

Development and Application of Lipid Nanotechnology on Infectious Diseases of CNS- Current Scenario

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ABSTRACT

Background: This is an era of inventive technology illuminating fundamental mechanisms of diseases and fabricating drug molecules according to prerequisite condition, but it is still a challenge to target infectious diseases specially in CNS due to various restrictions of drug delivery to the brain and drawbacks of various conventional antimicrobial agents. These are prone to development of multiple drug resistances as sufficient amount of drug cannot reach to the site of infection. **Materials and Methods:** This review summarizes the problems associated with the amount of drug delivered to CNS and the emergence of new tools like lipid nanoparticles to deal with the current challenges in treating infectious diseases of CNS. **Results:** This article discusses the anatomical and physiological barriers of CNS and development of various drug delivery system, specially the development of lipid nanoparticles including solid lipid nanoparticles, nanostructured lipid carriers, lipid drug conjugated nanoparticles to address the challenges. **Conclusion:** This article is an extensive review on current status of drug therapy of infectious diseases of CNS. Lipid nanoparticles like SLN and NLCs have proven to be effective tools for improved drug delivery to CNS and PNS.

Key words: Multiple drug resistance, Solid lipid nanoparticles, Nanostructured lipid carriers, Lipid drug conjugated nanoparticles, CNS, Blood-brain barrier.

INTRODUCTION

The futile treatment of CNS disorders by most of the neurotherapeutics can be due to their ineffective drug delivery. Although brain has relatively high blood flow yet drug delivery to the brain is most challenging because of the two physiological barriers *i.e.*, Blood-Brain Barrier (BBB) and Blood-Cerebrospinal Fluid Barrier (BCFB). BBB and BCFB separates the brain from its blood supply controlling the transport of compounds and this is the reason why most of the brain or CNS associated diseases remain untreated by effective therapies. Contemporary approaches like ligand conjugation and nanotechnology are used to target the barriers of CNS by means of various transport pathways and various surface fabrication.¹

Infectious diseases were the main cause of death at the juncture of 19th and 20th century.² The advent of antibiotics led to a

decrease in morbidity and mortality in the last century. However, of late microbe developing resistance to antibiotics is posing a serious problem in health administration.^{3,4} The cause of brain infection are viruses, bacteria, fungi or occasionally, protozoa or parasites listed in Table 1.⁵⁻¹⁹ Another group of brain disorders, called spongiform encephalopathies, are caused by abnormal substances called prions.^{5,6}

Challenges Associated with Infectious Disease of Brain

There can be possibly three main causes which makes the management of infectious disease difficult:

Delay in Clinical Diagnosis

In case of patients where the classic symptom may be minimal or absent.

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Table 1: List of Infectious Brain Diseases and their Causative Organism.			
S. No	Causative micro-organism	Disease	Reference
1	Fungal	<ul style="list-style-type: none"> • Cryptococcal meningitis • Brain abscess 	7 8
2.	Protozoal	<ul style="list-style-type: none"> • Toxoplasmosis • Malaria • Primary amoebic meningoencephalitis 	9 10 11
3.	Bacterial	<ul style="list-style-type: none"> • Tuberculosis • Leprosy • Neurosyphilis • Bacterial meningitis • Late stage Lyme disease • Brain abscess • Neuroborreliosis 	12 13 14 15 16 7 17
	Viral	<ul style="list-style-type: none"> • Viral meningitis • Eastern equine encephalitis • St Louis encephalitis • Japanese encephalitis • West Nile encephalitis • Herpes simplex encephalitis • Rabies • California encephalitis virus • Varicella-zoster encephalitis • La Crosse encephalitis • Measles encephalitis • Nipah virus encephalitis • Poliomyelitis • Slow virus infections, which include: <ul style="list-style-type: none"> • Subacute sclerosing panencephalitis • Progressive multifocal leukoencephalopathy • Acquired immunodeficiency syndrome (AIDS) 	18 19
	Prionic	<ul style="list-style-type: none"> • Creutzfeldt–Jakob disease • Fatal familial insomnia • Gerstmann–Sträussler–Scheinker syndrome • Kuru 	5,6

Misinterpretation of Laboratory Diagnosis

Problem arises due to wrong diagnosis of infectious and non-infectious diseases, secondary infections and causative organism, leading to wrong treatment.

Treatment

The most challenging part is the delivery of appropriate dose and maintenance of required dose in CNS.

This review discusses various aspects of nanotechnology which will help us get success in the war against infectious disease caused in CNS. The brain, which, is a very important organ and made of soft tissues, is well protected with a skeletal system and underlining network of capillary system, which, in turn, restrict or prevent the entry of intrusive chemicals, including therapeutic agents.¹⁹

Factors Preventing the Entry of Drugs into CNS

Barrier Membranes

In CNS there are two barriers.

Blood Brain Barrier

Brain capillaries walls are composed of specialized endothelial cells that are connected to each other with tight junctions and have no fenestration.^{20,21} Usually micro vesicles are absent for vesicular transport. A thick basement membrane covers the endothelial cells of brain capillaries. The other components of BBB are astrocytes and pericytes. The rear part of astrocyte also covers a significant section of endothelial cell. The pericytes are engulfed in the basal membrane and covers 22%-33% of the endothelial membrane. The tight junction along with no fenestration, low transcytosis and paracellular diffusion of hydrophilic substance, inhibits the brain from uptake of therapeutic agents.²²⁻²⁵ Only those molecules whose mass is less than 150 Da for hydrophilic compounds and mass less than 400 to 500 Da for hydrophobic compounds cross by passive diffusion through the membrane but majority of antibiotics and antitumoral molecules cannot cross the barrier membrane.^{26,27}

Blood Cerebrospinal Fluid Barrier

BCFB plays an important role in regulating CNS homeostasis and transfer of material from systemic circulation and the CSF.²⁸ The Choroid Plexus (CP) is made up of capillary bed, the piamater and large number of epithelial cell. BCFB prevent the entry of endogenous substance into the brain, thus, plays an important role in preventing the entry of therapeutic agents. BCFB prevent the transport of small molecules and ions through the intercellular space of the membrane and prevent the passage of comprehensive membrane proteins between the apical and basolateral membrane of the cell. Membrane and luminal surface of brain capillary, constituents of CSF or ISF, functional groups, change on molecular and ionic surfaces or presence of charged residues of the molecules are the factors which influences the membrane permeability. Choroid plexus participates in different functional and developmental activities like movement of materials between the systemic circulation and the CSF, early stages of brain development, immune function of brain, neuronal functional maturation and regulate neuroendocrine system. Researchers has studied influence of the blood-CSF barrier role in various neurological disorders like chemical-induced neurotoxicity, aberrant brain development.²⁹⁻³¹

Efflux transport mechanism

The efflux mechanism also helps in detoxifying system for brain. BBB pumps xenobiotics and other endogenous compounds out of the brain. Efflux pumps have vital role in the multi drug resistance of Gram-negative bacteria and provides the main hurdles in the drug discovery process. Drug-efflux transporters that are present at the blood brain barrier limit the ability of many drugs to enter the brain. These efflux systems play a vital part in drug resistant brain disorders. From Keith Poole review it is clear that formulating drugs with already present or new efflux transporter agents has to be considered to treat drug-resistant infection.

Efflux transporter expressed on the BBB belongs to ATP-Binding Cassette (ABC) gene family, which, are needed for drug distribution and elimination from brain. The ABC efflux transporter P glycoprotein which is expressed in the BBB plays an active role in transporting different lipophilic drugs out of the brain. It has been reported that apart from P-gp, other ABC efflux transporters such as multi drug resistance protein (MRP) family and Breast Cancer Resistance Protein (BCRP) also impact to BBB-efflux function.³²⁻³⁴ Thus, ABC efflux transporter inhibits both endogenous and exogenous transport of substances. This reason also contributes to the limitation of accessibility of thera-

peutic agents which are essential for treatment of CNS disorders.³⁵

These multi drug resistance proteins are mostly found in gram-positive bacteria. Importance of efflux pumps in bacterial antibiotics resistance, hence, has to be considered while designing the treatment strategy. In addition to the above factors, surface activity of the molecules, its relative size and specific binding of transporter proteins, energy driven cassettes and opening and closing of ion channels due to ionic concentration are the key factors which play an important role in drug delivery.^{36,37}

Approaches to Increment the Delivery Drugs to the Affected Site

The main challenges associated with treatment of brain had already been discussed above. The important point is how to address these problems. Confined and controlled delivery of drugs to the required site is necessary to minimize toxicity and enhance the treatment efficiency (Figure 1).

Noninvasive Technique

Chemical Method

In this approach, the drugs functionalities are changed by altering its chemical structure which, in turn, enhance their solubility and membrane penetration.³⁸

Lipophilic Analogs

Lipid analogs are attached to the polar ends of the drug to increase the lipophilicity of the drug. Lipidization increases the permeability of the drug through BBB.

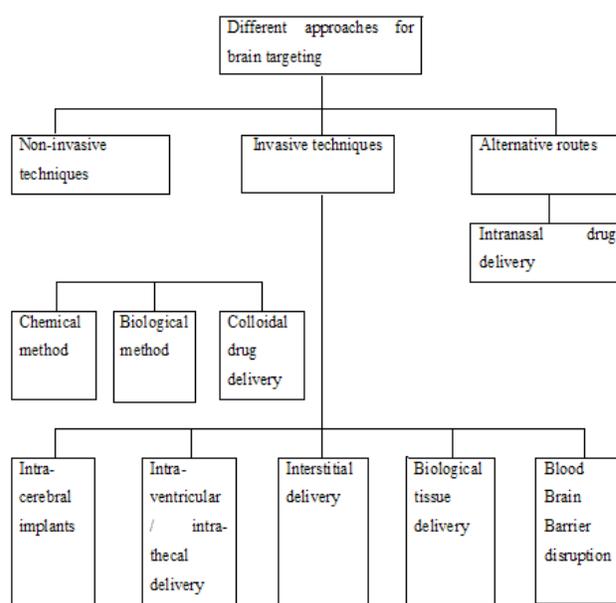


Figure 1: Different Approaches used for Treatment of Diseases in CNS.

Prodrugs

Prodrugs are those compounds which are inactive when administered and become an active pharmacological agent after it enters into the body. With chemical modification, the prodrug method is used to make a drug more lipophilic. However, it should be taken into consideration that certain prodrug molecules and process involved in prodrug synthesis may alter the original tissue distribution, efficacy and toxicity of parent drug.

Molecular Packaging

This approach has been developed with three aims: first, improve lipophilicity to enhance passive transport, secondly, increase enzymatic stability which in turn prevent the premature degradation of the drugs, thirdly manipulation of lock-in mechanism to target the CNS. Thus, this is a promising strategy to enhance the penetration of peptides across the BBB. It has been reported that certain peptide drugs, such as DADLE (Tyr-D-Ala-Gly-Phe-D-Leu) and thyrotropin-releasing hormone has been delivered to brain using molecular packaging.

Biological Approaches

For biological approaches a thorough consideration of physiology and anatomy of brain and its barrier regarding its transportation is necessary.

Receptor/Vector-Mediated Delivery of Chimeric Peptides

Peptide and protein therapeutics have negligible permeability to the brain capillary endothelium. So, these are normally left out from transport from blood to brain. For these peptide drugs the chimeric peptide strategy can be used to deliver across the brain. When a non-transportable peptide therapeutic is coupled to a BBB drug transport vector, a chimeric peptide is formed. Transport vectors are proteins such as cation albumin or the OX26 monoclonal antibody to the transferrin receptor; these proteins undergo absorptive-mediated and receptor-mediated transcytosis through the BBB, respectively.³⁹

Cell-Penetrating Peptide (CPP)-Mediated Drug Delivery

CPPs consist of various amino acids sequence of different size giving a positive charge on the peptide. These can transport the molecules that are tagged to them across the cell membrane and even across BBB. The first CPP, Trans-Activator of Transcription (TAT), derived from Human Immunodeficiency Virus-1 (HIV-1), can be efficiently taken up from the surrounding media, regarded to be the first group of CPPs derived from natural proteins. The second group of CPPs con-

sists of chimeric molecules, such as Transportan (TP), which consists of 12 amino acids derived from the neuropeptide galanin fused with a 14 amino acid peptide from the wasp venom mastoparan. The third group of CPPs consists of the synthetic peptide family, of which polyarginines are the best studied.⁴⁰

Viral Vectors

The delivery of recombinant genes into the brain is becoming an increasingly important approach for responding queries related to the molecular mechanisms of brain function. HSV possesses several features that make it an ideal vector for delivery of genes into the nervous system.⁴¹

Colloidal Drug Carriers

Micelles and microemulsions Theoretically, natural polymer and synthetic polymer materials can be used to prepare micelles and microemulsions. Currently, polymeric micelles, which are the most investigated, usually have a hydrophobic polymer core (eg, poly (propylene glycol), poly (D, L-lactide) and poly (caprolactone)) and a shell of hydrophilic polymer blocks (eg, poly (ethylene glycol) [PEG]).

Liposomes

Liposome-based strategies for effective drug delivery across the blood-brain barrier have been used for their unique physico-chemical characteristics. Liposome are used in drug delivery and *in vivo* bioimaging for the treatment and/or diagnosis of neurological diseases, such as Alzheimer's, Parkinson's, stroke and glioma. For receptor-targeting liposomes, they are covalently attached with macromolecules like peptides, antibodies and RNA aptamers which allows their blood-brain barrier penetration and/or the delivery of their therapeutic molecule specifically to the disease site effective.⁴²

NPs (Nanospheres and Nanocapsules)

Nanoparticles with certain surface modifications can deliver drugs of interest beyond the BBB for diagnostic and therapeutic applications in neurological disorders. In addition to this, it also prevents opsonization. The different physico-chemical properties of the NPs due to different surfactant concentrations, stabilizers and amyloid-affinity agents could influence the transport mechanism.⁴³

Alternative Routes

Use of alternative routes to overcome the physiological barriers like BBB and BCFB are intranasal drug delivery and trigeminal pathways. The nose-brain pathway helps rapid transport of lipophilic and small drug molecules

to CNS within few minutes. Many researchers has carried out delivery of drug via this route, research reports of Sharareh *et al.* had proved that when NLCs of valporic acid were formulated and administered through intranasal route in rats they showed that brain: plasma concentration ratio was much higher and provided a better protection against MES seizure.⁴⁴

Abdelrahmana *et al.* had formulated cubosomal gel of risperidone and administered through intranasal route to enhance permeability and biodistribution to brain. They prepared these cubosomal gel using glycerol mono-oleate, Pluronic F127 and Tween 80 and evaluated their particle size polydispersity index, zeta potential, entrapment efficiency, *in vitro* drug release and transmission electron microscopy. They found that these Cubosome showed drastically elevation in intranasal permeation and better distribution to the brain, when compared to the used control (Drug solution and/or suspension).^{45,46}

Invasive Method

Very few orally or parenterally administered drugs and peptides can cross BBB but cause systemic toxicity before reaching target areas in the brain. To overcome this, invasive methods are used to deliver sufficient amount of therapeutic agents directly to the brain by disrupting the BBB.⁴⁷

Intraventricular Delivery/Intrathecal Delivery

The intraspinal routes of the drug administration is comprised of intrathecal and epidural drug delivery where the drug is administered to the cerebrospinal fluid. In case of intrathecal delivery the drug is directly injected into the CSF present in the intrathecal space in the spinal column, but in case of drugs which are injected in the epidural space have to cross the dura membrane to get to the CSF so there are chances that drug administered through epidural space can also reach the systemic circulation so the intrathecal route reduces the side effects of drugs compared to that of systemic routes of drug delivery. The intrathecal route administer the drug directly into the CSF circumventing the blood brain barrier. Persistent intracranial drug concentration of anticancer drug was achieved by administering locally to an intracranial target.⁴⁸⁻⁵⁰

BBB Disruption (BBBD) strategies

It was reported by, Rapoport *et al.* that CNS tissues were stained by Evans Blue as a result of intra-arterial infusion of hypertonic arabinose.⁵¹ Evans Blue which binds to albumin do not permeate through intact BBB; the above observation suggests that permeability of BBB is changed by hypertonic arabinose which induces contraction of cerebrovascular endothelial cells causing distraction of inter-endothelial tight junctions. This hypothesis

was supported by Brightman and co-workers when they effectively visualized opened endothelial tight junctions with electron microscopy after intra-carotid infusion of mannitol in several species.⁵² In 1984, Dorovini-zis *et al.* also practically observed opened inter-endothelial tight junctions when endothelial cell cultures were exposed to a hypertonic solution.⁵³

Intracerebral Implants

In most of the clinical trials intracerebral implantation are utilized which contains therapeutic agents imbibed in biodegradable polymeric matrix or reservoir. The FDA approved a BCNU (bischloroethylnitrosourea) (carmustine)-contained polyanhydride polymer wafer for recurrent high-grade gliomas in 1996.⁵⁴ This matrix was made with a blend of diffusion and hydrolytic polymers and maintains a sustained drug release for about 2 months. Intracerebral implantation has also been tried in some chemotherapeutics.⁵⁵⁻⁵⁷ But the augmented risk of trauma and poor drug infiltration beyond the resection cavity restricted the local delivery approach.

Convection-Enhanced Delivery (CED)

The therapeutic agents are administered directly into the embattled brain parenchyma or tissue by CED. One and more catheter stereo tactically placed through cranium by inflecting holes into the brain in CED. The micro infusion pump are used to administer the therapeutic agents.^{58,59} CED has shown its exceptional characteristics for CNS delivery compared with conventional delivery methods.⁶⁰ When defined infusion measurements are used through CED it does not produce cerebral edema or measurable increase in intracranial pressure.⁶¹ Bobo *et al.* first proposed CED in 1994.⁶² CED involves maintenance of continuous positive-pressure infusion of a solute containing a therapeutic agent. It relies on pressure-driven bulk flow of infuscate for delivering therapeutic agents to the CNS. The bulk flow mechanism is created by a small pressure gradient from a pump that pushes solute through a catheter targeted within the CNS: (i) CED bypasses the BBB and can be used to infuse therapeutic agents with large or small molecular weights via bulk interstitial flow; (ii) CED provides targeted delivery to the region into which the catheter is placed and the potential for real-time monitoring of distribution, which would allow intelligent adjustment of flow rates; (iii) and unlike diffusion-limited delivery, CED provides pressure-driven delivery that enhances interstitial drug distribution.⁶³

Biological Tissue Delivery

This is one of the approaches to accomplish interstitial drug delivery from biological tissue. In this method, a tissue is implanted into the brain that secretes a desired

therapeutic agent. This strategy was used to treat Parkinson's disease.⁶⁴ But due to lack of neovascular innervations the transplanted tissue dies soon. With advancement in the technique the survival of foreign tissue grafts is improved. In recent times it has been established that superior vascularization and microvascular permeability occurs in cell-suspension embryonic neural grafts as compared to solid grafts.^{65,66}

Recent Development in Lipid Nanoparticles to Combat Infectious Brain Diseases

Nanoparticles used in CNS disorders: In infectious condition the BBB get disrupted but the main problem associated with it is the rejuvenation of BBB as the infection starts to cure and after which the required amount of drug is not available to the site. It has been found by many researchers that nanoparticles especially surfactant coated and lipid nanoparticles has mammoth contribution in escalating biodistribution of drugs in CNS as well as increases the retention in BBB. Based on the above considerations, a proper tuning of NP surface characteristics and size, can represent a highly important approach to alter NP biodistribution, thus, enhancing their blood circulation time and deposition in non-RES organs.^{67,68} In this article we briefly discuss on the various work done in this field.

Outline of Various Mechanisms for Nanoparticle Mediated Drug Uptake by the Brain

1. Enhanced retention in the brain–blood capillaries, with an adsorption on to the capillary walls, resulting in a high concentration gradient across the BBB.
2. Opening of tight junctions due to the presence of nanoparticles.
3. Transcytosis of nanoparticles through the endothelium.

Nano carriers increases pharmacokinetics and biodistribution while minimizing the toxicity of therapeutic agents at the site of accumulation because these nano-carriers have larger ratio of surface area and volume.^{69,70} Nanoparticles used to deliver drugs against CNS infection.

Nano particles for the treatment of Human African Trypanosomiasis (HAT) were designed. The causative agent of HAT *T. brucei* resides, mainly, in the blood stream. Flaig *et al.* have studied the worth of daunomycin nanoparticles against the blood forms of *T. brucei*.⁷¹⁻⁷³ Both Growth inhibition and trypanocidal action of nanoparticulate daunomycin either plain or coated with PEG, transferrin, human serum albumin and transferrin antibodies was evaluated. On the *T. brucei* surface transferrin receptors are expressed, the highest effec-

tiveness was observed with transferring receptor antibody and transferrin coupled nanoparticles signifying the usefulness of surface receptors targeting approach. From the biodistribution studies of these nanoparticles it was conclusive that they are also transported to the brain, which could be very useful in the chronic phase of trypanosomiasis.

Lipid Nanoemulsion

Lipid nanoemulsion are prepared by the dispersion of two immisible liquid in which one is water and the other is oily phase. The mean particle size is less than 500nm and these ultrafine dosages form plays a very important role in enhancing the bioavailability of poorly water soluble drugs and also increases the permeability and retention of polar drug.⁷⁴ Due to small particle size they have more kinetic stability compared to the coarse emulsion. Nanoemulsion protect the drug against severe physiological conditions (like pH, oxidation and hydrolysis) and also used to solubilize in parenteral form.⁷⁵ Hitendra *et al.* formulated intranasal nanoemulsion of saquinavir mesylate targeting CNS (anti-HIV drug with poor solubility and permeability) and found that the permeability of drug through BBB was significantly increased.⁷⁶

Liposomes

Liposomes are bilayer vesicular structure made up of phospholipids and cholesterol surrounding the aqueous compartment, which may be multilamellar or unilamellar. Liposomes due to their inimitable physico-chemical characteristics are able to include both hydrophilic and lipophilic. Lipophilic drugs are entrapped in the lipid bilayer while hydrophilic drugs are entrapped in the aqueous compartment. Liposomes are biocompatible, biodegradable, less toxicity, target specific and can control drug release. The surface of liposomes can be modified by addition of macromolecules like polymers, polysaccharides, peptides, antibodies or aptamers to improve blood circulation and brain-specific delivery.⁷⁷⁻⁸⁰

Liposome-based drugs developed for brain-targeted drug delivery are now in various stages of development. Researchers^{81,82} have developed liposome-based amphotericin B for treatment of cryptococcal meningitis. Similarly, cytarabine⁸³ is being developed for treatment of lymphomatous meningitis. Lippens⁸⁴ has used DSPC and cholesterol for developing liposomal daunorubicin, which is in phase I of clinical trial, for treatment of pediatric brain tumor. Liposome based doxorubicin⁸⁵⁻⁹¹ is in phase II of clinical trial. There is a patent to conjugates and liposomes are used for targeted drug delivery

of drugs to intracellular target sites within cells, tissues and organs, in particular to target sites within the central nervous system (CNS), into and across the blood-brain barrier, by targeting to internalizing uptake receptors present on these cells, tissues and organs.⁹²

Lipid Nanoparticles

Lipid nanoparticles are made of solid lipophilic matrix embedded with drug molecules with their size ranging between 150 to 300 nm but depending on requirement the size can be varied from less than 100 to 1000 nm. These lipid nanoparticles are prepared by replacing the liquid lipid used in emulsions with the solid lipids. The solid lipids used are of high-melting point glycerides or waxes to produce SLN. The advantage of lipid nanoparticles is that it remains solid even after administration to the body so they provide controlled release. There are two generations of lipid nanoparticles, first generation are solid lipid nanoparticle, which are made of solid lipids only and the second generation are nano-structure lipid carriers, in which both solid lipid and liquid lipids are used. Due to the inclusion of the oil compound the perfect lipid structure get destroyed and this, in turn, forms a imperfect structure or amorphous form which increases the loading volume for drug. So, if we compare SLN and NLC the latter has imperfect structure hence the loading capacity increases and there is a less chance of drug expulsion over time or during sterilization than the former. One more problem associated with solid lipids, as for SLN, is that they undergo polymorphic changes which leads to drug expulsion and causes precipitation of drug in aqueous phase. But these problems can be resolved by addition of liquid lipids to the solid lipids.^{93,94} Hence NLC possess a higher physical stability than SLN.

Lipid nanoparticles (NLC, SLN) are composed of hydrophobic biodegradable carrier lipids and the drug is either dissolved or dispersed in the core, thus, rendering it suitable for administrating through IV.⁹⁵ The small size of lipid nanoparticle causes it to cross tight endothelial cells of BBB in CNS and bypass reticuloendothelial system and liver. In addition, these lipid nanoparticles provide higher drug entrapment efficiency, more stability to drug in lipid matrix and prolonged release of drug for longer period of time, which, at times, may last for several weeks. Sometimes the surface of these lipid nano-structure are coated with hydrophilic (Cationic) polymer or surfactant so that they can penetrate the BBB.⁹⁶

Most of the antimicrobial's agents targeting CNS infection has problem in crossing the barriers present in the brain. So, lipid nanoparticles are used as carriers and administered parenterally or through nasal route.

Lipid nanoparticles possesses advantage of controlled release over nanoemulsion, when drug loaded nano-emulsions are injected the drug partitions from the oil phase to aqueous phase of blood in few seconds, depending on the log P of the drug. Thus, lipid nanoparticles remain in circulation for a longer time.

Bondi *et al.* have patented a NLC based riluzole for treatment of sclerosis. The authors used compitrol as solid lipid for the preparation of NLC and have effectively demonstrated that NLC based riluzole crossed BBB more easily than free riluzole.⁹⁷ Awasthi and Lagisetty have developed and patented a variety of solid lipids (2carboxyheptadecanoyl heptadecylamide (CHHDA), 1,4dipalmitoyl-tartarate-2,3-disuccinic acid (DPTSA), 1,4-di palmitoyl-tartarate-2,3-diglutaric acid (DPTGA) or Cholesteryl Hemisuccinate (CHEMS)) and used these solid lipids along with Vitamin E as liquid lipid for preparing lipid matrix.⁹⁸ Wang *et al.* have successfully bound a biotinylated protein antibody to lipid nanoparticles that can recognize a receptor on surface of a neuronal cell and, hence can target cells of CNS or PNS.⁹⁹ Gupta *et al.* had investigated the delivering ability of Transferrin (Tf) conjugated solid lipid nanoparticles loaded with quinine dihydrochloride to brain for the management of cerebral malaria. SLNs were prepared by an ethanol injection method using hydrogenated soya phosphatidyl choline (HSPC), Triolein, cholesterol and distearyl phosphatidylethanolamine (DSPE). Coupling of SLNs with Tf was achieved by incubation of Tf with quinine-loaded SLNs in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) hydrochloride in phosphate buffered saline (pH 7.4) as a cross-linker. The particle size range of SLNs formed and drug entrapment was 38.4-42.7%. A dialysis technique was used to determined the *in-vitro* release profile. The release rate of non-conjugated SLNs was more than Tf-SLNs but the fluorescence studies revealed that the uptake of Tf-SLNs in brain tissue is more compared to that of unconjugated SLNs. They also found that in case of intravenous administration of quinine dihydrochloride solution the concentration of drug in the serum was much higher concentrations than with SLNs.¹⁰⁰ Manoj Kumar *et al.* had prepared SLN of streptomycin by nano colloidal aqueous dispersion technique to increase the permeability of streptomycin sulphate through BBB to CNS via nasal route. The authors found that the biodistribution of streptomycin sulfate increases 3.15 and 11.0 times more in brain and blood respectively compared to free streptomycin sulphate administered through IN route.¹⁰¹

Inability to cross the blood-brain barrier and deliver drugs to the central nervous system has hindered the

developments of nanocarriers.¹⁰² On the other hand, the highly vascularized nature of brain tissue makes it an attractive choice for intravenous delivery of therapeutic drugs. SLN and NLC take benefit of the high capillary density of the brain and at the same time has the capability to overcome blood-brain barrier restrictions.¹⁰⁰ Using these formulations the delivery of antiretrovirals to the brain, such as the HIV protease inhibitor Atazanavir have been boosted.¹⁰³ Researchers have also demonstrated that thiamine-coated SLN successfully bind to the blood brain barrier thiamine transporter and result in a gradual buildup of SLN that is responsible for increased brain uptake.¹⁰⁴ SLN and NLC shows potential drug-delivery systems, but in the case of the brain, they are even more important in terms of successfully overcoming the limitation imposed by the blood-brain barrier.¹⁰⁵ Lipid nanocarriers are well known to cross the BBB and exhibit required therapeutic effect without surface modification of drugs. SLNs and NLCs were found to bind Apolipoproteins and target brain tissues like polymeric nanoparticles containing PBCA.¹⁰⁶ Lim *et al.* had developed and characterized itraconazole (ITZ)-loaded nanostructured lipid carriers (NLCs) using Precirol® ATO 5 and Transcutol® HP as the lipid phase and Tween® 80 and Solutol® HS15 as surfactants. The ITZ-NLCs were prepared by a hot and high-pressure homogenization method. The entrapment efficiency for the best formulation batch was analyzed using high-performance liquid chromatography and was found to be 70.5%±0.6%. The average size, zeta potential and polydispersity index for the ITZ-NLCs used for animal studies were found to be 313.7±15.3 nm, -18.7±0.30 mV and 0.562±0.070, respectively. Transmission electron microscopy confirmed that ITZ-NLCs were spherical in shape, with a size of less than 200 nm. An *in vivo* study showed that ITZ-NLCs could increase the ITZ concentration in the brain by almost two-fold.¹⁰⁷

CONCLUSION

The astonishing growth in current years of CNS drugs has generated massive research scope in the develop of new dosage forms for brain diseases. The main challenges involved in targeting brain are the blood brain barrier and efflux transport mechanism. Various strategies were attempted in order to overcome this issue, but the best answer obtained were by using lipid nanoparticles e.g. SLN, NLC, LDC NPs, these forms indicate less toxicity, production feasibility and scalability compared to other formulations. The main problem associated with these forms are selection of lipids and surfactants. But it has been found by researchers the toxicity of

surfactants becomes less in these lipid formulations.¹⁰⁸ Moreover, the high vascularization of brain facilitates the transfer of these dosages form through intravenous parenteral. When we discuss about the infectious diseases it is required that the drug should reach to the CNS and remain there till the infection is completely cured. However, the main problem associated with antibiotics is that the microbial resistance variants is a serious threat fighting against infectious diseases.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CNS: Central nervous system; **PNS:** Peripheral nervous system; **CP:** Choroid plexus; **BCFB:** Blood cerebrospinal fluid barrier; **CSF:** Cerebrospinal fluid; **ISF:** Interstitial fluid; **BBB:** Blood brain barrier; **ABC:** ATP-binding cassette; **ATP:** Adenosine triphosphate; **P-gp:** Permeability glycoprotein; **BCRP:** Breast cancer resistance protein; **MRP:** Mitochondrial RNA processing; **DADLE:** [D-Ala2,D-Leu5]-Enkephalin; **CPP:** Cell penetration peptide; **TAT:** Trans-activator of transcription; **TP:** Transportan; **HSV:** Herpes simplex virus; **HIV:** Human immuno deficiency virus; **PEG:** Polyethylene glycol; **NLCs:** Nanostructured lipid carriers; **MES:** Maximum electroshock seizure; **BCNU:** Bischloro ethyl nitroso urea; **FDA:** Food and drug authority; **CED:** Convention-enhanced delivery; **RES:** Reticuloendothelial system; **HAT:** Human African Trypanosomia; **HSPC:** Hydrogenated soya phosphatidyl choline; **DSPE:** Distearyl phosphatidyl ethanolamine; **CHHDA:** 2carboxyheptadecanoyl heptadecylamide; **DPTSA:** 1,4dipalmitoyl-tartarate-2,3-disuccinic acid; **DPTGA:** 1,4-di palmitoyl-tartarate-2,3-diglutaric acid; **CHEMS:** Cholesteryl hemisuccinate; **Tf:** Tissue factor; **EDC:** 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; **PBCA:** Polybutylcyanoacrylate; **ITZ-NLCs:** Itraconazole-loaded nanostructured lipid carriers; **LDC NPs:** Lipid drug conjugated nanoparticles.

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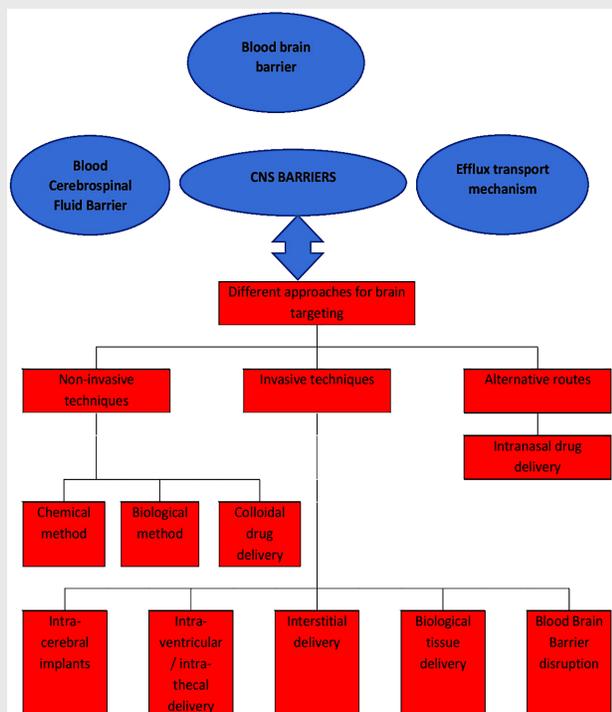
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PICTORIAL ABSTRACT



SUMMARY

- Delivery of drug to CNS has been challenging for formulating researchers even with continuous development in the field of pharmaceutical sciences.
- This review article basically focuses on the various infectious diseases of CNS and the problems and challenges associated with drug development for such infectious diseases of CNS.
- Various anatomical and physiological barriers of brain which protect the brain also render drugs ineffective by preventing passage of sufficient amount of drug molecules.
- The advent and application of different invasive and non-invasive techniques are proving to be effective in improving drug delivery to the brain. Nano technology in particular has been extensively applied for development and formulation of lipid nanoparticle dosages form.

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