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Review Article

Drug Targeting to Brain: A Review

Yogesh Kalwane, Abhay Joshi, Dipali Deshpande, Mahesh Bhosale, Ashish Jagtap, Ashwini Khairnar
Yash Institute of Pharmacy, Aurangabad, Maharashtra, India- 431134

ABSTRACT:
The Overall prevalence rate for CNS pathology has demonstrated that approximately 1.5 billion people undergoing from disorders of central nervous system. The most distressing fact about delivery of drugs to the CNS is the presence of blood brain barrier that have a tendency to impair the drug distribution and denotes the major impediment for the development of CNS drugs. Neuropeptides and many drugs which are hydrophilic in nature possibly will encompass the intricacy while passing the blood brain barrier. The net amount of delivered drug (medicinal agent) and its capability to gain access to the pertinent target sites are the main considering points for CNS drug development. In order to distribute the drugs into the CNS via passing the blood brain barrier, many new emerging approaches have been developed for example Magnetic drug targeting, chemical delivery Systems, Drug carrier systems (antibodies, liposomes or Nanoparticles). Among drug carrier system, Nanoparticles exhibit an impressive attention in the field of targeted drug delivery system because of possessing solid colloidal particles with a size range between 1- 1000nm. Gradual drug release reduced peripheral toxicity and potential to target specific brain sites by crossing the blood brain barrier are major benefits contributed by Nanoparticles. In this review we will discuss the methodologies for targeting the brain site, advancements in drug targeting to the brain, different approaches, nasal drug delivery system, nasal gels and concept of micro emulsion.
Keywords: Blood Brain Barrier, Drug delivery to brain, Nanotechnology, Colloidal drug carriers, Liposomes, Prodrugs, Blood cerebrospinal fluid barriers, Ependyma

Address for Correspondence:
Yogesh Bhaginath Kalwane
Yash Institute of Pharmacy, South City, Bajaj Nagar, Aurangabad (M.S.) India-431134
Email id: kyogesha91@gmail.com
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INTRODUCTION

The brain is the center of nervous system in all vertebrate, and most invertebrate, animals. Brains can be extremely complex. The cerebral cortex of the human brain contains roughly 15-33 billion neurons, perhaps more, depending on gender and age, linked with up to 10,000 synaptic connections each. Each cubic millimeter of cerebral cortex contains roughly 1 billion synapses. These neurons communicate with one another by means of long protoplasmic fibers called axon, which carry trains of signal pulses called action potential to distant parts of the brains or body and target them to specific recipient cells. Brain controls the other organ systems of the body, either by activating muscles or by causing secretion of chemicals such as hormones. This centralized control allows rapid and coordinated responses to changes in the environment. Some basic types of responsiveness are possible without brain even single celled organisms may be capable of extracting information from the environment and acting in response to it. Sponges, which lack a central nervous system, are capable of coordinated body contraction and even locomotion. In vertebrates, the spinal cord by itself contains neural circuitry capable of generating reflex responses as well as simple motor patterns such as swimming or walking. However, sophisticated control of behavior on the basis of complex sensory input requires the information-integrating capabilities of a centralized brain.[1,2,3]

Advantages:

- Side effect and toxicity reduces

- Dose of drug reduces by targeting organ
- Avoids degradation of drug
- Bioavailability increases
- Fluctuation in concentration decreases
- Permeability of protein and peptide increases.[4]

Disadvantages:

- Enhances clearance from target
- Difficult to target tumor cells
- Advanced techniques requirements
- Skill persons required
- Sometimes it may causes toxicity
- Difficult to maintain stability of dosage form.

Limitations of the Prodrug:

- Approach is the adverse pharmacokinetics
- The increased molecular weight of the drug that follow from lipidation

Limitations of Liposomes:

- High production cost
- Leakage and fusion of encapsulated drug
- Sometimes phospholipid undergoes oxidation and hydrolysis
- Short half-life
- Low solubility
- Less stability

Limitations of using nanoparticles for CNS targeted drug delivery:

- Their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.
- In addition, small particles size and large surface area readily result in limited drug loading and burst release.[2]

Hindrances in Drug Targeting to the Brain:

In this above bit of the article we plainly comprehended that little molecules promptly cross the BBB. In any case, actually, <2% of every little molecule crosses the BBB effortlessly. In the comprehensive restorative chemistry (CMC) database, there are >7000 drugs set up, and just 5% of these medications treat the CNS illnesses. It has been researched that 100% of large molecule medications and 98% of small molecule drugs don't cross BBB. For a small molecule medication to cross the BBB in critical amounts, the molecule must have two imperative qualities like molecular mass must be under 400 Da and high lipid solvency. Because of these reasons the brain drug focusing on turns out to be more troublesome for the pharmaceutical researchers. Presently it is an extremely difficult to all pharmaceutical organization around the world how the enhance brain targeting on medication delivery and minimize the CNS illness.[5]

Barriers in the Brain:

There are three barriers that limit drug transport to the brain parenchyma. These are the blood-brain barriers [BBB], localized in the capillaries in the brain; the blood-cerebrospinal-fluid barrier [BCSFB], which is presented by the choroid plexis epithelium in the ventricles; and the ependyma, which is an epithelial layer of cells covering the brain tissue in the ventricles and limits the transport of compounds from the cerebral spinal fluid [CSF] to the brain tissue.[6,7,8]

Blood-Brain Barrier (BBB):

The blood-brain barrier is the specialized system of capillary endothelial cells that protects the brain from harmful substances in the blood stream, while supplying the brain with the required nutrients for proper function. Unlike peripheral capillaries that allow relatively free exchange of substance across/between cells, the BBB strictly limits transport into the brain through both physical and metabolic barriers. Thus the BBB is often the rate-limiting factor in determining permeation of therapeutic drugs into the brain. Additionally, BBB breakdown is theorized to be a key component in CNS associated pathologies. BBB investigation is an ever growing and dynamic field studied by pharmacologists, neuroscientists, pathologists, physiologists and clinical practitioners.[1,9,10]

Structure of BBB and transport mechanisms:

The BBB is considered to be a dynamic and complex barrier separating blood and the central nervous systems that strictly controls the exchange between the compartments of blood and brain. Blood brain barrier is a natural biological barrier that plays a crucial role in the protection of the brain by restricting the entry of untoward substances such as toxic molecules, pathogens, and numerous other external molecules and thereby maintaining the brain homeostasis. The endothelial cells present in brain differ significantly from cells present in other parts of the body, due to the presence of intracellular tight junctions, lesser paracellular diffusion of hydrophilic molecules, presence of relatively high number of mitochondrial cells and thereby with high metabolic activity, and a relatively higher number of active transporters. The basal lamina composed mainly of collagen, glycoproteins, and proteoglycans, is involved in the dynamic regulations of blood brain barrier with the aid of multiple basal lamina proteins, matrix metalloproteases. The astrocytes and glial cells present in the BBB also contribute to a great extent for the barrier integrity through glial-

derived neurotrophic factor, angiopoietin-1 and angiotensin 2. Brain microvessels have numerous pericytes and ratio of pericytes to endothelial cells was linked with the barrier capacity. Endothelium, pericytes, perivascular astrocytes are very close contact with neuronal projections.[11,12]

General Transport Mechanisms across BBB:

The major transport mechanism to the BBB are paracellular aqueous pathway, transcellular lipophilic pathway, transport protein pathway, receptor mediated transcytosis, and adsorptive transcytosis. Paracellular aqueous pathway is a rare pathway across BBB through which small water-soluble molecules diffuse into the brain. Lipophilic molecules such as alcohol, steroid hormones etc penetrate transcellularly by dissolving in their lipid plasma membrane. In carrier-mediated transport, a protein transporter binds to glucose or amino acids which triggers a conformational change in the protein and helps in the transport of the molecule to the other side. The receptor-mediated transcytosis type of transport mechanism is for the selective uptake of macromolecules. These systems include receptors for transferrin, insulin; lipoprotein etc and those are also explored for the ligand based nanoformulations. Since traditional approaches could not solve these problems, pharmaceutical scientists looked forward and found out newer approaches such as nanotechnology in order to deliver drugs across BBB successfully.[4]

Blood-Cerebrospinal Fluid Barrier:

The second barrier that a systemically administered drug encounters before entering the CNS is known as the blood-cerebrospinal fluid barrier (BCB). Since the CSF can exchange molecules with the interstitial fluid of the brain parenchyma, the passage of blood-borne molecules into the CSF is also carefully regulated by the BCB. The choroidplexus and the arachnoid membrane act together at the barriers between the blood and CSF. On the external surface of the brain the ependymal cells fold over onto them-selves to form a double layered structure, which lies between the dura and pia, this is called the arachnoid membrane. The arachnoid membrane is generally impermeable to hydrophilic substances, and its role is forming the Blood-CSF barrier is largely passive. The choroid plexus forms the CSF and actively regulates the concentration of molecules in the CSF. The choroid plexus consist of highly vascularized, "cauliflower-like" masses of pia mater tissue that dip into pockets formed by ependymal cells. The preponderance of choroid plexus is distributed throughout the fourth ventricle near the base of the brain and in the lateral ventricles inside the right and left cerebral hemispheres. The cells of the choroidal epithelium are modified and have epithelial characteristics. These ependymal cells have microvilli on the CSF side, basolateralinterdigitations, and abundant mitochondria. The ependymal cells, which line the ventricles, form a continuous sheet around the choroid plexus. While the capillaries of the choroid plexus are fenestrated, non-continuous and have gaps between the capillary endothelial cells allowing the free-movement of small molecules, the adjacent choroidal epithelial cells form tight junctions pre-venting most macromolecules from effectively passing into the CSF from the blood.[13]

Blood-Tumor Barrier:

Intracranial drug delivery is even more challenging when the target is a CNS tumor. The presence of the BBB in the microvasculature of CNS tumors has clinical consequences. For example, even when primary and secondary systemic tumors respond to chemotherapeutic agents delivered via the cardiovascular system, intracranial metastases often continue to grow. In CNS malignancies where the BBB is significantly compromised, a variety of physiological barriers common to all solid tumors inhibit drug delivery via the cardiovascular system. At the same time, intra-capillary distance increases, leading to a greater diffusional requirement for drug delivery to neo-plastic cells and due to high interstitial tumor pressure and the associated peritumoral edema leads to increase in hydrostatic pressure in the normal brain parenchyma adjacent to the tumor. As a result, the cerebral micro vasculature in these tumor adjacent regions of normal brain may be even less permeable to drugs than normal brain endothelium, leading to exceptionally low extra tumoral interstitial drug concentrations. Brain tumors may also disrupt BBB, but these are also local and non homogeneous disruptions.[14]

Novel Methods for Drug Delivery:

Biological method:

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.[15]

Colloidal Drug Carriers:

Colloidal drug carrier system such asmicellarsolutions, vesicle and liquid crystal dispersions,as well as nanoparticle dispersions consisting of small particles of 10-400 nm diameter shows great promise as drug delivery systems .The goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and ormesogenic properties.[1]

Molecular Trojan Horses:

Endogenous ligands for specific BBB receptors, also known as Trojan horses, have the capacity to shuttle drugs into the brain.Vasoactive intestinal polypeptide (VIP) participates in the regulation of cerebral blood flow; however, in vivo studies showed no neuropharmacological effect as a result of low transport of peptide to the brain, which is attributable to the presence of the BBB.[16]

Micelles:

Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions are of great interest for drug delivery applications. The drug can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water-solubility. Moreover the hydrophilic blocks can form a tight shell around the micellar core.[17]

As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation. In addition; the corona may prevent recognition by the reticuloendothelial system and therefore preliminary elimination of the micelles from the blood stream.[18] The fact that their chemical composition, total molecular weight and block length ratios can be easily changed, which allows control of the size and morphology of the micelles. Functionalization of block copolymers with cross linkable groups can increase the stability of the corresponding micelles and improve their temporal control.[1]

Liposomes:

Liposomes were first produced in England in 1961 by Alec D. Bangham.[19] One end of each molecule is water soluble, while the opposite end is water insoluble. Water-soluble medications added to the water were trapped inside the aggregation of the hydrophobic ends; fat-soluble medications were incorporated into the phospholipid layer.[20] In some cases liposomes attach to cellular membranes and appear to fuse with them, releasing their or drugs into cell. In the case of phagocytic cells the liposomes are taken up, the phospholipid walls are acted upon by organelles called lysosomes, the medication is released. Liposomal delivery systems are still largely. [1]

Strategies for Enhanced Brain Targeted Drug Delivery:

Prodrugs:

Brain uptake of drugs can be improved via prodrug formation. Prodrugs are pharmacologically inactive compounds that results from transient chemical modifications of biologically active species.[21] The chemical change is usually designed to improve some deficient physicochemical property,such as membrane permeability or water solubility. After administration, the prodrug, by virtue of its improved characteristics, is brought closer to the receptor site and is maintainedthere for longer periods of time.[22] Here it gets converted to the active form, usually via single activating step. Unfortunately, simple prodrugs suffer from several important limitations. Going to extremes on the lipophilic precursor scale, a possible choice for CNS prodrugs is coupling the drug to a lipid moiety, such as fatty acid, glyceride or phospholipids. Such prodrug approaches were explored for a variety of acid-containing drugs, like levodopa, GABA, Niflumic acid, valporate or vigabatrin are coupled to increased diglycerides or modified diglycerides. While increased lipophilicity may improve movement across the BBB, it also tends to increase uptake into other tissue, causing an increased tissue burden. [1]

Chemical Drug Delivery:

Chemical drug delivery systems (CDDS) represent novel and systematic ways of targeting active biological molecules to specific target sites or organs based on predictable enzymatic activation[23]. They are inactive chemical derivatives of a drug obtained by one or more chemical modifications so that the newly attached moieties are monomolecular units (generally comparable in size to the original molecule) and provide a site- specific or site

enhanced delivery of the drug through multi-step enzymatic and /or chemical transformations. During the chemical manipulations, two types of bioremovable moieties are introduced to convert the drug into an inactive precursor form.[24]A targeter (T) moiety is responsible for targeting, site-specificity, and locks in, while modifier functions F1…FN) serve as lipophilisers, protect certain functions, or fine tune the necessary molecular properties to prevent premature unwanted metabolic conversions. The CDDS is designed to undergo sequential metabolic conversions, disengaging the modifier functions and finally the targetor, after this moiety fulfils its site or organ-targeting role.[1]

Carrier Mediated Drug Delivery:

Carrier-mediated transport (CMT) and receptor mediated transport (RMT) pathways are available for certain circulating nutrients or peptides.[25] The availability of these endogenous CMT or RMT pathways means that portals of entry to the brain for circulating drugs are potentially available. In the brain capillary endothelial cells, which make up the BBB there, there are several transport systems for nutrients and endogenous compounds. They are the hexose transport system for glucose and mannose, the neutral amino acid transport system phenylalanine, leucine and other neutral amino acids, the acidic amino acid transport system for glutamate and aspartate, the basic amino acid transport system for arginine and lysine, the b-amino acid transport system for b- alanine and taurine, the monocarboxylic acid transport system for lactate and short-chain fatty acids such as acetateand propionate, the choline transport system for choline and thiamine, the amine transport system for mepyramine bases, nucleoside transport system for purine bases such as adenine and guanine, but not pyrimidine bases, and the peptide transport system for small peptides such as enkephalins, thyrotropin-releasing hormone, arginine vasopressin etc.[26] Utilization of differences in the affinity and the maximal transport activity among these transport systems expressed at the BBB is an attractive strategy for controlling the delivery and retention of drug into the brain.[1]

Biochemical Blood-Brain Barrier Disruption : Recently, new and potentially safer biochemical techniques have been developed to disrupt the BBB. Selective opening of brain tumor capillaries, by the intracarotid infusion of leukotriene C4 was achieved without concomitant alterations of the adjacent BBB.[27] In contrast to osmotic disruption methods, biochemical opening utilizes the novel observation that normal brain capillaries appear to be unaffected when vasoactive leukotriene treatment are used to increase their permeability. However, brain tumor capillaries or injured brain capillaries appear to be sensitive to treatment with vasoactive leukotrienes, and the permeation is dependent on molecular size. [1]

Advances in Brain Targeted Drug Delivery: Nanoparticulate Systems

Nanotechnology in Brain Targeting:

The application of nanotechnology for the drug delivery to the brain opens the doors of opportunities for the formulation scientists for the better and selective brain delivery of existing and newer potential molecules with CNS activity.[28] It has been assumed that the delivery to brain of majority of the potential CNS drugs which have inability to cross BBB could be modified by nanotechnology in order to achieve better therapeutic action and better patient compliance. It would bring about rebirth to many drugs which have been discontinued due to their failure to gain therapeutic concentration in the brain. Kreuter et al. describe number of possibilities that could explain the mechanism of the delivery of nanoparticulate formulations across the BBB and are discussed below. As compared to the pure drugs, there is an increased retention of the nano formulations in the brain blood capillaries combined with more adsorption to the capillary walls.[29] These retention and adsorption create a higher concentration gradient that would enhance the transport across the endothelial cell layer and result in better delivery to the brain.

1. The nanoparticles could lead to an opening of the tight junctions between the brain endothelial cells. The drug could then permeate through the tight junctions in either free form or as nanoparticles in bound form.
2. There is a general surfactant effect of nanoformulations characterized by solubilization of the endothelial cell membrane lipids that would further lead to membrane fluidization and thereby enhanced drug permeability through BBB.
3. The nanoformulations may been docytosed by the endothelial cells of the brain capillaries which would further result in the release of the drug within these cells and delivery to the brain.
4. Drug loaded nanoformulations could be transcytosed through the endothelial cell layer.
5. Surfactant which is used as the coating agent could inhibit the efflux systems, especially p-glycoprotein. Endocytosis via the low density

lipoprotein(LDL) receptor, mediated by the adsorption of apolipoprotein B and /or E from the blood is also a suggested mechanism for the nanoformulations coated with polysorbate such as Tween 20,40,60 and 80, and poloxamers such as pluronic F68.[4]

Nanoformulations Investigated:

Numerous nanoformulations have been investigated successfully for better brain delivery which includes nanoparticulate systems, liposomes, dendrimers, nanoemulsions, nanosuspensions, and ligand mediated nanosystems.[30]

Polymeric nanoparticles:

Nanoparticles are, colloidal particles, less than 1000nm that can be used for better drug delivery and prepared either by encapsulating the drug within a vesicle and or by dispensing the drug molecules within matrix.[31]Nanoparticulate drug delivery systems have been extensively studied in recent years for spatial and temporal delivery, especially in tumour and brain targeting. Nanoparticles have great promise for better drug delivery as found in both pharmaceutical and clinical research. As a drug carrier, nanoparticles have significant advantages like better bioavailability, systemic stability, high drug loading, long blood circulation time and selective distribution in the organs/tissues with longer half life. These systems have been increasingly used in order to improve selective brain delivery of the therapeutic agents. Nanoparticles, prepared from a wide variety of biodegradable polymers such as poly (D,L-lactide-co-glycolide) (PLGA), poly(D,L-lactide) (PLA), polycaprolactone (PCL) etc are extensively used for the delivery of drugs to the CNS.[32] They provide numerous advantages which include protecting drug from degradation, releasing a therapeutic load in the optimal dosage range and enabling the delivery of the therapeutic agents to the preferential site and thus decreasing the total dose.

Coating of the nanoparticles with surfactants is another useful approach as it can induce increased brain uptake. Its mechanism has already been described in the earlier section of this review. Numerous studies have been performed in this direction and it has been found that coating with surfactant systems resulted in enhanced brain concentration of drug/dye as compared with uncoated systems.[4,33]

Solid Lipid Nanoparticles (SLN):

Solid lipid nanoparticles are colloidal particles composed of biocompatible lipid matrix that is solid at body temperature and exhibit size in range of 100 to 400 nm.

A newer version of SLN called nanostructured lipid carrier (NLC), with increased drug loading are also becoming popular recently for brain targeting which are composed of a solid lipid and a certain amount of liquid lipid (oil), maintaining the solid state at both room and body temperature.[4]

Targeting drug to brain is becoming a challenging task for inventors of advanced drug delivery systems. Solid lipid nanoparticles (SLNs) are the effective lipid based colloidal carriers which were introduced as an alternative to the conventional carriers such as micro emulsions, liposomes, microparticles and nanoparticles based on synthetic polymers or natural macromolecules. SLNs were introduced to overcome problems of polymeric nanoparticles by putting forward physiological safe lipids in place of polymers to prepare lipid nanoparticles, a novel formulation technique came into light. An approach undertaken here is to focus on various production methods for preparation of SLNs.[34]

Dendrimers:

Dendrimers are a unique class of synthetic polymers which has a major role in nanotechnological advances of drug delivery. The term “dendra” in “dendrimer” is derived from Greek which means tree and therefore appropriately describes its architecture.[35] Novel dendrimer-based drug delivery systems consisting of G3 polyamidoamine (PAMAM) and surfactant conjugated dendritic nanoconjugates have been successfully applied for targeted brain delivery.[36]

Nanoemulsions:

Nanoemulsions have also gained considerable attention in research as well as in therapeutics due to their advantages such as ease of preparation, thermodynamic stability, optical clarity, and their ability to incorporate both hydrophobic and hydrophilic solutes etc.[37] Intranasal nanoemulsion based brain targeting drug delivery system of risperidone was studied by Mukesh Kumar et al. They have found higher drug transport efficiency and direct nose to brain transport for these muco adhesive nanoemulsion. Similar results have been obtained with saquinavir-loaded nanoemulsions which also resulted in efficient brain delivery.[4]

Ligand-Mediated Active Targeting:

Advances in cell biology with respect to internalization pathways and problems associated with delivery of new macromolecular drugs such as peptides and proteins paved the path of receptor mediated targeting for selective uptake

and internalization of drugs.[38] The flexibility of nanoformulations for the attachment of ligands for specific receptors further improved the scope of ligand mediated active targeting since these systems also provide additional advantages such as controlled release of drug and protection from external degradation before reaching the targeted site. Numerous receptors which are over expressed in brain such as transferring receptors, insulin receptors, low density lipoprotein receptors etc have been widely explored for the ligand mediated targeted brain delivery.

Membrane transferrin receptor-mediated endocytosis is an efficient cellular uptake pathway for drug delivery of therapeutic agents to the brain.[39] Ulbrich et al prepared human serum albumin nanoparticles-conjugated with antibodies against the transferrin receptor, which could deliver loperamide across BBB whereas, pure loperamide has shown no or very poor permeation. Same group have explored insulin receptors also for brain targeting of loperamide using anti-insulin receptor monoclonal antibody and found similar results which showed many fold increase in antinociceptive effects in the tail-flick test in mice as compared to pure loperamide.[40]

Manufacturing methods of Nanoparticles:

- Emulsion polymerization.
- Interfacial polymerization.
- Desolvation evaporation.
- Solvent deposition.[41],[42],[43],[44]

Drug delivery to the brain using polymeric Nanoparticles:

Nanoparticle drug carriers consist of solid biodegradable particles in size ranging from 10 to 1000 nm (50–300 nm generally). The use of minute particles as drug carriers for targeted treatment has been studied over a long period of time. A selective accumulation of active substances in target tissues has been demonstrated for certain so-called nanocarrier systems that are administered bound to pharmaceutical drugs. Great expectations are placed on nanocarrier systems that can overcome natural barriers such as the blood-brain barrier (BBB) and transport the medication directly to the desired tissue and thus heal neurological diseases that were formerly incurable. Polymeric Nanoparticle have been shown to be promising carriers for CNS drug delivery due to their potential both in encapsulating drugs, hence protecting them from excretion and metabolism, and in delivering active agents across the blood – brain barrier without inflicting any damage to the barrier. Different polymers have been used and different strategies like surface modification have been done to increase the retention time of nanoparticles.[45]

Nasal Drug Delivery System:

The nasal route is especially advantageous as an alternative means for the delivery of drugs that undergo extensive first-pass metabolism or are sensitive to gastrointestinal decomposition[46]. The nasal delivery seems to be a favourable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS)-active compounds. It is the only site in the human body where the nervous system is in direct contact with the surrounding environment. The nasal route, therefore, offers a potential for drugs targeting the brain providing more opportunities to enter the CNS and then act on CNS disorders. This review enlightened vast applications for nose to brain drug delivery.[47,48,49]

Microemulsion as Intra Nasal Drug Delivery:

Microemulsions or micellar emulsions are defined as single optically isotropic and thermodynamically stable multi component fluids composed of oil, water and surfactant (usually in conjunction with a cosurfactant). The droplets in a microemulsion are in the range of 1 nm-100 nm in diameter7-11. The basic difference between emulsions and microemulsions is that emulsions exhibit excellent kinetic stability but they are thermodynamically unstable as compared to microemulsions. In recent years microemulsions have attracted a great deal of attention because of their biocompatibility, biodegradability, ease of preparation and handling and most importantly solubilization capacity for both water and oil soluble drugs. Microemulsions have various textures such as oil droplets in water, water droplets in oil, bi continuous mixture. In recent years microemulsion have attracted a great deal of attention because of their following advantages: Ease of manufacturing and scale-up, Wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release, Helps in solubilization of lipophillic drug hence Increase the rate of absorption and bioavailability of drugs, Eliminates variability in absorption, Provides a aqueous dosage form for water insoluble drugs, Various routes like tropical, oral and intravenous can be used to deliver the drugs, Rapid and efficient penetration of the drug moiety, Helpful in taste masking, Same microemulsions can carry both lipophilic and hydrophilic drugs.[50],[51]

Gels as Nasal Drug Delivery System:

Topical dosage forms:

Topical dosage forms are intended for administration into eye, rectum, vagina or skin. Skin is considered most appropriate for administration of topical dosage forms. The major inherent problem with them is that regular or systemic absorption of drug through skin is different to be assured. Usually gels are non-greasy and easily washable. These properties have made it be the most popular and acceptable. Gel have gained more and more importance because the gel bases formulation are better percutaneous absorbed than cream and ointment, the formulated gel were evaluated for various physicochemical parameters like pH, viscosity, spreadability, stability, skin irritation, in vitro release and antifungal activity. The topically used gels have several characteristics like sol-gel transition, non greasy, easily washable, stable and inert. Permeability coefficient of the drug is higher in case of gel due to its higher lipid solubility. Other formulation do not provide long term stability, therefore delivery of drug through gels are the better option to overcome the stability of formulation. A gel is a semi-solid mass of hydrophilic carrier in which all the dispersion medium has been absorbed by the carrier. A gel is a cross linked polymer network and swells in aqueous medium. Gel is composed of two interpenetrating phases. The term gels are the suspension of colloidal clays which dispersed at two components, they exhibit mechanical properties characteristic of the solid state and both dispersed component and the dispersion medium extend throughout the whole system. Gels are defined in USP as semisolid are either suspension of small non-polar particles or large polar molecules interpenetrated with aqueous. Gels are either translucent or transparent semisolid formulations which containing the solubilised ingredient. The gels are constrained within a three-dimensional polymeric matrix in which a high degree of physical cross-linking has been introduced. The matrix structure is responsible for thixotropic behavior. Gels are prepared by either a fusion process or special procedure used by the gelling agent. In the development of plant tissue culture the gel system used successively sustained the cultures and found to be cheap and easily available. The structure of gel colonies and silica gel are given in. Gels are semi-rigid system in which the movement of the dispersing medium is restricted by an interlacing three dimensional network of particles or solvated macromolecules in the dispersed phase.[8]

Recent approaches:

Quantam dots:

A quantum dot is a semiconductor nanostructure that confines the motion of conduction band electrons, valence band holes, or excitons (bound pairs of conduction band electrons and valence band holes) in all three spatial directions. The confinement can be due to electrostatic potentials (generated by external electrodes, doping, strain, impurities), the presence of an interface between different semiconductor materials (e.g. in core-shell nanocrystal systems), the presence of the semiconductor surface (e.g. semiconductor nanocrystal), or a combination of these. Quantum dots are particularly significant for optical applications due to their theoretically high quantum yield. The ability to tune the size of quantum dots is advantageous for many applications and it is one of the most promising candidates for use in solid-state quantum computation and diagnosis , drug delivery, Tissue engineering, catalysis, filtration and also textiles technologies.[52]

Transdermal Approach:

Transdermal drug delivery system is topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. In theory, transdermal patches work very simply. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.[9]

Future Prospective:

It may be feasible to develop a number of systemically effective neuro-pharmaceuticals that will be effective following systemic administration. Novel strategies based mainly on exploitation of specific transport systems at the BBB are being planned and developed. The advancement for delivering drug or peptide across BBB requires the integration of antibody engineering, pharmacokinetics, and receptor-based drug design. The development of a successful BBB drug delivery system seems

possible. Thus, there is need of development of CNS drug delivery.[53]

Important Future Research Areas in Brain Drug Targeting:

An overall goal of future research in brain drug targeting is to expand the CNS drug
space from lipid-soluble small molecules to the much larger space of pharmaceutics that include molecules that do not normally cross the BBB. The following specific areas have been identified:

1. Identify new BBB transporters that could be portals of entry for brain drug targeting systems.
2. Develop brain drug targeting systems that enable the brain delivery of recombinant protein neurotherapeutics.
3. Validate new drug targeting systems using in vivo models.
4. Optimize pharmacokinetics of in vivo brain drug targeting systems.
5. Develop genomic and proteomic discovery platforms that enable the identification of new BBB transporters.
6. Improve understanding of the regulation of BBB transport by astrocyte foot processes.
7. Improve understanding of the interaction of the neuronal and microvascular components of the neurovascular unit, their participation in the permeability barrier, in transport receptor expression, and their facilitation of the passage of agents into the neuropil.

CONCLUSION

Brain targeting drug delivery system has essential in management of CNS disorders. It can be concluded from this review that by means of nanotechnology, nasal routes, disruption of BBB, prodrugs, etc the drug can be delivered across the BBB efficiently. Additional drug exposure to brain can be improved by utilizing modified colloidal particles and liposomes. Because it is assumed that they have prolong blood circulation, which helps in more interaction and penetration into brain endothelial cells. Thus these approaches can be useful in the brain targeting offers a improved clinical efficiency but still there is need of most reliable techniques or methods which high clinical significance and cost effective.

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