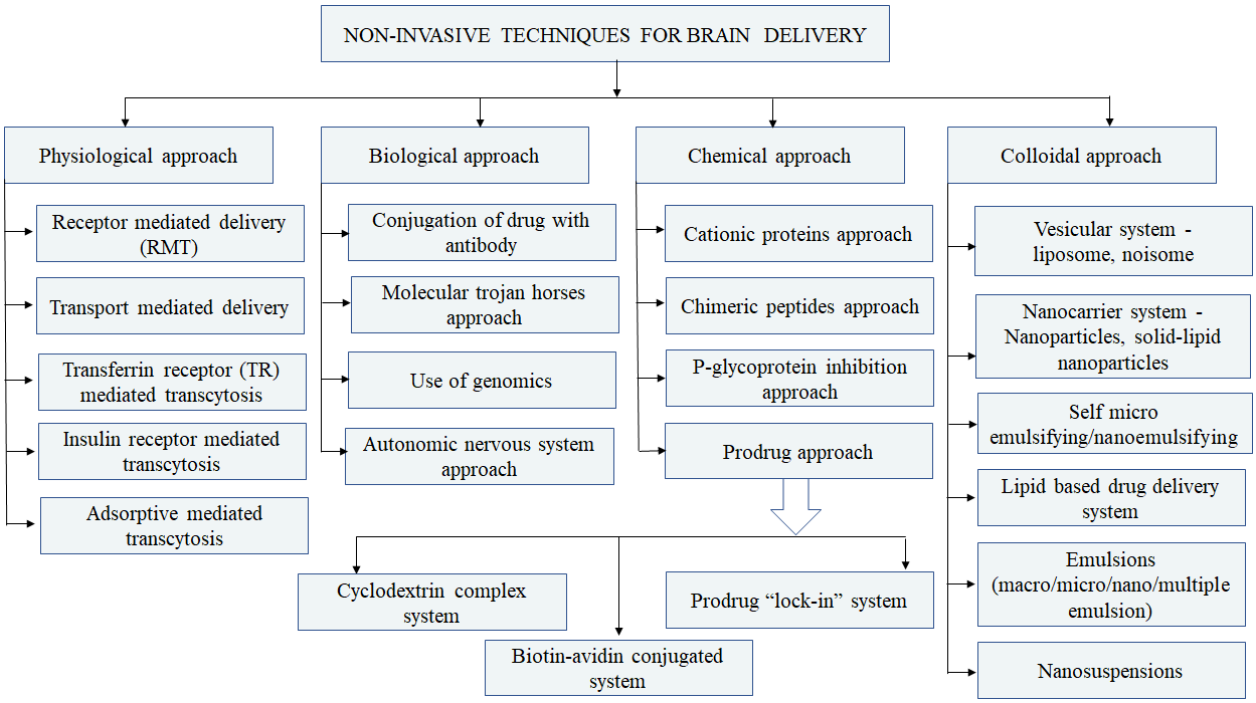

Fig. 4. Non-invasive techniques for brain targeted drug delivery

Advantages of approaches [15]:

1. The BBB disruption approach using osmotic opening is invasive and may allow the entry of unwanted components into the brain.

2. The infusion of hypertonic mannitol leads to eversible shrinkage of the cerebrovascular endothelial cells and subsequently increase in permeability of the drug.

3. The colloidal delivery systems take the advantage of already existing biochemical transport systems (like, LDL system, insulin receptor system, etc.) of the brain as the brain is dependent on blood for delivery of useful substrates as well as removal of metabolic wastes.

4. Various types of nanoparticular drug delivery systems have been exploited for brain-targeted delivery. This system enhanced the brain uptake.

2.1. Invasive approach

• Merits of invasive approach

Broad range of formulations can be given by this approach either IC /ICV route. This type of approach can be applicable for the delivering small as well as large molecules and it is also given in combination or alone itself [16].

• Demerits of invasive approach

It requires high cost hospitalization and anesthetic condition. Disruption of Blood brain barrier results in spreading of cancerous cells. It may be possible the entering of unwanted blood components. Neurons can be lastingly damaged after applying this approach [16].

2.1.1. Intracerebral implants (IC) or injection

Both are bolus injection of active-chemotherapeutic agents and it is a placement of a biodegradable compounds, active-chemotherapeutic impregnated, wafer into a tumor resection cavity and it is based on the principle of diffusion to drive the drug into the infiltrated brain [17, 18]. The drugs directly delivered into the brain parenchymal space or surrounding the spinal cord and drugs can be administered by [1, 19]:

1. Direct injection via intrathecal catheter route.
2. Control release matrices.
3. Microencapsulated chemicals.

2.1.2. Intracerebral ventricular infusion (ICV)

The described concentration of a drug in the brain is only 1–2 % of the CSF concentration at just 1–2 mm from the surface. Drugs are easily distributed to the surface of the brain via an ICV but drugs are not properly delivered to the brain parenchyma [20]. The pharmacological effects can be seen after ICV administration, if the target receptors of the drugs (for example, opioid, peptides) are located near the ependymal surface of the brain [17, 21].

• Limitations:

– very low parenchymal diffusion of drug [20];

– unless the target is close to the ventricles it is not an effective method of brain targeted drug delivery [17].

2.1.3. Convection-enhanced delivery (CED)

In this type of approach, by applying surgical exposure of brain, direct placement or insertion of a small diameter catheters into the brain parenchyma takes place. Through this catheter drug is actively pumped into brain for several days and drug is an eventually penetrated in the interstitial spaces [22, 23]. Convection-enhanced delivery have been performed in laboratory experiments for delivery of high molecular weight proteins 2 cm from the injection site of the brain parenchyma after 2 h of continuous infusion [17, 20].

2.1.4. Polymer or microchip

The number of biodegradable polymers has been used to formulate interstitial wafers and microchips for local delivery to the brain and natural and synthetic polymers like chitosan, gelatin, human serum albumin, polycaprolactone, polylactic acid and poly lactic-co-glycolic acid are used to controlled drug delivery to the brain [24]. The combined drug is released by a combination of polymer degradation and diffusion mechanism. It can be controlled by modifying the composition of the polymer. Microchips hold each drug containing its own reservoirs and in divergence to interstitial wafers, they can be used to deliver either single or multiple drugs, each drug has its unique release profile to the surrounding parenchyma [25–27].

2.1.5. BBB disruption

Neuwelt discovered this technique in year 1989 [10], it was used for humans. Disruption of the BBB can open access of the brain to components in the blood by making the tight junction between the endothelial cells of the brain capillaries leaky [17, 28]. According to this approach the temporary disruption of barrier by injecting mannitol sugar solution into neck arteries so that brain capillaries possess a high sugar concentration with water oozing out of endothelial cells, thereby shrinking them and opening the tight junction [10, 29].

Some of the important techniques for disrupting BBB are:

Osmotic disruption

These BBB disruption techniques allow the opening of CNS for delivery of a several drugs and it is enhanced the BBB permeation of drugs molecules [30]. Endothelial cells shrink due to osmotic shock arise, there by disrupting of the tight junctions. Intracarotid administration of a hypertonic mannitol solution with subsequent administration of drugs can increase drug concentration in brain and tumor tissue to reach therapeutic concentration [20, 31].

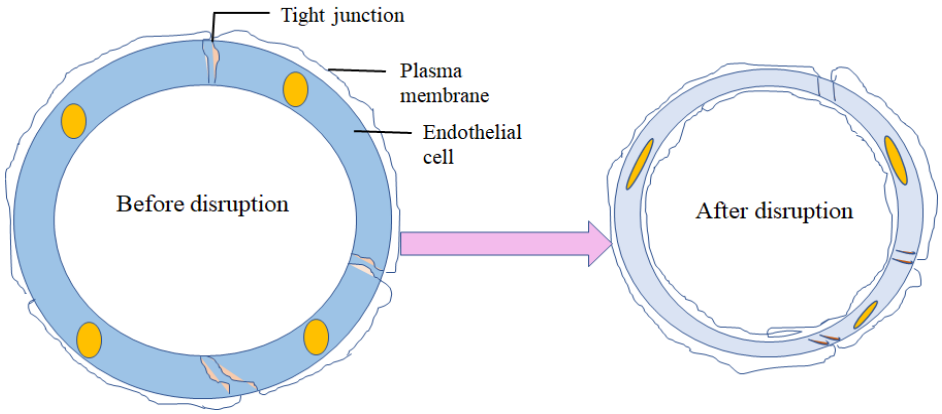

Fig. 5. Representation of osmotic disruption

MRI-guided focused ultrasound BBB disruption technique

Ultrasound has been shown to be capable of BBB disruption [32]. The combination of microbubbles (preformed microbubbles of ultrasound contrast agent, with a diameter of 2–6 μm which is injected into the blood stream before exposures to ultrasound). This technique has been shown to increase the distribution of Herceptin in brain tissue by 50 % in a mice model [17, 33].

Side effects: some side effects cause by BBB disruption approach [10]:

1. Unwanted delivery of anticancer agents to normal brain tissue.
2. Transient increase in intracranial pressure.
3. Physiological stress.

2.2. Non-invasive techniques

The non-invasive approaches mainly contain adsorption mediated drug transport mechanism (AMT), carrier mediated drug transport mechanism (CMT) and receptor mediated drug transport mechanism (RMT). The carrier mediated drug transport (CMT) mechanism can mediate the entrance of main nutrients like amino acid, glucose, monocarboxylic acid, nucleotides and vitamins into the brain [34]. Different variation of non-invasive technique of brain targeted drug delivery methods have been investigated, that make use of the brain blood vessel networking system for drug distribution [20].

2.2.1. Physiological approach

Receptor mediated delivery

RMT is comprised of three steps [35, 36]

• Receptor – mediated endocytosis at the luminal membrane of the capillary endothelial cell.

• Movement through the 300 nm of endothelial cytoplasm**.**

• Exocytosis across the abluminal endothelial membrane into the brain interstitial fluid.

Transferrin receptor (TR) mediated transcytosis

The TfR might be the most well-known RMT system, which might mediate the delivery of iron to the brain by bonding of the transferrin (Tf). Human TfR is a transmembrane glycoprotein, containing of two identical monomers with 90-kDa linked by intermolecular disulfide bonds [37]. The TfR is highly expressed on the BCECs, and has a high affinity toward the Tf. Sufficiently studies have been shown that the TfR-Tf conjugated mechanism could mediate the targeting delivery of drug to the brain [10-36].

Insulin receptor mediated

Insulin receptor (IR) has been extensively studied as a part of RMT system. It could mediate the transport of blood-borne insulin into the brain parenchyma. IR is a transmembrane glycosylated protein, which consists of two α and two β chains linked by disulfide bonds [38]. The so-called insulin molecular pocket is formed by the two α subunits. This results in an increase in tyrosine phosphorylation of the β subunit, and induce a conformational change of the insulin receptor to form a channel (that could allow transmembrane transport of molecule). The application of insulin as an RMT-targeting vector is limited in vivo, due to the short serum half-life of insulin (10 minutes) and hypoglycemia caused by exogenous administration of insulin [35, 39].

Biological approach

Biological approaches of CNS drug delivery primarily emanate from the understanding of the physiological and anatomical nuances of the BBB transportation. Of the many available approaches, conjugation of a drug with antibodies is an important mechanism. Other biological methods for targeting exploit ligands in the form of sugar or lectins, which can be directed to specific receptors found on cell surfaces. The antibody-drug conjugate is directed towards an antigen residing on or within the target tissues. Antibodies are particularly well suited for targeting BBB receptor-mediated transcytosis systems given their high affinity and specificity for their ligands [38, 40].

Chemical approach

In non-invasive techniques, chemical structure of drugs is transformed to improve physicochemical properties and functionalities. The prodrug method is used in chemical modification, where drug modified in to the more lipophilic drug. In chemical method, molecular packaging is used to increase the penetration of peptides through the BBB [5-41]. In molecular packaging three steps are followed:

1. Increased lipophilicity to enhance passive transport.
2. Prevention of premature degradation by increasing enzymatic stability.
3. Exploitation of the lock to provide targeted.

Prodrug

Prodrugs are defined as compounds that, on administration, must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent, with chemical modification, the prodrug method is used to make a drug more lipophilic [42, 43]. For example, morphine cannot enter the CNS by itself. After latentiation via acetylation of both hydroxyl groups, morphine can easily traverse the BBB and reach an effective concentration in brain [44, 45].

Prodrug delivery in brain/CNS:

a. Lipidization approach [46].

b. Endogenous transporters in CNS Prodrug Delivery [46].

c. Receptor-mediated Prodrug Delivery [46].

d. Antibody and gene directed Prodrug Therapies [46].

e. Neuropeptides delivery in CNS by Prodrug Approach [47].

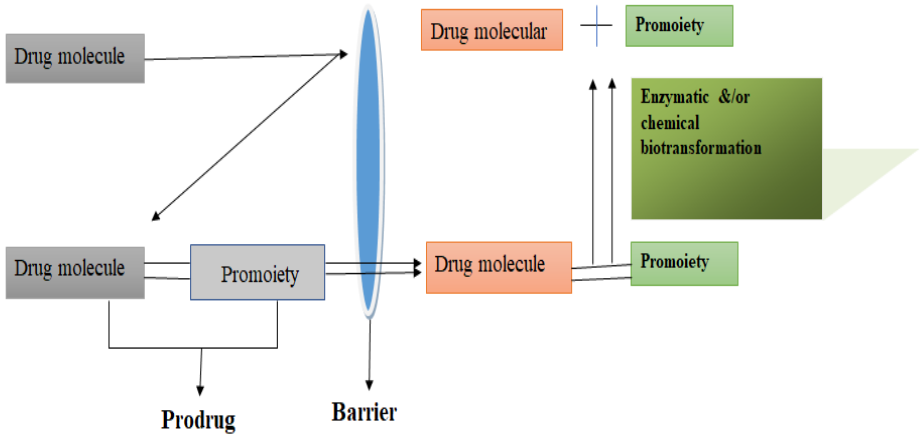

Fig. 6. Representation of prodrug approach for brain delivery

2.2.4. Colloidal approach

Colloidal drug carriers such as liposomes and NPs are able to modify the distribution of an associated substance. They can therefore be used to improve the therapeutic index of drugs by increasing their efficacy and/or reducing their toxicity. If these delivery systems are carefully designed with respect to the target, they may provide one solution to some of the delivery problems posed by new classes of active molecules such as peptides, proteins, genes, and oligonucleotides [48]. Colloidal drug delivery vehicles have been studied for almost 30 years, but the few liposome-based formulations already on the market are mainly concerned with reducing the side effects of the encapsulated drugs. Now that the interactions between particles and biological milieu are better understood, "stealth" liposomes and NPs which show diminished phagocytosis have been developed and the range of sites which can be reached has been extended [48, 49].

Vesicular system. Liposome

Liposomes are self-assembling vesicular structures based on one or more lipid bilayers encapsulating an aqueous core [50]. The major lipidic components of liposomes are usually phospholipids, which are amphiphilic moieties with a hydrophilic head group and two hydrophobic chains [51, 52]. On the basis of their size and their number of lipid bilayers, liposomes are generally classified into multilamellar vesicles (MLVs, diameter > 200 nm), large unilamellar vesicles (diameter 100–1000 nm) and small unilamellar vesicles (diameter < 100 nm) [48, 53, 54]. Although liposomes have been reported to enhance the uptake of certain drugs into the brain after intravenous injection. Liposomes are sterically stabilized by attaching ligands to the surface of the liposomes. A recent application of transferrin surface-conjugated liposomes includes the delivery of the anticancer drug 5-fluorouracil (5-FU) to brain. 5-FU is one of the most powerful anticancer agents [55]. Various liposomal formulations have been used to transport peptide and protein drugs across the BBB. For example, the intraperitoneal administration of liposomes entrapping GABA led to a decrease of the epileptic activity in rat models of the disease, in contrast to that observed with the free drug. Immunoliposomes bearing an OX26 antibody on their surface have been successfully used to deliver digoxin to the CNS [48].

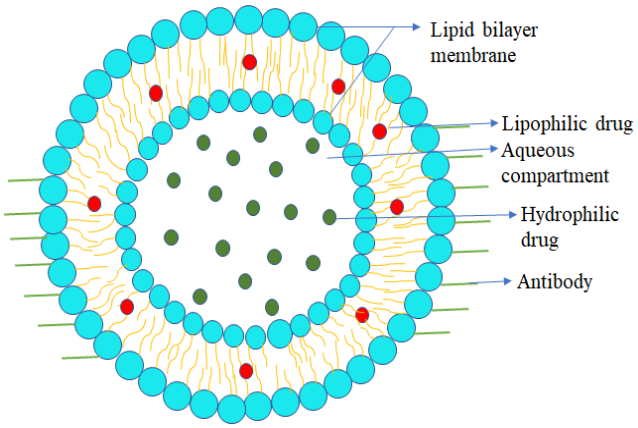

Fig. 7. Generalized structure of liposome

Niosomes

Niosomes are vesicular nanocarriers and have gained much attention as novel drug delivery systems in the last three decades due to their unique characteristics for transdermal application. Niosome are self–assembling non–ionic surfactants also called as non–ionic liposomes formed from non-ionic surfactants in an aqueous environment [56, 57]. It has high potential to act as carriers for poorly soluble drugs. Liposomes and niosomes are same in structure [58].

One of the key advantages of liposomes and niosomes is the possibility that they could be targeted to the brain by exploiting receptor-mediated transcytosis, by incorporating a targeting moiety on their surface. For example, glucose bearing niosomes, encapsulating VIP, have been shown to deliver VIP to the brain after intravenous administration thus demonstrating that the glucose transporter GLUT1 is a useful carrier for efficient drug delivery to the CNS [48].

Nanocarrier systems. Nanoparticles

Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size from 10 nm to 1000 nm [59, 60]. The drug of interest is either dissolved, entrapped, adsorbed, attached or

encapsulated into them nanoparticle matrix. Depending on the method of preparation, nanoparticles, nanospheres or nano capsules can be obtained with different properties and release characteristics for the encapsulated therapeutic agent [61]. NPs possess the advantage of a high drug loading capacity and can provide protection against chemical and enzymatic degradation. Examples of synthetic polymers used to prepare NPs are poly (alkyl cyanoacrylate) (PACA), acrylic copolymers, poly D, L-lactide-co-glycolide), and poly(lactide). NPs have also been prepared from natural proteins (albumin and gelatin) and polysaccharides, starch and chitosan [48].

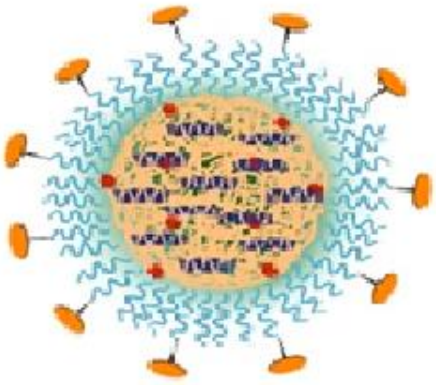

Fig. 8. Generalized structure of nanoparticle

Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) are colloidal particles composed of biocompatible/biodegradable lipid matrix that is solid at body temperature and exhibit size in a range of 100 to 400 nm. SLN offer several advantages such as controlled drug release, targeted delivery, increased drug stability, high drug payload, least biotoxicity, large scale production and ease of sterilization [62 – 64]. General ingredients used in the preparation of SLN are solid lipid(s), emulsifier(s) and water. The term "lipid" has a broader sense here and includes triglycerides (e.g. tristearin), fatty acids (e.g. stearic acid), partial glycerides (e.g. Imwitor), steroids (e.g. cholesterol) and waxes (e.g. acetyl palmitate) [65]. SLN are widely used for the delivery of active pharmaceutical ingredients to the brain because of the advantages mentioned above and its enhanced ability to cross BBB. A higher affinity of the SLN to the porcine brain capillary endothelial cells (BCEC) was shown in comparison to macrophages. In vivo studies in rats showed that fluorescent labelled SLN were detected highly in the brain after i.v. administration [66]. In particular, delivery to the brain of antitumor drugs, including camptothecin, doxorubicin and paclitaxel, incorporated into SLNs and PEGylated SLNs is studied. In comparison with surfactant coated polymeric NPs (specifically useful in bypassing BBB), SLN have also been evaluated for brain delivery of the potent and frequently used HIV protease inhibitor (PI), atazanavir, that, like other PIs exhibits low brain permeability [55].

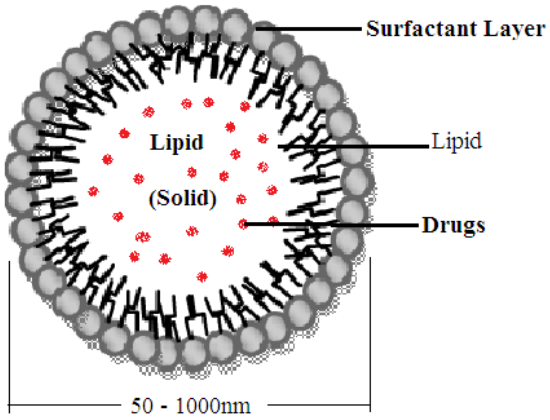

Fig. 9. Generalized Structure of Solid-Lipid Nanoparticle

Nanoemulsion

Nanoemulsion (NEs) are oil-in-water (O/W) or water-in-oil (W/O) coarse dispersions system of two immiscible liquids stabilized by using appropriate amount of surfactant(s), with a mean droplet diameter of about 100 nm, even if in literature upper size limits of Nanoemulsion up to 300 nm have been reported. As the size of the droplets is expressively smaller than the wavelength of visible light. Visible appearance of NEs are transparent or from transparent-to-milky-white [67, 68]. Nanoemulsion by virtue of their lipophilic nature and low globule sizes are significantly absorbed by intranasal delivery due to increased uptake by nasal mucosa. Nanoemulsion are modified to nano gelling systems (in-situ gelling system), coated particulate system or mucoadhesive systems to overcome issues arise during fast nasal clearance and to improve mucosal absorption [69, 70].

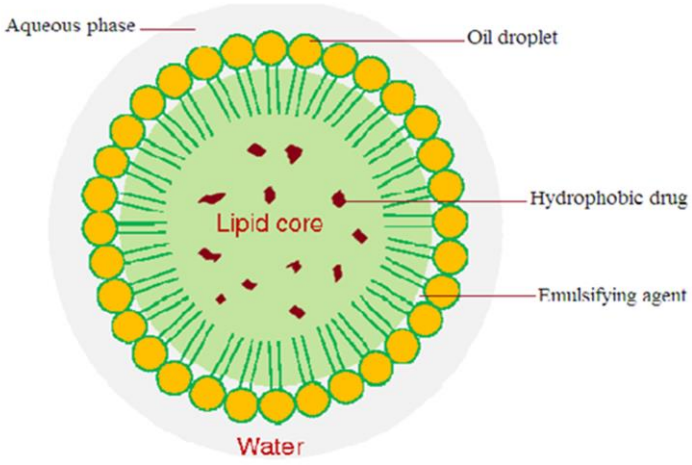

Fig. 10. Generalized structure of nanoemulsion

Microemulsion

MEs are pseudo ternary systems including oil, water and surfactant, frequently used in combination with co-surfactants which exhibit specific physicochemical properties like clarity, thermodynamic stability, low

viscosity and isotropic nature [71]. They are fundamentally stable, single-phase swollen micellar solutions which form spontaneously and offer the benefit of incorporation of large amount of lipophilic and/or hydrophilic drugs [72, 73].

The droplets in a microemulsion are in the range of 0.1–1.0μm [74].

Types of microemulsions:

1. o/w microemulsion
2. w/o microemulsion

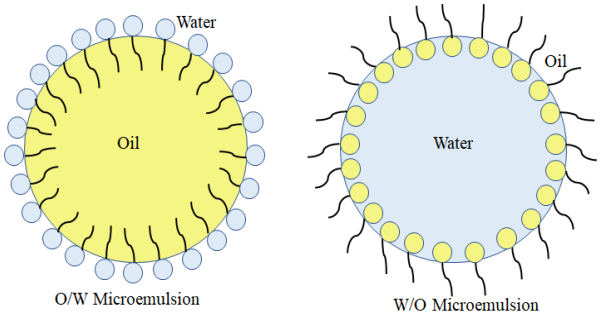

Fig. 11. Generalized structure of microemulsion

2.3. Miscellaneous techniques

Iontophoretic delivery

Recently, there has been an increased interested area in using the iontophoretic technique for CNS drug targeted delivery. Iontophoresis is a method to deliver ionized molecules across the BBB by applying external electric filed (current) [75]. Iontophoretic devices using the olfactory pathway have been designed for drug delivery to the CNS and brain. Devices have also been presented for enhancing delivery of macromolecule agents to the brain and CNS. With programmable transportation, these devices allow ions to enhanced drug delivery into the brain under controlled manipulation [76, 77]. Iontophoretic technique is used to deliver the protein and peptide into brain [78].

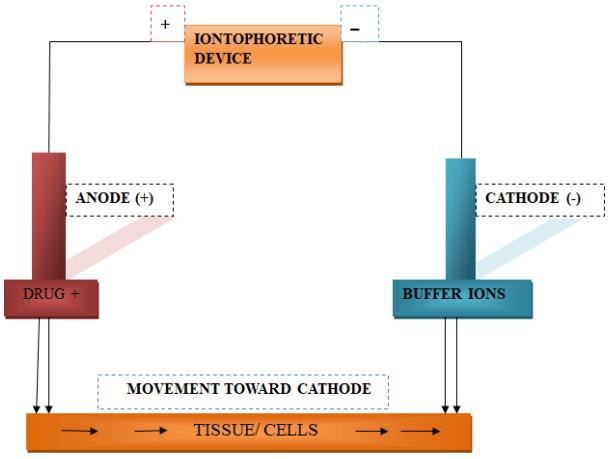

Fig. 12. Schematic representation of iontophoretic delivery

Focused Ultrasound (FUS) Technique

Technological advancement with FUS has been demonstrated the capability to use the ultrasound in combination with gas microbubbles to momentarily and reversibly enhancing BBB permeability, aiding in drug delivery into the brain [79, 33]. FUS concentrates sound energy and deposits it in a small target volume in the brain with minimal or no consequences to the surrounding tissue. The focal spot (area of highest energy) is contained within a small area at a targeted distance from the transducer surface [80]. When electronic power is applied, the piezoelectric material of the transducer converts that energy into mechanical motion [20, 81]. Thus, generating ultrasound, which spreads through the skull and brain [82].

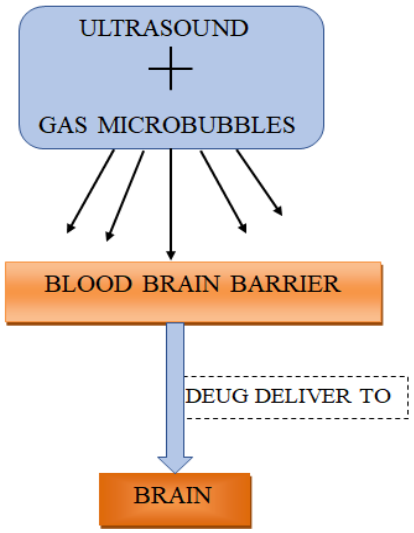

Fig. 13. Schematic representation of focused ultrasound (FUS) approach

Intranasal delivery

Nasal delivery also known as olfactory delivery of drug. The nasal pathway is administration route of active pharmaceutical ingredients for local action, systemic action and direct targeting to brain and CNS [83]. For some time, the BBB has delayed the advance of many exciting CNS drug applicants due to their less distribution into the CNS. Due to the different connection of the nose and the CNS, the olfactory route can deliver pharmacological active agents into the brain by crossing the BBB. The absorption of drug across the olfactory area of the nose offers a different feature and greater option to targeting drugs into brain [84, 85]. Drug administered through intranasal route of administration is absorbed by the systemic circulation. Drug absorption through nasal respiratory epithelium follows paracellular, transcellular absorption, carrier-mediated transport, and transcytosis mechanism [86, 87]. Administration of drug cavernous into the nasal cavity to nasal mucosa, it is led to direct transfer of drug into brain via olfactory pathway. Olfactory region consists of olfactory neurons that transmit the drugs from olfactory mucosa to the brain and it is a slow process of drug transfer [88]. Olfactory epithelium pathway is affective way of drug transportation [89, 90]. Drug is passed through olfactory epithelium pathway via paracellular drug transport mechanism into perineural space and transferred directly to the brain [97, 92].

Intranasal drug delivery pathway. Olfactory neural pathway

Drug material is moving from the olfactory region in the nasal cavity to CSF or brain parenchyma, it is also

transverse to the nasal olfactory epithelium. In this pathway, the arachnoid membrane surrounding the subarachnoid space having three different pathways across the olfactory epithelium, first is transcellular pathways Second is a paracellular pathway in which, the tight junctions between Sustentacular cells having the clefts between Sustentacular cells and olfactory neurons [93]. Nasal absorption of hydrophilic drugs under go diffusion mechanism through aqueous channels or pores. The passive diffusion for the lipophilic drugs is mediated rapidly and at a high rate. This route is mainly responsible for the transport of lipophilic drug molecules and the transport rate is depended in their lipophilicity [93, 94].

Terminal neural pathway

Trigeminal nerve pathways are the largest nerve pathway among all cranial nerve pathways in which, innervates the respiratory and olfactory epithelium of the nasal passages and enters the central nervous system (CNS). The trigeminal nerve is communicating the sensory information from the nasal cavity, oral cavity, eyelids and the cornea to CNS via ocular, maxillary and the mandibular divisions of trigeminal nerves. The ocular and maxillary nerve is important for nose to brain delivery as neurons from these branches passed directly through the nasal mucosa [95].

Glymphatic pathway

Glymphatic system deals with CSF-ISF exchange, including transport of solutes and clearance of accumulated metabolites as well as solutes. Impairment of glymphatic system increases CSF influx without increase in ISF efflux causing accumulation of extracellular solutes which leads to cognitive decline. Altering CSF-ISF exchange promotes solute and metabolite clearance and this may be important in management of CNS related diseases [93].

Factors affecting nasal drug delivery [96]:

– molecular weight and solubility;
– osmolality and volume;
– blood flow and pH;
– pharmaceutical dosage forms;
– mucociliary clearance;
– transport systems.

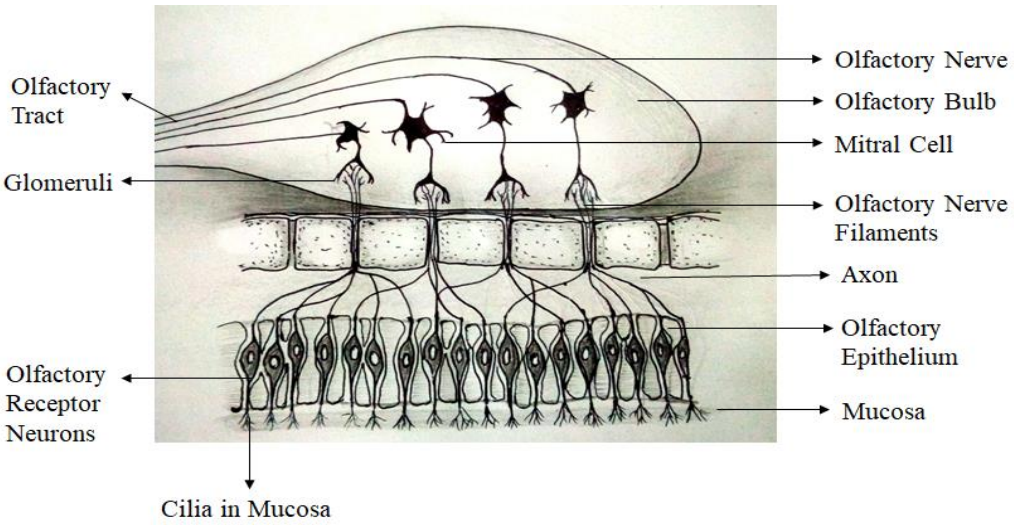

Fig. 14. Olfactory Region of Brain

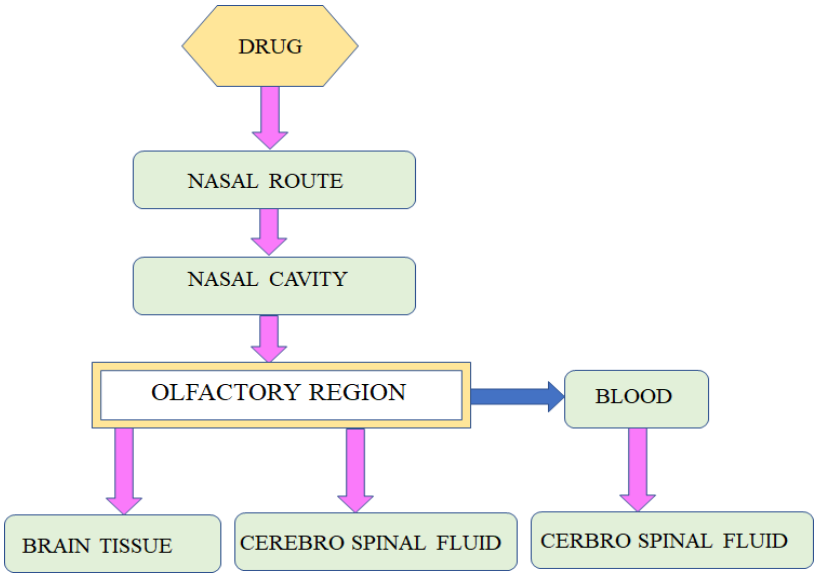

Fig. 15. Schematic representation of intranasal drug delivery

3. Name of models used for study of brain delivery and investigation of brain problems

In vitro models [97]:

– Human stem cell-derived BBB models

– Immortalized cell lines model

– Primary cells model

– Dynamic in vitro BBB models

– Monocultured cocultured, static and dynamic models

– Endothelial monocultured

– Cocultured of BECs with astrocytes

– Cocultured of BECs with pericytes

– Tri-culture models of BBB

– Testing of biomimetic BBB models

– Microfluidic models

– BBB-on-chip

3D cultured multicellular spheroid tumor models in tumor-targeted drug delivery [98, 99].

Brain organoids: human 3D models [100]:

– organoid-on-a-chip: a platform for system biology;

– gene-regulatory logic of the human cortex modelled in brain organoids;

– the epigenetic landscape of brain organoids;

– single-cell transcriptional maps of brain organoids;

– sliced cerebral organoid cultures;

– long-term brain organoid culture-to-model circuit formation;

– engineered cortical organoids vascularization.

Zebrafish – In vivo model [101].

4. Conclusion

Drug delivery to brain for treating a various diseases and disorders are very difficult and challenging because the delivery of drug molecules must be pass through the BBB and BCSF. Overcome this difficulties and challenges certain approaches and technique such as invasive, non-invasive, intranasal delivery of drug, ocular delivery of drug and focused ultrasound technique are used to brain targeting. They are help to penetrate the drug molecule through BBB and CSF very easily and enhance the efficacy of treatment.

This review article covered current approaches and strategies of brain targeting drug delivery in past five to ten years. These approaches and strategies are used to the brain delivery of drug, proteins, peptides, amino acids, etc.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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