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Review Article

NOVELISTIC APPROACHES IN BRAIN TARGETED DRUG DELIVERY SYSTEM: AN UPDATE

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ABSTRACT

Targeted delivery of drug molecules to human central nervous system is one of the most challenging research fields in pharmaceutical sciences and technology. The blood-brain barrier (BBB) represents a major obstacle for a large number of drugs, including antibiotics, anti carcinogenic agents, and a variety of central nervous system (CNS) active drugs, especially neuropeptides. Therefore, various strategies and techniques have been proposed to improve the delivery of different drugs which includes liposomes, colloidal drug carriers, micelles, chimeric peptide technology, intranasal and olfactory route of administration and nano technology. This article deals in brief about the status of the BBB, BCF, different pathologies of brain like neurodegenerative, cerebrovascular and inflammatory disorders. The first part of this article aims to review the strategies developed to circumvent the BBB and deliver drugs into the brain. The use of nano technology and liposomes are discussed which are crucial part of this article as mainly used to target various CNS disorders. The later part contains future aspects of brain drug targeting.

Keywords: Nanotechnology, Neurological dysfunctions, CNS targeted drug delivery.

INTRODUCTION

The world market for drugs for the central nervous system is greatly under penetrated and would have to grow by over 6times just to be comparable to the global market for cardiovascular drugs. Targeted drug delivery is the most important goal of pharmaceutical research and development. In the broadest sense, it is to optimize a drug's therapeutic index by strictly localizing its pharmacological activity to the site or organ of action. This is an important distinction from the basic targeting concept, where the specific drug receptor is the target and the objective is to improve fit, affinity, and binding to the specific receptor that ultimately will trigger the pharmacological activity. This distinction is made since the overall distribution of many drug receptors does not follow the various diseases. Actually, most of the time, drug toxicity is receptor related and receptor mediated; thus, improving intrinsic drug affinity and activity, as well as receptor binding, does not improve the therapeutic index. The main reason for this under-development of the global brain drug market is that the great majority of drugs do not cross the brain capillary wall, which forms the blood brain barrier (BBB) *in-vivo*. The BBB represents a major concern for delivery of a large number of drugs, including antibiotics, anti-carcinogenic agents and a variety of CNS active drugs, especially neuropeptides. It is located at the level of brain capillaries, where there is a convergence of different cell types; endothelial cells, pericytes, astrocytes and microglias or perivascular macrophages. The brain micro vessel endothelial that

form the BBB, display important morphological characteristics such as the presence of tight junctions between the cells, the absence of fenestrations and a diminished pinocytics activity, that together help to restrict the passage of compounds from the blood into the extra cellular environment of the brain **[8,9]**. This barrier permits the exchange of essential gases and nutrients between the bloodstream and the brain, while blocking larger entities such as microbes, immune cells and most drugs from entering. This barrier system is a perfectly logical arrangement, since the brain is the most sensitive and complex organ in the human body and it would not make sense for it to become the battleground of infection and immune response. This biological demilitarization zone is enforced by an elaborate and dense network of capillary vessels that feeds the brain and removes waste products. **[7-9].** Each capillary vessel is bound by a single layer of endothelial cells, connected by tight junction, thereby making it very difficult for most molecules to exit the capillaries and permeate into the brain. Tight junctions provide significant trans-endothelial electrical resistance (TEER) to BMEC and impede the penetration of potential therapeutic agents such as oligo- nucleosides, antibodies, peptides and proteins. Furthermore, BMEC express a variety of enzymes, both cytosolic and on the extra cellular membrane which also contribute to the restrictive nature of the BBB. P-glycoprotein (P-gp) is also present in the luminal plasma membrane of BMEC. This is an ATP-dependant efflux pump and a member of a family of intrinsic membrane proteins. **[4-6].** P-gp is known to prevent the intracellular accumulation of an extensive variety of chemotherapeutic agents and hydrophobic compounds. Under normal conditions the BBB acts as a barrier to toxic agents and safeguards the integrity of the brain. Nevertheless, several disorders and diseases can affect the brain leading to some loss of BBB integrity **[16]**.The major neurological diseases affecting the brain may be categorized as neuro degenerative, cerebro vascular, inflammatory infections or autoimmune and cancer.

Role of the BBB in brain drug development:-

Present-day incongruities in brain drug development are illustrated by a consideration of some of the characteristics of the CNS drug industry. Whereas 98% of all small-molecule drugs do not cross the BBB, and nearly 100% of large-molecule drugs do not cross the BBB, with some studies having co injected Polysorbate-80, a detergent that can disrupt the BBB, with the drug as a stabilizing agent, and incorrectly attributing the detergent effects to their own nanoparticles. In other studies, the large size of the liposomes that were used produced micro embolisms that gave a false impression of brain uptake. **[1]**

Brain Targeting Technology:-

The usual noninvasive approach to solving the brain drug delivery problem is to lipidize the drug, The water-soluble parts of the drugs restricts BBB transport conversion of water-soluble drug into lipid-soluble pro drug is the traditional chemistry driven solution to the BBB problem. **[15]**

Strategies for drug delivery to the brain:-

Several drugs do not have adequate physiochemical characteristics such as high lipid solubility, low molecular size and positive charge which are essential to succeed in traversing BBB.

Disruption of the BBB: -

The thought behind this approach was to break down the barrier momentarily by injecting mannitol solution into arteries in the neck. The resulting high sugar concentration in brain

capillaries takes up water out of the endothelial cells, shrinking them thus opening tight junction. The effect lasts for 20-30 minute, during which time drugs diffuse freely, that would not normally cross the BBB. This method permitted the delivery of chemotherapeutic agents in patients with cerebral lymphoma, malignant glioma and disseminated CNS germ cell tumors **[4, 17].** Physiological stress, transient increase in intracranial pressure, and unwanted delivery of anticancer agents to normal brain tissues are the undesired side-effects of this approach in humans.

Intra-ventricular/Intra-thecal delivery: -Here using a plastic reservoir which implanted subcutaneously in the scalp and connected to the ventricles within the brain by an outlet catheter. Drug injection into the CSF is a suitable strategy for sites close to the ventricles only.

Intra nasal drug delivery: -

After nasal delivery drugs first reach the respiratory epithelium, where compounds can be absorbed into the systemic circulation by Transcellular and Paracellular passive absorption, carrier-mediated transport, and absorption through trancytosis **[50,53].** When a nasal drug formulation is delivered deep and high enough into the nasal cavity, the olfactory mucosa may be reached and drug transport into the brain and/or CSF via the olfactory receptor neurons may occur. **[53,55]**.

FEASIBLE SYSTEMS FOR DRUG DELIVERY:-

Colloidal drug carriers:-

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10 400 nm diameter show great promise as drug delivery systems **[5]**. 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/or mesogenic properties. **[5]**

Micelles:-

Micelles formed by self-assembly of amphiphilic block copolymers (5-50nm) in aqueous solutions are of great interest for drug delivery applications **[4]**. The drugs 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 hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation **[7].** In addition, the corona may prevent recognition by the reticulo endothelial system and therefore preliminary elimination of the micelles from the bloodstream **[9]**.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 **[4,7,9]**.

Liposomes:-

Liposomes were first produced in England in 1961 by Alec D.Bangham **[17].**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 **[22].** In some cases liposomes attach to cellular membranes and appear to fuse with them, releasing their or drugs into the cell **[23].** In

the case of phagocytic cells, the liposomes are taken up, the phospholipid walls are acted upon by organelles called lysosomes, and the medication is released. Liposomal deliveries systems are still largely experimental; the precise mechanisms of their action in the body are under study, as are ways in which to target them to specific diseased tissues **[6, 17-20, 22-27, 56-58]**.

Nano-technology:-

Nanoparticulate systems for brain delivery of drugs:-

One of the possibilities to deliver drugs to the brain is the employment of nanoparticles. Nanoparticles are polymeric particles made of natural or artificial polymers ranging in size between about 10-1000nm. Drugs may be bound inform of a solid solution or dispersion or be adsorbed to the surface or chemically attached. Poly(butyl-cyanoacrylate) nanoparticles represent the only nanoparticles that were so far successfully used for the in vivo delivery of drugs to the brain **[8]**.The first drug that was de-livered to the brain using nanoparticles was the hexa-peptide dalargin (Tyr-D-Ala-Gly-Phe-Leu-Arg), a Leu-enkephalin analogue with opioid activity. Nano particles and nanoformulations have already been applied as drug delivery systems with great success and nanoparticulate drug delivery systems have still greater potential for many applications, including anti-tumors therapy, gene therapy, and AIDS therapy, radiotherapy, in the delivery of proteins, antibiotics, virostatics, and vaccines and as vesicles to pass the BBB **[8, 9]**. Nanoparticles provide massive advantages regarding drug targeting, delivery and release and, with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in nanomedicine **[9].**The main goals are to improve their stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers. The cytotoxicity of nano-particles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research**[10].** Nowadays nanotechnology is proved to be more efficient for enhancing drug delivery to brain. The nanoparticles are the drug carrier system which is made from a broad number of materials such as poly (alkylcyano acrylates) (pacas), polyacetates, polysaccharides, and copolymers. The methods of preparation of nanoparticles, their characterization and medical application have been reviewed **[8,10].**The exact mechanism of nanoparticle transport into brain is not understood, but it is thought to depend on the particles size, material composition, and structure. In some cases it is reported to mimic molecules that would normally be transported to brain. For example, polysorbate-coated nanoparticles are thought to mimic low-density lipoprotein (LDL), allowing them to be trans-ported across the capillary wall and into the brain by hitching ride on the LDL receptor **[8, 10]**.

The nanotechnology includes;-

1) Coated nanoparticles
2) Pegylated nanoparticles
3) Solid Lipid nanoparticles (SLN)
4) Nanogels

Advantages of nanotechnology:-

1) Due to their small size nanoparticles penetrate into even small capillaries and are taken up within cells, allowing an efficient drug accumulation at the targeted sites in the body **[10].**
2) The use of biodegradable materials for nanoparticle preparation, allows sustained drug release at the targeted site after injection over a period of days or even weeks.

RECENT ADVANCES IN NANOTECHNOLOGY:-

The research team of University of Michigan has developed a tool to diagnose and treat the most virulent forms of brain cancer. That is 20 to 200 nanometer diameter nanoparticles; they dubbed Probes Encapsulated by Biologically Localized Embedding (pebbles). They designed the pebbles to carry a variety of agents on their surface, each with a unique function. The major potential advantage of using these nanoparticles to treat cancer is of multifunctional. One target molecule immobilized on the surface could be used to help visualize the target using magnetic resonance imaging (MRI), while a third agent attached to the PEBBLE could deliver a destructive dose of drug or toxin to nearby cancer cells. All three functions can be combined in a single tiny polymerspere to make a potent weapon against cancer. Kopelman introduced the common MRI contrast element gadolinium to the pebbles. When injected into the bloodstream, the nanoparticles travel their way through the bloodstream. And because they can transverse they have a targeting agent attached, the pebbles accumulate in the brain tumor enabling a clear MRI image within just a few hours **[10]**.

Researchers incorporated a drug called Photofrin along with iron oxide into nanoparticles that would target cancerous brain tumors. Photofrin is a type of photodynamic therapy (PDT), in which the drug is drawn through the blood stream to tumors cells; a special type of laser light activates the drug to attack the tumor. Iron oxide is a contrast agent used to enhance magnetic resonance imaging (MRI)

Chimeric peptide technology:-

Chimeric peptides are formed when a drug that is normally not transported through the BBB is conjugated to a brain drug-targeting vector **[11]**. The latter is an endogenous peptide, modified protein, or peptide mimetic monoclonal antibody (Mab) that undergoes RMT(Rapid metabolic transfer) through the BBB on endogenous receptor systems such as the insulin receptor or the tfr. Peptido mimetic mabs bind to exofacial epitopes on the BBB receptor that are removed from the endogenous ligand binding site and piggyback across the BBB on the endogenous RMT system within the BBB, In this , a drug is mono biotinylated in parallel with the production of a vector/ avid in or a vector/streptavidin (SA) fusion protein **[11]**.The biotinylated drug is produced in one vial and the vector/avid in fusion protein is produced in another vial, and the 2 vials are mixed before administration.

Owing to the extremely high affinity of avid in or SA binding of biotin, there is instantaneous capture of the biotinylated neurotherapeutic agent by the vector/avid in or vector/SA fusion protein **[16].** Monoclonal antibody/avid in and Mab/SA fusion genes and fusion proteins are produced with genetic engineering. Brain drug delivery in rats is possible with the OX26 mousemab to the rat tfr. Brain drug delivery in humans is possible with the genetically engineered chimeric HIRmab. The activity of the genetically engineered chimeric HIRmab is identical to that of the original murine HIR mab and the chimeric antibody is avidly taken up by the primate brain**[33].** The brain uptake of the HIRmab in the rhesus monkey is 2% to 4% of the injected dose which is a level of brain uptake that is 1 to 2 log orders greater than the brain uptake of a neuroactive small molecule such as morphine **[11,16,33].**

Neuro-protection with peptide radiopharmaceuticals:-

The practice of brain imaging uses small-molecule radio chemicals that bind to monoamine or amino acid neurotransmitter systems. Whereas there are less than a dozen mono aminergic or amino acidergic neurotransmitter systems, there are hundreds of peptidergic neurotransmission systems **[40].** Therefore, the use of peptide radiopharmaceuticals could greatly increase the diagnostic potential of neuro imaging technology **[37].** Potential candidates for neuro imaging

include epidermal growth factor (EGF) peptide radiopharmaceuticals for the early detection of brain tumors and A peptide radiopharmaceuticals as a diagnostic brain scan for Alzheimer disease. Many malignant gliomas over express the EGF receptor (EGF-R) and EGF are a potential peptide radiopharmaceutical for the imaging of brain tumors **[34,37,40,32].**

Protein Neuro-therapeutic agent and neuro-protection in stroke:-

Virtually all small-molecule neuro-protective agents have failed in clinical stroke trials because either (*a*) these molecules have unfavorable safety profiles or (*b*) the drugs do not cross the BBB. The therapeutic window for neuro-protection is the first 3 hours after stroke, and during this time, the BBB is intact **[45].** The BBB is disrupted in later stages following stroke, but at this time, chances for neuro-protection have been lost. Therefore, if effective neuro-protective agents for stroke are to be developed, these molecules must have favorable safety profiles and must be able to cross the BBB**[41].**A model neurotrophin, brain-derived neurotrophic factor (BDNF), was reformulated to enable BBB transport, and the BDNF chimeric peptide is neuro-protective following delayed intravenous administration in either regional or global brain ischemia. **[35,36, 41,42-45]**

Intranasal and olfactory route of administration:-

Nasal transport routes:-

After nasal delivery drugs first reach the respiratory epithelium, where compounds can be absorbed into the systemic circulation utilizing the same pathways as any other epithelia in the body: Transcellular and Paracellular passive absorption, carrier-mediated transport, and absorption through trancytosis. Although absorption across the respiratory epithelium is the major transport pathway for nasally-administered drugs and may represent a potentially timesaving route for the administration of certain systemic drugs delivered in cryonics medication protocols (e.g., epinephrine or vasopressin), problem of BBB-mediated exclusion of brain-therapeutic agents to be of greater immediate concern. Accordingly, the remainder of this article will deal primarily with the transport of drugs to the CNS by way of the olfactory epithelium **[46]**.

When a nasal drug formulation is delivered deep and high enough into the nasal cavity, the olfactory mucosa may be reached and drug transport into the brain and/or CSF via the olfactory receptor neurons may occur. The olfactory pathways may be broadly classified into two possible routes: the *olfactory nerve pathway* (axonal transport) and the *olfactory epithelial pathway* **[48]**.

Axonal transport is considered a slow route whereby an agent enters the olfactory neuron via endocytotic or pinocytotic mechanisms and travels to the olfactory bulb by utilizing the same anterograde axonal transport mechanisms the cell uses to transport endogenous substances to the brain **[53].** Depending on the substance administered, axonal transport rates range from 20-400 mm/day to a slower 0.1-4 mm/day **[54].** The epithelial pathway is a significantly faster route for direct nose-to-brain transfer, whereby compounds pass paracellularly across the olfactory epithelium into the perineural space, which is continuous with the subarachnoid space and in direct contact with the CSF. Then the molecules can diffuse into the brain tissue or will be cleared by the CSF flow into the lymphatic vessels and subsequently into the systemic circulation **[46-55]**.

Factors Affecting Nasal Drug Delivery to the CNS:-

The size of the molecule is the major determinant in whether a substance will be absorbed across the nasal respiratory epithelium and/or transported along the olfactory pathway. It demonstrated

an almost linear relationship between the log (molecular weight) and the log (% drug absorbed) of water-soluble compounds **[51]**.

Other factors affecting delivery to the brain include the degree of dissociations and lipophilicity (higher lipophilicity results in better transport). Once a drug is in the brain, it can be further influenced by BBB efflux transporter systems like P-glycoprotein (P-gp). Graff and Pollack (2003), however, found that uptake into the brain was enhanced when drugs were administered in combination with the P-gp efflux inhibitor, rifampin **[48,49]**.

Nose-to-Brain Research:-

Researching nose-to-brain transfer of drugs in humans must, for obvious reasons, either employ indirect visualization of drug transfer (e.g., effects on event-related-potentials), measurement of drug concentrations in the CSF during surgery, or simple monitoring of CNS effects. Such studies have clearly indicated that drugs can be delivered to the brain in this manner, but they give no clear-cut evidence regarding the role of transfer. Because of this limitation, studies of the olfactory pathway as a conduit for transmission of drugs to the CNS have mostly made use of animals having substantially different ratios of olfactory-to-respiratory epithelium than humans **[52].** However, the mechanisms of transfer remain the same and are worthy of thorough investigation. To date, more than 50 drugs and drug-related compounds have been reported to reach the CNS after nasal administration in different species **[49].**

A growing number of recent reports have demonstrated the effectiveness of intranasal administration of neuroprotective agents in decreasing ischemic brain injury. For example, it recently reported that intranasal administration of NAD+ profoundly decreased brain injury in a rat model of transient focal ischemia. Similarly, it showed that intranasal administration of the PARG inhibitor Gallo tannin decreased ischemic brain injury in rats. Such agents are believed to provide neuroprotection by diminishing or abolishing activation of poly (ADP-ribose) polymerase-1 (PARP-1), which plays a significant role in ischemic brain damage. NAD+ was observed to reduce infarct formation by up to 86% even when administered at 2 hours after ischemic onset. Because PARP activation appears to be a downstream ischemic event, it may be worthwhile to also investigate the ability of IN (intranasal) administration of agents such as antiporters or NMDA receptor blockers to provide neuroprotection against the more upstream events of global ischemia such as membrane depolarization and excite toxicity **[51].**

FUTURISTIC APPROACHES OF CNS TARGETING [2,3,12,29,30]:-

There are many technological challenges to be met, in developing the following techniques. Nano-drug delivery systems that deliver large but highly localized quantities of drugs to specific areas to be released in controlled ways. Controllable release profiles, especially for sensitive drugs **[1].**Materials for nanoparticles those are biocompatible and biodegradable. Architectures / structures, such as biomimetic polymers, nanotubes. Technologies for self-assembly. Functions (active drug targeting, on-command delivery , intelligent drug release devices/bioresponsive triggered systems, self-regulated delivery systems, systems interacting with the body, smart delivery) **[13-15].** Virus-like systems for intracellular delivery. Nanoparticles to improve devices such as implantable devices/nanochips for nanoparticle release, or multi reservoir drug delivery-chips; Nanoparticles for tissue engineering; e.g. For the delivery of cytokines to control cellular growth and differentiation, and stimulate regeneration; or for coating implants with nanoparticles in biodegradable polymer layers for sustained release. Advanced polymeric carriers for the delivery of therapeutic peptide/proteins (biopharmaceutics). And also in the development of combined therapy and medical imaging, for example, nano-particles for diagnosis and manipulation during surgery (e.g. Thermotherapy with magnetic particles) **[31].** Universal

formulation schemes that can be used as intravenous, intramuscular or per oral drugs for cell and gene targeting systems. User-friendly lab-on-a-chip devices for point-of-care and disease prevention and control at home. Devices for detecting changes in magnetic or physical properties after specific binding of ligands on paramagnetic nanoparticles that can correlate with the amount of ligand. Better disease markers in terms of sensitivity and specificity **[38,39].**

CONCLUDATORY COMMENTS:-

Brain Targeting has got the attention of the many researchers due to its application in various diseases related to CNS. Only few drugs can penetrate the BBB and enters the CNS, so various systems are developed for drug delivery. It emerges that the nanotechnology and by using other routes of drug administration like intra nasal technique drug can penetrate the BBB efficiently. Further the modified colloidal particles and various modified liposomes enhance exposure of the BBB due to prolonged blood circulation, which favors interaction and penetration into brain endothelial cells. This system has clinical benefits like reduced drug dose, decreased side effects, non invasive routes, and more patient compliance. We still require developing a cost effective system that can be used in various CNS disorders efficiently with minimum side effect.

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