Journal of Applied Pharmaceutical Science Vol. 5 (07), pp. 154-164, July, 2015
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2015.50724
ISSN 2231-3354

Progress in Brain Delivery of Anti-HIV Drugs

Malay K Das, Tapash Chakraborty

Division of Pharmaceutics, Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh 786004, India.

ARTICLE INFO

Article history:
Received on: 17/01/2015
Revised on: 22/04/2015
Accepted on: 17/06/2015
Available online: 27/07/2015

Key words:
Brain targeting, Anti-HIV, nanoparticles, liposomes, SLN, NLC.

ABSTRACT

The HIV/AIDS pandemic is an increasing global burden with devastating health-related and socioeconomic effects. The widespread use of antiretroviral therapy has dramatically improved life quality and expectancy of infected individuals. But currently available drug regimens and dosage forms are not good enough to eradicate HIV. Suboptimal adherence, toxicity, drug resistance and viral reservoirs make the lifelong treatment of HIV infection challenging. Along with some other organs, highly vascularized and secured with blood-brain barrier (BBB), brain acts as a great reservoir for the HIV virus. But all the available drug delivery techniques are not capable of bypassing the BBB and deliver anti-HIV drugs to the brain. In this review, all the brain delivery techniques available till date has been reviewed and recent noble ideas for delivering anti-HIV drugs to brain has been discussed.

INTRODUCTION

From the studies of Dr. Luc Montagnier of French and Robert Gallo of USA and their teams, it was clear that acquired immunodeficiency syndrome (AIDS) of humans is caused by a type of lentiviruses, the Human Immunodeficiency Viruses (HIV), which most of the scholars believe was originated in non-human primates in Sub-Saharan Africa and was transferred to humans during the late 19th or early 20th century (Clercq 2009; Neves *et al.*, 2010).Subsequent studies proved that HIV can spread from one infected person to another healthy person through any type of unprotected sex (oral, vaginal, or anal) if one of the partners has the virus. This can happen when body fluids such as semen (cum) & pre-cum, vaginal fluids, or blood from an infected person get into the body of someone who is not infected. Other means also contribute significantly to the spread of the infection, namely by transfusion of contaminated blood products, sharing of contaminated needles among injected drug users, and transmission from mother-to-child during pregnancy, labour or breastfeeding, accidents etc. HIV may get transmitted either as free virions or with associated cells, macrophages being the primary transmission carriers for HIV present in vaginal, seminal and other body secretions(Neves *et al.*, 2010; Gupta *et al.*, 2010). HIV mainly targets the Cluster of Differentiation- 4 positive (CD4+) T lymphocytes and cells of the monocyte-macrophage lineage (Dalgliesh *et al.*,1984).

CD4− negative cells may also be targeted, but these viral strains are highly sensitive to neutralization by host antibodies and are present only at sites where circulating antibody levels are low (e.g. in brain) (Kolchinsky *et al.*, 2001; Martin *et al.*, 2001).Unfortunately this CD4+ cells are those cells, which organizes all immune responses in human body, from getting dirt in a cut to fighting off pneumonia. Once it infects these cells, it takes it over and uses the cell's machinery to make more copies of itself. These copies go on to infect other CD4+ cells, and the cycle continues. Each CD4+ cell that's infected is rendered useless, and after sometime it becomes harder for the persons body's immune system to fight of any infections.

When a person is infected with the human immunodeficiency virus (HIV), it is said that he/she is "HIV positive," or "has HIV." A person who has HIV is classified as having AIDS only if the CD4+T cell count of that person has dropped below 200 cells/mm^3 (A normal CD4+ T count can range from 500 cells/mm^3 to 1,000 cells/mm^3), or an HIV-related infection or HIV-related cancer develops (Ghate *et al.*, 2009). In the early 1980s when the HIV/AIDS epidemic began, people with AIDS were not likely to live longer than a few years.

* *Corresponding Author*
Malay K Das, Division of Pharmaceutics, Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh 786004 India. Email: mail id: mkdps@dibru.ac.in

Currently, there are 31 anti-retroviral drugs (ARVs) approved by the US Food and Drug Administration (US FDA) to treat HIV infection, which roughly can be divided under 8 different classes of drugs. There are some fixed dose combinations too, which normally contains more than two different classes of drugs (Fauci, 2007). Highly Active Antiretroviral Therapy (HAART) is the name given to the aggressive treatment regimens used to suppress HIV viral replication and the progression of HIV disease began with the 11th International Conference on AIDS in Vancouver, British Columbia, July7-16, 1996 (Chiappini *et al.,* 2014). The usual HAART regimen combines three or more different drugs such as two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), two NRTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or other such combinations. Different HAART therapies were suggested by different experts (Oliveira *et al.,* 2014).The "triple-drug therapy" using Nevirapine-based treatment, was suggested by Julio Montaner of the British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital of Vancouver, Canada. Triple-drug therapy with Indinavir-based treatment was described by Roy Gulick from New York University School of Medicine, New York, NY; and the potential benefit of Ritonavirin boosting Saquinavir, described by Martin Markowitz from the Aaron Diamond AIDS Research Centre, New York, NY. This group of observations converged to initiate a decade of progress against an important disease that is truly extraordinary in terms of the intensity of the effort and the progress achieved. Together, they constituted what is often considered to be the beginning of the HAART era (Lima *et al.,* 2009).

NEED OF BRAIN TARGETED DELIVERY SYSTEMS FOR ANTI-HIV DRUGS

HAART regimens have proven to reduce the amount of active virus and in some cases can lower the number of active virus until it is undetectable by current blood testing techniques. HAART does not completely eliminate HIV from the body, meaning that if treatment is stopped, residual virus present in several potential reservoirs rapidly expands allowing disease progression to continue. These treatments do not cure people of HIV or AIDS. Rather, they suppress the virus, even to undetectable levels, but they do not completely eliminate HIV from the body. By suppressing the amount of virus in the body, people infected with HIV can now live longer and healthier lives. However, they can still transmit the virus and must continuously take antiretroviral drugs in order to maintain their health quality (Kahn *et al.,* 2002). However, HAART is not free of concerns, complications, or challenges. Major concerns and challenges are (Kulkosky *et al.,* 2003):

1. Emerging virus in patients not adherent to therapy.
2. Formation of new mutant viral strains that develop resistance to HAART.
3. Inability of HAART to eradicate HIV-1 from patients despite prolonged administration.
4. Serious side effects from HAART usage over time.

There may be two reasons behind the failure of HIV eradication by HAAR Therapy:

1. HIV-1 persists in reservoirs (Finzi *et al.,* 1997).
2. Ongoing virus production even in patients on HAART in whom viremia is suppressed to undetectable levels (Persaud *et al.,* 2000).

HIV viral reservoir is defined as a cell type or anatomical site in association with which a replication-competent form of the virus accumulates and persists with more stable kinetic properties than in the main pool of actively replicating virus. HIV persists in cellular and anatomical reservoirs during Highly Active Antiretroviral Therapy (HAART). HIV-1 replicates extraordinarily rapidly in infected persons, with a virion half-life in plasma of 28–110 minutes. The HIV reservoir is established during primary infection (Blankson *et al.,* 2002). Administration of HAART in very early acute infection seems to result in a low post-treatment total, and integrated DNA and HIV-RNA concentrations, suggesting that aggressive treatment can decrease the size of the viral reservoir (Katlama *et al.,* 2013).Though early treatment can substantially reduce the size of the total reservoir, a stable population of latently infected CD4+ cells transits into the long-lived latent reservoir, and is unaffected by early combination ART (Chun *et al.,* 2007).Most HIV pro-viral DNA is detected in CD4+ T lymphocytes in lymphoid tissue. In blood, most HIV DNA is found in central memory and transitional memory T cells, which maintain the reservoir because of their intrinsic capacity to persist through homoeostatic proliferation and renewal. Other cellular reservoirs that might exist include naive CD4+ T cells, monocytes and macrophages, astrocytes, and microglial cells. Chronic production of HIV from a stable reservoir of long-lived infected cells is probably the main source of this persistent HIV. However, persistent low-level replication could also play a part, especially in tissues in which continuing persistent viral replication, despite ART, might be caused by cell-to-cell spread and insufficient drug penetrance in tissues (Archin *et al.,* 2012). Hence the brain targeted drug delivery systems are warranted:

To eradicate HIV hidden inside brain

Brain also acts as an anatomical reservoir for HIV along with some other compartments of the body like the lymphoid organs such as the spleen, lymph nodes and gut-associated lymphoid tissue (GALT) (Dahla *et al.,* 2010). HIV is known to invade the central nervous system (CNS) early in the course of the infection and primarily targets brain mononuclear macrophages, perivascular macrophages and microglia. The virus can enter the CNS compartment from the systemic circulation either through the blood-cerebrospinal fluid barrier (BCSFB) at the choroid plexus as cell-free viral particles, or through the BBB in form of infected monocytes. The later one is also known as the "Trojan horse approach". In brief, monocytes infected by HIV-1 are able to cross the BBB between the capillary endothelial cells in a complex process regulated by the secretion of chemokines from glial cells

(Wong *et al.,* 2010). In the CNS HIV can infect four types of macrophages: perivascular macrophages, meningeal macrophages, macrophages of the choroid-plexus, and microglia (Williams *et al.,* 2002). Also astrocytes can be infected even though it remains unclear if a productive infection can be established in vivo in this cell type. In untreated patients there are signs of "compartmentalization" in CSF and plasma, suggesting independently replicating viral populations. Under HAART however, patients with <50 copies/ml in plasma have <50 copies/ml in CSF. It remains unclear if cells from CNS can serve as reservoir or maintain viral infection during HAART (Harrington *et al.,* 2009). There may be several reasons for the comfortable thriving of HIV inside the blood brain, which includes poor bioavailability of anti-HIV drugs, poor availability of anti-HIV drugs inside the brain due to selective and restricted permeation of exogenous materials through the BBB, and presence of efflux mechanisms in BBB.

The mechanisms involve in the passage of drugs across the BCSFB and BBB via passive diffusion and carrier-mediated transport. Transport of anti-HIV drugs across the BCSFB and BBB has been found asymmetric, being efflux greater than influx. It has been found that efflux of AZT is five times greater than the influx for the BBB and three times larger for BCSFB in rabbits (Li *et al.,* 1999). ATP-Binding Cassette (ABC) efflux transporter, P-glycoprotein (P-gp) has been demonstrated as a key element of the BBB that can actively transport a huge variety of anti-HIV and other drugs out of the brain capillary endothelial cells that form the BBB. Along with the ABC efflux transporter P-gp, the multidrug resistance protein (MRP) family is also responsible for the efflux of anti-HIV drugs (Loscher *et al.,* 2005).

To eliminate HIV-associated neurological disorders

When the epidemic of HIV started, severe neurocognitive conditions in HIV-infected individuals were reported, usually which resulted to death of those individuals. These central nervous system (CNS) conditions were initially identified in persons with advanced HIV-1 infection and were named as "HIV-Associated Dementia" (Snider *et al.,* 1983; Antinori *et al.,* 2007; Navia *et al.,* 1986). Histo-pathological abnormalities in the brains of patients with HIV-Associated Dementia include disseminated foci of activated microglia, perivascular macrophage infiltration, multi-nucleated giant cells, and reactive astrogliosis (Pumarola-Sune *et al.,* 1987). Later investigations revealed that milder forms of neurocognitive impairment could be detected in HIV-1-infected persons before the onset of advanced systemic disease (Grant *et al.,* 1987).

Though after the introduction of HAART, the incidence of HIV-Associated Dementia declined dramatically (Bhaskaran *et al.,* 2008), but milder forms of HIV-associated neurological disorders became highly prevalent, identified inup to 50% of HIV-infected individuals (Heaton *et al.,* 2010). The increased occurrence of mild neurological impairments led to a new disease nosology called "HIV-Associated Neurocognitive Disorders" (HAND).HAART-treated patients with HAND differ from non-treated patients in many ways. In their cerebrospinal fluid, they are less likely to have detectable HIV-1 RNA or have high levels of certain inflammatory biomarkers (McArthur *et al.,* 2004), and at autopsy, they are less likely to manifest florid neuro-pathological changes (Cherner *et al.,* 2002; Everall *et al.,* 2009). These observations have led to a re-evaluation of the pathogenic mechanisms of HAND, including interest in persistent CNS inflammation, persistent viral reservoirs, and neurotoxicity, all of which are associated with the roles of activated macrophages during long-term HIV infection. In part, this is due to poor drug penetration of some regimens (Letendre *et al.,* 2008). However, the preference ofHIV-1 to reside in CNS macrophages and microglia, which harbour a large reservoir of provirus and unintegrated DNA that is unaffected by HAART, is also a likely factor (Zhao *et al.,* 2009).

Thus, progressive neuronal loss/dysfunction and CNS inflammation can be measured even in well-suppressed patients on long-term therapy (Harezlak *et al.,* 2011; Lamersa *et al.,* 2014).

CHALLENGES OF BRAIN TARGETING OF DRUGS

From the stain studies of Paul Ehrlich (1854-1915), it became clear that brain is physiologically different from other parts of the body when intravenously injected dye distribution is considered. He saw that aniline dyes rapidly distributed to whole body after I.V. injection, except the brain. Later studied on brain, revealed that the brain is protected by the BBB from extraneous substances (Bicker *et al.,* 2014). There are two physiological barriers separating the brain from its blood supply controlling the transport of compounds. One is the BBB and the other is the blood–cerebrospinal fluid barrier (BCSFB).

The blood brain barrier (BBB)

Physiologically BBB is made up of three layers such as inner endothelial cell layer which forms the wall of the capillary and contains tight junctions followed by presence of basement membrane upon which Pericytes and astrocytic feet processes lies. Dueto the presence of such tight junctions between endothelial cells a very high electrical resistance of around 1500–2000Ωcm^2 results as compared to 3.33Ωcm^2 in other body tissue proving the barrier function of BBB. Astrocytes and Pericytes helps in differentiation as well as maintenance of BBB function. Astrocytes are most abundant non-neuron cells and play many essential roles in the healthy central nervous system (CNS), including biochemical support of endothelial cells which form the BBB, regulation of blood flow, provision of nutrients to the nervous tissue, maintenance of extracellular ion balance, and a principal role in the repair and scarring process of the brain and spinal cord following traumatic injuries. Pericytes are perivascular cells which are important for the maturation, remodeling and maintenance of the vascular system via the secretion of growth factors or modulation of the extracellular matrix. They are also involved in the transport across the BBB and the regulation of vascular permeability (Doolittle *et al.,* 2014).

The blood–cerebrospinal fluid barrier (BCSFB)

This is another barrier (after BBB) that a systemically administered drug encounters before entering the CNS. It functions together with the BBB and the meninges, to control the internal environment of the brain. It is sited at the choroid plexus epithelium, secretes CSF, which circulates through the ventricles and around the outside of the brain and spinal cord(Bock *et al.,* 2013).

Efflux mechanism of the barriers

Greater CNS efflux than influx has been demonstrated with certain anti-HIV suggesting the involvement of efflux transporters. Specific transporters are expressed on the endothelial cells of the BBB that transport many lipophilic drugs entering the brain back to the blood. A multitude of influx and efflux transporters from several families have been detected. These include the multi-drug resistant protein (MDR), multi-drug resistance-associated protein (MRP), system L-transporters(LAT), organic anion transporter (OAT), organic cation transporter (OCT), monocarboxylate transport system (MCT), concentrative nucleoside transporter (CNT), and equilibriative nucleoside transporter (ENT). The most important amongst these is the ATP-binding cassette transporter, P-gp. P-gp is an energy-dependant transporter, encoded by the MDR1 gene and is highly localized on the apical surface of the endothelial cells of the brain capillaries. The poor passage of these drugs, particularly the PIs across the BBB is mainly attributed to their P-gp mediated efflux. In humans, P-gp is also expressed on the kidneys, hepatocytes, testes and on intestinal cells. P-gp expressed in intestinal cells is responsible for reduced oral bioavailability of PIs (Loscher *et al.,* 2005).Hence, to develop a successful drug delivery system to deliver drugs to the brain one has to consider two aspects, the BBB as well as the efflux mechanism.

BRAIN DRUG DELIVERY STRATEGIES

From ancient times, doctors tried to deliver therapeutic agents to the brain to treat different ailments of CNS. Though all those techniques are not frequently used today, we are explaining all those techniques in very brief.

Invasive strategies for brain targeting

Disruption of the BBB

Osmotic Blood-Brain Barrier Disruption

Intra-carotid injection of an inert hypertonic solution such as mannitol or arabinose has been employed to initiate endothelial cell shrinkage and opening of BBB tight junctions for a period of a few hours, and this permits delivery of antineoplastic agents to the brain (Neuwelt *et al.,* 1979; Foley *et al.,* 2014).

Biochemical Blood-Brain Barrier Disruption

Selective opening of brain tumour capillaries can be achieved by the intra-carotid infusion of leukotriene C4 without concomitant alteration of the adjacent BBB. Normal brain capillaries appears to be unaffected when vasoactive leukotriene C4 treatments are used to increase their permeability. The mechanism was shown to be related to the abundance of g-Glutamyl trans-peptidase (g-GTP) in normal brain capillaries; this enzyme requires glial inductive influence for its expression, and it is down- regulated in tumours, resulting in a reduction of the enzymatic barrier in tumour endothelial cells (Stamatovic *et al.,* 2008; Russell *et al.,* 2014).

Intracerebral Implants

Drug added to polymer pellet implants intra-cranially, bypass the BBB and release drug molecules locally in the brain in a sustained fashion. The implants prepared with polymers like poly (bis (p-carboxyphenoxy)-propane:sebacic acid) copolymerto treat tumour can be administered directly to the affected area of the brain and release the drug in a sustained manner for a long period of time (Owen *et al.,* 1974; Björklund *et al.,* 1987; Grossman *et al.,* 1992).

Intra-ventricular/Intrathecal route

It includes intra-lumbar injection or intra-ventricular infusion of drugs directly into the CSF. Drugs can be infused intra-ventricularly using an Ommaya reservoir, a plastic reservoir implanted subcutaneously in the scalp and connected to the ventricles within the brain via an outlet catheter. Drug solutions can be subcutaneously injected into the implanted reservoir and delivered to the ventricles by manual compression of the reservoir through the scalp (Karaiskos *et al.,* 2013).

Injections, Catheters and Pumps

Several implantable pumps have been developed that possess several advantages over the Ommaya reservoir. This can be implanted subcutaneously and refilled by subcutaneous injection and are capable of delivering drugs as a constant infusion over an extended period of time. Furthermore, the rate of drug delivery can be varied using external handheld computer control units (Johnstone *et al.,* 2013). Currently, three different pumps are available for interstitial CNS drug delivery each operated by a distinct mechanism.

i. InfusAID pump uses the vapour pressure of compressed Freon to deliver a drug solution at a constant rate (Vallande *et al.,* 1993).
ii. MiniMed PIMS system uses a solenoid pumping mechanism (Wang *et al.,* 2002).
iii. Medtronic SynchroMed system delivers drugs via a peristaltic mechanism (Turner, 2010).

Non-invasive strategies

Biological delivery

BBB Carrier-Mediated Transport

These are naturally present carrier systems of the BBB, which selectively carries molecules through the barrier. If the BBB CMT systems are to be exploited to overcome the BBB drug-delivery problem, the drug must be reformulated such that the

drug assumes a molecular structure mimicking that of the endogenous ligand (Smith, 2005).

Inhibition of BBB Active Efflux Transport

P-glycoprotein active drug efflux transporter is present at high densities in the luminal membranes of brain endothelium. It pumps out some cytotoxic agents used to treat brain tumours and excludes them from the brain. P-glycoprotein inhibitors enhance the effects of cytotoxic agents and have the potential of enhancing chemotherapeutic effects on the brain (Löscher *et al.,* 2005).

BBB Receptor-Mediated Transport

Certain endogenous large-molecule neuropeptides such as insulin, transferrin, or leptin access the brain from blood via receptor-mediated transport (RMT) across the BBB. This transport is mediated by specialized ligand-specific receptor systems, including the insulin receptor (IR) or the transferrin receptor (TfR), which are highly expressed on the capillary endothelium of brain. Certain peptidomimetic monoclonal antibodies (MAbs) bind to exofacial epitopes on the BBB receptors. These epitopes are spatially separated from the endogenous ligand-binding site, and the binding of MAbs to the BBB receptor enables RMT of the peptidomimeticMAb across the BBB in vivo. These peptidomimeticMAbs may be used as "molecular Trojan horses" to ferry large-molecule drugs (e.g. Recombinant proteins, gene-based medicines) across the BBB (Manich *et al.,* 2013).

Physiological/physical strategies

Ligand Binding Protein

Protein ligands possess various properties like high affinity to receptor and selectivity for targeting, which increase the interest towards the use of protein as a delivery tool for targeting the drug to the brain. Various system have been developed that incorporate protein as the central ligand binding component such as lectin used as a ligand binding protein for brain targeting of glucose triggered glycosylated insulin and by specific antibodies. Other ligand binding protein classes include biotin binding protein. Lipid binding protein and avidin binding proteins. Cationized albumin appears to be useful for the delivery of the active agents across the BBB to the brain (Zádor *et al.,* 2014).

Chimeric Peptide

A new strategy for peptide delivery through the brain capillary wall, i.e., the blood-brain barrier (BBB), is the synthesis of chimeric peptides which are formed by the covalent coupling of a non-transportable peptide (e.g., β-endorphin) to a transportable peptide that undergoes receptor or absorptive-mediated trans-cytosis at the BBB (Pardridge *et al.,* 1987).

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. 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 bio-removable moieties are introduced to convert the drug into an inactive precursor form. A targetor (T) moiety is responsible for targeting, site-specificity, and lock-in, while modifier functions serve as lipophilizers, protect certain functions, or fine-tune the necessary molecular properties to prevent premature, unwanted metabolic conversions (Ţînţaş *et al.,* 2014).

Pharmacological strategies

Liposomes

Nano-particulate systems for brain delivery of drugs (Nanotechnology)

- Coated nanoparticles
- Pegylated nanoparticles
- Solid Lipid Nanoparticles (SLN)
- Nano gels

Nano-conjugates: These are low molecular weight conjugates of a small drug or toxin and a targeting ligand coupled through a cleavable linker group which is consisted of three functional domains, the targeting group, a linker, and an active agent/ drug. Typically Nano-conjugates have a molecular weight similar to that of standard cytotoxic drugs.

New techniques

Trojan horses approach in drug delivery to brain

Attaching an active drug molecule to a vector that accesses a specific catalyzed transporter mechanism creates a Trojan horse-like deception that tricks the blood-brain barrier into welcoming the drug through its gates. Transport vectors, such as endogenous peptides, modified proteins, or peptidomimetic monoclonal antibodies are a way of tricking the brain into allowing these molecules to pass. The therapeutic peptide or protein drug is fused to a molecular Trojan horse, which may be a monoclonal antibody that binds to a specific receptor on the blood-brain barrier and enables receptor-mediated delivery of the fusion protein across the barrier to exert the desired pharmacological effect on the brain. The Trojan horse approach has been applied to delivery of non-viral gene and RNAi therapeutics, particularly in experimental models of Parkinson disease and brain tumours (Pardridge 2006).

Intranasal drug delivery technique

The olfactory nerve is the target when direct absorption into the brain is the goal because it is the only site in the human body where the CNS is directly expressed on the nasal mucosal surface. Though the traditional blood-brain barrier is not present at

the interface between nasal epithelium and brain, P-glycoprotein and other barrier transporters are present at this interface, which can be modulated with nasal administration of appropriate inhibitors. Nasal administration of 2 prodrugs (L-dopa butyl esters) has been reported to result in higher CSF levels of L-dopa than those observed after intravenous administration. The percentage of the applied dose that passes to the brain and CSF is about 2% to 3%. This indicates that a nasal route may be a viable method for the delivery of peptides, analgesics, and other drugs for the treatment of CNS disorders (Serralheiro *et al.*, 2014).

Targeting the brain with sound waves

Low-frequency, MRI-guided, focused ultrasound has been shown to induce localized and reversible disruption of the blood-brain barrier without undesired long-term effects in experimental animals. A frequency range of approximately 260 kHz enables the passage of ultrasound through the skull and produced focal disruption of blood-brain barrier without extravasation of red blood cells. The exact mechanism is not known, but ultrasound-induced micro-bubbles may temporarily expand the capillary wall and open the tight junctions. This non-invasive technique offers a potential method for targeted drug delivery in the brain aided by a relatively simple low-frequency device (Aryal *et al.*, 2014).

Cell and gene targeting systems

Brain drug targeting technology is based on the application of four gene technologies that enable the delivery of drugs or genes across the blood-brain barrier (BBB) *in vivo*.

i. Genetic engineering is used to produce humanized monoclonal antibodies that target endogenous BBB transporters and act as vectors for delivery of drugs or genes to the human brain. The conjugate of a neuro-therapeutic and a BBB transport vector is called a chimeric peptide. Epidermal growth factor chimeric peptides have been used for neuroimaging of brain cancer. Brain-derived neutrophic factor chimeric peptides have marked neuro-protective effects in brain stroke models.

ii. Imaging gene expression in the brain in vivo is possible with sequence-specific antisense radiopharmaceuticals, which are conjugated to BBB drug targeting vectors.

iii. Brain gene targeting technology enables widespread expression of an exogenous gene throughout the central nervous system following an intravenous injection of a non-viral therapeutic gene.

A. A BBB genomics program enables the future discovery of novel transport systems expressed at the BBB. These transporters may be carrier-mediated transport systems, active efflux transporters, or receptor-mediated trans-cytosis systems. The future discovery of novel BBB transport systems and the application of brain drug targeting technology will enable the delivery to the brain of virtually any neuro-therapeutic, including small molecules, large molecules and gene medicines (Yao *et al.*, 2015).

TECHNIQUES APPLIED FOR BRAIN TARGETING OF ANTI-HIV DRUGS

Ineffectiveness of existing therapies in the delivery of anti-HIV drugs to the CNS, aggressive research has been directed towards the development of new strategies for effective delivery of drugs to the brain for the treatment of the CNS infection of HIV. These strategies includes modifying the drug, disrupting the BBB, or by developing novel drug delivery systems. In this review we will focus only on the novel CNS drug delivery techniques.

Pro-drug and conjugate strategies

Pro-drugs are those drugs that are activated by undergoing transformation in vivo to form the active drug. Modification of drugs for brain targeting includes chemically modifying the functional groups of drugs to make them more lipophilic. Pro-drugs are developed for those drugs which are poorly aqueous soluble, chemically instable, having low oral bioavailability, lack of BBB penetration, and high first pass metabolism. Most of the antiviral drugs developed so far suffer from one or more of the above-mentioned limitations (Palombo*etal*2009). Fosamprenavir (pro-drug of Amprenavir) and Tenofovir disoproxil fumarate are the two pro-drugs that have been developed for HIV therapy till date. Both Fosamprenavir and Tenofovir disoproxil fumarate improve the drug delivery capabilities of their parent drug by increasing intestinal absorption (Rao *et al.*, 2009). Though no anti-HIV drugs has not been developed for brain targeting with this approach so far, research done with other category of drug has proven the efficiency of this technique (Rautio *et al.*, 2008).

Nano-carrier drug delivery strategies

Because of their success in drug delivery to other parts of the body, nano-carrier systems such as polymeric nanoparticles, dendrimers, micelles, liposomes, SLNs, NLCs etc. have been under investigation for delivery of therapeutic agents to the CNS(Kreuter *et al.*, 2001). Some possible reasons of improved drug delivery by nanoparticles to the brain are;

- Increased retention of the nanoparticles in the brain blood capillaries combined with an adsorption to the capillary walls, leading to a higher concentration gradient that would increase the transport across the endothelial cell layer and as a result enhance the delivery to the brain.
- Surface modified nanoparticles with some coating agents (e.g. Polysorbate 80) are able to inhibit the efflux system.
- Surfactants used with nanoparticles can solubilize the endothelial cell membrane lipids that would lead to membrane fluidization as well as opening of the tight junctions between the endothelial cells which leads to an enhanced drug permeability across the BBB.

- Endocytosis of nanoparticles by the endothelial cells.
- Transcytosis through the endothelial cell layer.
- A combination of the above effects (Kreuter *et al.,* 2014;Gelperinaa *et al.,* 2010).

All of the above mentioned Nano-carrier systems have their own advantages and disadvantages. Each of them will be discussed in brief.

Polymeric Nanoparticles

Nanoparticles appeal to scientists across many disciplines of science due the opportunity to engineer many properties that might otherwise be incompatible on a single device. Nanoparticles are solid colloidal particles ranging in size from 10 to 1000 nm, usually containing no lipids as a major component material. Drug is dissolved, entrapped, encapsulated and/or to which the drug is adsorbed or attached. Nanoparticles may be prepared from different types of materials. Inorganic materials like silica, alumina, metals, metal oxides and metal sulphides have been used for the purpose. But, in drug delivery to CNS, polymeric nanoparticles are more prevalent. Most polymeric nanoparticles are prepared from biodegradable and biocompatible polymers, and have been adopted as a preferred method for nanomaterial drug delivery(Wong *et al.,* 2010). They also exhibit a good potential for surface modification via chemical and other types of transformations, provide excellent pharmacokinetic control, and are suitable for the entrapment and delivery of a wide range of therapeutic agents. Polymers used for nanoparticle preparation includes gelatine, chitosan, poly (lactic-co-glycolic acid) copolymer, polylactic acid, polyglycolic acid, poly (alkylcyanoacrylate), poly (methylmethacrylate), and poly (butyl) cyanoacrylate. Furthermore, polymer-based coatings may be functionalized onto other types of nanoparticles to change and improve their bio-distribution properties. The biologically inert polymer poly (ethylene glycol) (PEG) has been covalently linked onto the surface of nanoparticles (Kreuter *et al.,* 2001).

Different studies have been performed in laboratory with great success rates. Kuo and Chen investigated the effect of size of nano-scaled Polybutylcyanoacrylate (PBCA) and methylmethacrylate-sulfopropylmethacrylate (MMA-SPM) on the permeability of Zidovudine (AZT) and Lamivudine (3TC) across the blood brain barrier (BBB). They found that application of MMA-SPM NPs leads to about 100% increase in the BBB permeability of the two drugs (Kuo *et al.,* 2006). The also demonstrated the capability of CRM197-grafted polybutylcyanoacrylate (PBCA) nanoparticles (NPs) (CRM197/PBCA NPs) to carry Zidovudine (AZT) across the BBB (Kuo *et al.,* 2012). From these studies it becomes clear that polymeric nanoparticles have great potential to deliver anti-HIV drugs to brain.

Dendrimers

Dendrimers are a class of mono-disperse polymeric nanostructure (<100 nm) built around a core unit, distinguished by their repeated branching structure emanating from the central core. It has been used to carry anti-HIV drugs. Narrow molecular weight distribution, small size (less than 100 nm), and easy incorporation of targeting ligand are attractive features of dendrimers. Dendrons are formed after removal of core units and can be divided into core, the interior branching units and the periphery. The emptycore of dendron is utilized for the entrapment of drug molecules for solubilizing of poorly water soluble drugs, controlled release, targeting or protection from surrounding degrading environment. Dendrimers offer unique properties like uniform particle size, poly-valency of the end groups which helps in binding to diverse receptors and ability to bind a variety of targeting agents to the high density peripheral functional groups.

A group of researchers prepared G-5 PPI dendrimers to target Efavirenz (Dutta *et al.,* 2008) and Lamivudine (Dutta*etal* 2007) to human monocytes/macrophages and MT-2 cells, respectively. Studies done by Gajbhiye and his team revealed the potential of acid conjugated-mannosylated poly(propyleneimine) dendrimers to enhance biocompatibility and site specific delivery of antiretroviral drug, Zidovudine (Gajbhiye *et al.,* 2013).

Polymeric Micelles

Polymeric micelles are nanoscopic shell like structures which are prepared from amphiphilic block copolymers. Both the inherent and modifiable properties of polymeric micelles make them particularly well suited for drug delivery purposes. The advantages and applications of polymeric micelles includes, solubilizing poorly water soluble drugs, sustained release and size advantages, and protection of encapsulated substances from degradation and metabolism. The three most widely studied block copolymer classes are characterized by their hydrophobic blocks, and are poly(propylene oxide), poly(L-amino acid)s and poly(ester)s. The polymeric micelles used for drug delivery have shown the abilities to attenuate toxicities, enhance delivery to desired biological sites and improve the therapeutic efficacy of active pharmaceutical ingredients (Dhembre *et al.,* 2011). Batrakova and co-scientistsfound that micelles formed with Pluronic block copolymer ‘P85’ inhibits the P-gp drug efflux system and increases the permeability of a broad spectrum of drugs in the BBB. They performed the studies with different drugs; Ritonavir was one of them whose BBBpermeability was increased up to 19-fold (Batrakova *et al.,* 2003).

Liposomes

Liposomes are lipid vesicles consisting of either one or more phospholipid bilayers. They comprise of a polar core for encapsulation of hydrophilic drugs, while amphiphilic and lipophilic drugs are solubilized within the phospholipid bilayer. Liposomes are very rapidly removed from blood by the reticulo-endothelial system leading to lower plasma circulation time. Hence, liposomes need to be surface modified with polymers such as hydrophilic poly ethylene glycol to enhance their blood circulation time or by conjugating them to specific antibodies in order to improve their CNS targeting potential. Dusserre and co-

scientists found that encapsulation of Foscarnet, a drug used to treat highly treatment-experienced patients with HIV as part of salvage therapy, within liposomes resulted in a thirteen fold increase in drug accumulation within the rat brains as compared to pure drug in solution (Dusserre *et al.,* 1995). A few liposomal systems have been formulated to treat the cerebral ischemia by Citicholine, brain tumours by Cisplatin, and epilepsy by Phenytoin. Overall, significant improvement in brain drug levels were observed in these studies (Fresta *et al.,* 1994; Anda *et al.,* 1995). Some other liposomal formulations of the anti-HIV drugs also have been formulated, but they are not primarily for CNS target purposes.

SLNs

SLN are a relatively new class of lipid-based nano-carriers. They are prepared using solid lipids (i.e., lipids that are solid at room temperature as well as at body temperature). Theses lipids are biocompatible and biodegradable with GRAS (Generally Recognized as Safe) status (Almeida *et al.,* 2007). SLNs are beneficial in many aspects (Kaur *et al.,* 2008; Allen *et al.,* 2004) such as

- High drug payload as compared to polymeric nanoparticles
- The feasibility of incorporating both hydrophilic and hydrophobic drugs
- Use of organic solvent scan be avoided in the production of SLNs
- Degradation of environment sensitive molecules can be prevented by their incorporation in the lipid matrix
- Sustained drug release formulation can be obtained
- Possess negligible toxicity
- Bioavailability of highly lipophilic molecules can be increased via lymphatic uptake
- Penetration through skin or mucus barrier is possible due to very small size
- Feasible large scale production and sterilization.

Though SLNs have so many advantages, it itself have some stability issues too. In general, drug molecules stay in between the fatty acid chains or as amorphous clusters in crystal imperfections within SLN matrix. But, when lipid transform to low-energetic form, it form a perfect crystalline lattice that allows very small space for the drug molecules. Therefore, expulsion of encapsulated drug molecules may be observed during storage, especially when SLN matrix is composed of a highly purified lipid, which leads to limited drug-loading capacity of SLNs (Blasi *et al.,* 2007).

Smaller size, capability to bind with different ligands, high lipophilicity, lower toxicity are the desirable characters which makes SLNs good choice for brain targeted drug carrier system. Various studies has been done with this aim ahead and almost all of them have been so far successful. Although, anti-HIV drugs has not been studied widely, but other classes of drugs has shown promising results. Chattopadhyay and his team developed and evaluated a lipid nanoparticle system for enhanced brain delivery of Atazanavir, using a well characterized human brain micro vessel endothelial cell line (hCMEC/D3) representative of the blood-brain barrier. They found that delivery of Atazanavir by SLNs led to a significantly higher accumulation by the endothelial cell monolayer as compared to the drug aqueous solution. From the findings they suggested that SLNs could be a promising drug delivery system to enhance brain uptake of Atazanavir and potentially other PIs (Chattopadhyay *et al.,*2008). Singh and co-scientists developed solid lipid nanoparticles (SLN) of Zidovudine and investigated with stearic acid by w/o/w double-emulsion solvent-evaporation method using 32 factorial design. They used different triglycerides alone and in different combinations, with/without stearic acid to prepare SLN using similar procedure. They reported that fatty acids are more advantageous over triglycerides in the entrapment of hydrophilic drugs in SLN (Singh *et al.,* 2010). In 2012, Sankar and his team investigated the specific drug targeting of lamivudine and Zidovudine, after intra-peritoneal injection by incorporation intopolymeric nanoparticles (PNs) and solid lipid nanoparticles (SLNs). Their results showed that Glyceryl Monosterate-Poloxamer 188 SLNs shows higher concentration of drugs in RES organs than PLGA-P 188 PNs (Sankar *et al.,* 2012).

Brain targeted SLNs have been prepared with different drugs like Vinpocetine, Camptothecin, Clotrimazole etc. with improved brain delivery (Morsi *et al.,* 2013; Martins *et al.,* 2013).

NLCs

Nanostructured lipid carriers (NLC) were designed to overcome some of the drawbacks of SLN such as the limited drug payload, expulsion of loaded drug molecules etc. Studies done in 2012 by Das and his co-worker have clearly shown that NLCs are much more stable than SLNs (Das *et al.,* 2012). When SLNs primarily contains single lipid, NLCs are formulated with a mixture of solid lipid and liquid lipid, but particles are in solid state at body temperature and are in particular appropriate for drugs with higher solubility in oils than in solid lipids. A blend of a liquid and solid lipid creates a less perfect crystalline structure with many imperfections providing thus more space for drug accommodation. Lipids those are not soluble in room temperature as well as in body temperature are used as the solid lipid component. Examples of solid lipids are triglycerides (tristearine, tripalmitine, trimiristine), fatty acids (stearic acid, palmitic acid), waxes (carnauba, cetylpalmitate) etc. Lipids, which are liquid in room temperature are usedas the liquid lipids. Examples include medium chain triglycerides, oleic acid, isopropylmiristate etc. (Doktorovováa *et al.,* 2010). NLCs are suitable colloidal carrier systems to control the penetration/ permeation of drugs throughout the membranes of body. Depending on the lipid matrix composition, different release profiles may be obtained including a prolonged/ controlled release of the drug which can decrease the risk of burst effect, commonly reported by the use of conventional drug solutions (Hu *et al.,* 2006).

Joshy and his team developed and evaluated NLCs for enhanced brain delivery of Zidovudine using a well characterized human brain cell line representative of the BBB. They found that delivery of Zidovudine by NLCs led to a significantly higher accumulation by the brain cells. From their findings they suggested that NLCs could be a promising drug delivery system to enhance brain uptake of Zidovudine and potentially other non-nucleotide class of anti-retroviral drugs (Joshy *et al.*, 2012).

As NLCs are new in drug delivery research, currently lots of work is going on to take advantage of its extreme versatility. Different classes of drugs has been formulated withNLCs. For example Lamotrigine NLCs for brain delivery, Baicalein loaded in to NLCs for enhanced stability and brain targeting etc. (Alam *et al.*, 2014; Tsai *et al.*, 2012).

CONCLUSION

There is no doubt that HIV/AIDS is the deadliest disease till date. HAART has brought new hope to the affected people of this disease. Finding the way to eliminate viral reservoirs is the greatest challenge in front of humankind. Nanotechnology has the ability to fight the challenges against HIV. Newer techniques like SLNs and NLCs are having great potential in the brain delivery of anti-HIV drugs. Extensive study of SLN and NLCs with anti-HIV drug is the most required now. Though some studies already has been done and positive results also has been found, yet they are not quite enough. Formulation of cost effective, non-toxic, patient compliant NLCs which can eliminate the virus in reservoirs is the need of the time.

REFERENCES

Clercq ED. Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. International Journal of Antimicrobial Agents 2009; 33(4): 307–320.

NevesJD, Amiji MM, Bahia MF, Sarmento B. Nanotechnology-based systems for the treatment and prevention of HIV/AIDS. Advanced Drug Delivery Reviews 2010; 62(4-5): 458–477.

Gupta U, Jain NK. Non-polymeric nano-carriers in HIV/AIDS drug delivery and targeting. Advanced Drug Delivery Reviews 2010; 62(4-5): 478–490.

Dalgliesh AG, Beverley PCL, Clapman PR, Crawford DH, Greaves MF, Weiss RA. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature 1984; 312(5996):767–768.

Kolchinsky P, Kiprilov E, Sodroski J. Increased neutralization sensitivity of CD4-independent human immunodeficiency virus variants. Journal of Virology 2001; 75(5):2041–2050.

Martin J, LaBranche CC, Scarano FG. Differential CD4/CCR5 utilization, gp120 conformation, and neutralization sensitivity between envelopes from amicroglia-adapted human immunodeficiency virus type 1 and its parental isolate. Journal of Virology 2001; 75(8):3568–3580.

Ghate M, Deshpande S, Tripathy S, Nene M, Gedam P, Godbole S, Thakar M, Risbud A, Bollinger R, Mehendale S. Incidence of common opportunistic infections in HIV-infected individuals in Pune, India: analysis by stages of immunosuppression represented by CD4 counts. International Journal of Infectious Diseases 2009; 13(1):e8.

Fauci AS. 25 Years of HIV/AIDS Science: Reaching the Poor with Research Advances. Cell 2007; 131(3):429-432.

Chiappini E, Berti E, Gianesin K, Petrara MR, Galli L, Giaquinto C, Martino MD, Rossi AD. Pediatric Human Immunodeficiency Virus infection and cancer in the Highly Active Antiretroviral Treatment (HAART) era. Cancer Letters 2014;347(1):38-45.

Oliveira NM, Ferreira FAY, Yonamine RY, Chehter EZ. Antiretroviral drugs and acute pancreatitis in HIV/AIDS patients: is there any association? A literature review. Einstein 2014; 12(1):112-119.

Lima DV, Harrigan R, BangsbergDR,Hogg RS, Gross R, Yip B, Montaner JSG. The Combined Effect of Modern Highly Active Antiretroviral Therapy Regimens and Adherence on Mortality over Time. Journal of Acquired Immune Deficiency Syndromes 2009; 50(5): 529–536.

Kulkosky J, Sullivan J, Xu Y, Markham AM, Otero M, Calarota S, Zielinski J, Culnan DM, Pomerantz RJ. Genotypic alteration of HAART-persistent HIV-1 reservoirs in vivo. Virology 2003; 314(2):617–629.

Finzi D, Hermankova M, Pierson T, Carruth LM, Buck C, Chaisson RE, Quinn TC, Chadwick K, Margolick J, Brookmeyer R, Gallant J, Markowitz M, Richman DD,Siliciano RF. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science 1997; 278(5341):1295–1300.

Persaud D, Pierson T, Ruff C. A stable latent reservoir for HIV-1 in resting CD4C T lymphocytes in infected children. Journal of Clinical Investigation 2000; 105(7):995– 1003.

Blankson NJ, Persaud D, Siliciano RF. The Challenge of Viral Reservoirs in Hiv-1 Infection. Annual Review of Medicine 2002; 53:557–593.

Katlama C, Deeks SG, Autran B, Picado JM, Lunzen JV, Rouzioux C, Miller M, Vella S, Schmitz JE, Ahlers JR, Richman DD, Sekaly RP. Barriers to a cure for HIV: new ways to target and eradicateHIV-1 reservoirs. Lancet 2013; 381(9883): 2109–2117.

Chun TW, Justement JS, Moir S, Hallahan CW, Maenza J, Mullins JI, Collier AC, Corey L, Fauci AS. Decay of the HIV reservoir in patients receiving antiretroviral therapy for extended periods: implications for eradication of virus. Journal of Infectious Diseases 2007; 195(12): 1762–64.

Archin NM, Vaidya NK, Kuruc JD, Liberty AL, Wiegand A, Kearney MF, Cohen MS, Coffin JM, Bosch RJ, Gay CL, Eron JJ, Margolis DM, Perelson AS.. Immediate antiviral therapy appears to restrict resting CD4+ cell HIV-1 infection without accelerating the decay of latent infection. Proceedings of the National Academy of Sciences of the United States of America 2012; 109(24): 9523–28.

Dahla V, Josefssona L, Palmer S. HIV reservoirs, latency, and reactivation: Prospects for eradication. Antiviral Research 2010; 85(1):286–294.

Wong HL, Chattopadhyay N, Wu XT, Bendayan R. Nanotechnology applications for improved delivery of antiretroviral drugs to the brain. Advanced Drug Delivery Reviews 2010; 62(4-5):503–517.

Williams KC, Hickey WF. Central nervous system damage, monocytes and macrophages, and neurological disorders in AIDS. Annual Review of Neuroscience 2002. 25:537–562.

Harrington PR, Schnell G, Letendre SL, Ritola K, Robertson K, Hall C, BurchCL, Jabara CB, Moore DT, Ellis RJ, Price RW, Swanstrom R. Cross-sectional characterization of HIV-1 env compartmentalization in cerebrospinal fluid over the full disease course. AIDS 2009; 23(8):907–915.

Li X, Chan WK. Transport, metabolism and elimination mechanisms of anti-HIV agents. Advanced Drug Delivery Reviews 1999; 39(1-3):81–103.

Loscher W, Potschka H. Blood-Brain Barrier Active Efflux Transporters: ATP-Binding Cassette Gene Family. The Journal of the American Society for Experimental NeuroTherapeutics 2005; 2(1): 86–98.

Snider WD, Simpson DM, Nielsen S, Gold JW, Metroka CE, Posner JB. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. Annals of Neurology 1983; 14(4):403–418.

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robert-son KR, Sacktor N, Valcour V, Wojna

VE. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007; 69(18):1789–1799.

Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. Annals of Neurology 1986; 19(6):517–524.

Pumarola-Sune T, Navia BA, Cordon-Cardo C, Cho ES, Price RW. HIV antigen in the brains of patients with the AIDS dementia complex. Annals of Neurology 1987; 21(5):490–496.32.

Grant I, Atkinson JH, Hesselink JR, Kennedy CJ, Richman DD, Spec-tor SA, McCutchan JA. Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. Studies with neuro psychologic testing and magnetic resonance imaging. Annals of Internal Medicine 1987; 107(6): 828–836.

Bhaskaran K, Mussini C, Antinori A, Walker AS, Dorrucci M, Sabin C, Phillips A, Porter K. Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. Annals of Neurology 2008; 63(2):213–221.

Heaton RK, Clifford DB, Franklin Jr. DR, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 2010; 75(23): 2087–2096.

McArthur JC, McDermott MP, McClernon D, Hillaire C, Conant K, Marder K, Schifitto G, Selnes OA, Sacktor N, Stern Y, Albert SM, Kieburtz K, deMar-caida JA, Cohen B, Epstein LG. Attenuated central nervous system infection in advanced HIV/AIDS with combination antiretroviral therapy. Archives of neurology 2004; 61: 1687–1696.

Cherner M, Masliah E, Ellis RJ, Marcotte TD, Moore DJ, Grant I, Heaton RK. Neurocognitive dysfunction predicts postmortem findings of HIV encephalitis. Neurology 2002; 59(10):1563–1567.

Everall I, Vaida F, Khanlou N, Lazzaretto D, Achim C, Letendre S, Moore D, Ellis R, Cherner M, Gelman B, Morgello S, Singer E, Grant I, Masliah E. Cliniconeuropathologiccorrelates of human immunodeficiency virus in the era of antiretroviral therapy. Journal of NeuroVirology 2009; 15(5-6):360–370.

Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, Gel-man BB, McArthur JC, McCutchan JA, Morgello S, Simpson D, Grant I, Ellis RJ. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Archives of neurology 2008; 65(1):65–70.

Zhao L, Galligan DC, Lamers SL, Yu S, Shagrun L, Salemi M, McGrath MS. High level HIV-1 DNA concentrations in brain tissues differentiate patients with post-HAART AIDS dementia complex or cardiovascular disease from those with AIDS. Science in China Series C Life Sciences 2009; 52(7), 651–656.

Harezlak J, Buchthal S, Taylor M, Schifitto G, Zhong J, Daar E, Alger J, Singer E, Campbell T, Yiannoutsos C, Cohen R, Navia B. Persistence of HIV-associated cognitive impairment, inflammation, and neuronal injury in era of highly active antiretroviral treatment. AIDS 2011; 25(5):625–633.

Lamersa SL, Fogelb GB, Nolanc DJ, McGrathd MS, Salemic M. HIV-associated neuropathogenesis: A systems biology perspective for modelling and therapy. BioSystems 2014; 119(1):53–61.

Bicker J, Alves G, Fortuna A1, Falcão A. Blood-brain barrier models and their relevance for a successful development of CNS drug delivery systems: a review. European Journal of Pharmaceutics and Biopharmaceutics 2014; 87(3): 409-432.

Doolittle ND, Muldoon LL, Culp AY, Neuwelt EA. Delivery of Chemotherapeutics across the Blood–Brain Barrier: Challenges and Advances. Advances in Pharmacology 2014; 71:203-243.

Bock MD, Wang N, Decrock E, Bol M, Gadicherla AK, Culot M, Cecchelli R, Bultynck G, Leybaert L. Endothelial calcium dynamics, connexin channels and blood–brain barrier function. Progress in Neurobiology 2013; 108:1-20.

Neuwelt EA, Maravilla KR, Frenkel EP, Rapaport SI, Hill SA, Barnett PA. Osmotic blood-brain barrier disruption. Computerized tomographic monitoring of chemotherapeutic agent delivery. Journal of Clinical Investigation 1979; 64(2):684-688.

Foley CP, Rubin DG, Santillan A, Sondhi D, Dyke JP, Crystal RG, Pierre Gobin Y, Ballon DJ. Intra-arterial delivery of AAV vectors to the mouse brain after mannitol mediated blood brain barrier disruption. Journal of Controlled Release 2014; 196(28):71-78.

Stamatovic SM, Keep RF, Andjelkovic AV. Brain Endothelial Cell-Cell Junctions: How to “Open” the Blood Brain Barrier. Current Neuropharmacology 2008; 6(3): 179-192.

Russell KL, Berman NEJ, Gregg PRA, Levant B.Fish oil improves motor function, limits blood–brain barrier disruption, and reduces Mmp9 gene expression in a rat model of juvenile traumatic brain injury. Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA) 2014; 90(1):5-11.

Owen K, Wallace P, Thiessen D. Effects of intra-cerebral implants of steroid hormones on scent marking in the ovariectomized female gerbil (Merionesunguiculatus). Physiology &Behavior 1974; 12(5):755-760.

Björklund A, Lindvall O, Isacson O, Brundin P, Wictorin K, Strecker RE, Clarke DJ, Dunnett SB. Mechanisms of action of intracerebral neural implants: studies on nigral and striatal grafts to the lesioned striatum.Trends in Neurosciences 1987; 10(12):509-516.

Grossman SA, Reinhard C, Colvin OM, Chasin M, Brundrett R, Tamargo RJ, Brem H. The intracerebral distribution of BCNU delivered by surgically implanted biodegradable polymers. Journal of Neurosurgery 1992; 76(4): 640-647.

Karaiskos I, Galani L, Baziaka F, Giamarellou H. Intra-ventricular and intra-thecalcolistin as the last therapeutic resort for the treatment of multidrug-resistant and extensively drug-resistant Acinetobacterbaumanniiventriculitis and meningitis: a literature review. International Journal of Antimicrobial Agents 2013; 41(6):499-508.

Johnstone A, Fleming S, Guthrie A, Weston M. The use of central venous catheters for pump injection of intravenous contrast during CT examination. Are we safe? Clinical Radiology 2013; 68(1):S9-S10.

Vallande N, Hoover H, Gedrimas L, Hopkins C. Three cases of mrsa wound infections associated with chemotherapeutic infusaid pumps caused by nasal colonization of a healthcare worker. American Journal of Infection Control 1993; 21(2):82.

Wang PP, Frazier J, Brem H. Local drug delivery to the brain. Advanced Drug Delivery Reviews 2002; 54(7):987-1013.

Turner MS. Assessing Syndromes of Catheter Malfunction With SynchroMed Infusion Systems: The Value of Spiral Computed Tomography with Contrast Injection. PM&R 2010; 2(8):757-766.

Smith QR. Carrier-mediated transport to enhance drug delivery to brain. International Congress Series 2005; 1277:63-74.

Löscher W, Potschka H. Role of drug efflux transporters in the brain for drug disposition and treatment of brain diseases. Progress in Neurobiology 2005; 76(1):22-76.

Manich G, Cabezón I, Valle JD, Vilaregut JD, Camins A, Pallàs M, Pelegrí C, VilaplanaJ. Study of the transcytosis of an anti-transferrin receptor antibody with a Fab′ cargo across the blood–brain barrier in mice. European Journal of Pharmaceutical Sciences 2013; 49(4):556-564.

Zádor F, Kocsis D, Borsodi A, Benyhe S. Micromolar concentrations of rimonabant directly inhibits delta opioid receptor specific ligand binding and agonist-induced G-protein activity. Neurochemistry International 2014; 67:14-22.

Pardridge WM, Kumagai AK, Eisenberg JB. Chimeric peptides as a vehicle for peptide pharmaceutical delivery through the blood-brain barrier. Biochemical and Biophysical Research Communications 1987; 146(1):307-313.

Ţînţaş ML, Foucout L, Petit S, Oudeyer S, Gourand F, Barré L, Papamicaël C, LevacherV. New developments in redox chemical delivery systems by means of 1,4-dihydroquinoline-based targetor: Application to galantamine delivery to the brain. European Journal of Medicinal Chemistry 2014; 81(23):218-226.

Pardridge WM. Molecular Trojan horses for blood–brain barrier drug delivery. Current Opinion in Pharmacology 2006; 6(5):494-500.

Serralheiro A, Alves G, Fortuna A, Falcão A. Intranasal administration of carbamazepine to mice: A direct delivery pathway for brain targeting. European Journal of Pharmaceutical Sciences 2014; 60(18):32-39.

Aryal M, Arvanitis CD, Alexander PM, McDannold N. Ultrasound-mediated blood–brain barrier disruption for targeted drug delivery in the central nervous system. Advanced Drug Delivery Reviews 2014; 72(15):94-109.

Yao H, Wang K, Wang Y, Wang S, Li J, Lou J, Ye L, Yan X, Lu W, Huang R. Enhanced blood–brain barrier penetration and glioma therapy mediated by a new peptide modified gene delivery system. Biomaterials 2015; 37:345-352.

Palombo MS, Singh Y, Sinko PJ. Pro-drug and conjugate drug delivery strategies for improving HIV/AIDS therapy.Journal of Drug Delivery Science and Technology 2009; 19(1): 3–14.

Rao KS, Ghorpade A, Labhasetwar V. Targeting anti-HIV drugs to the CNS. Expert Opinion on Drug Delivery 2009; 6(8): 771–784.

Rautio J, Kumpulainen H, Heimbach T, Oliyai R, Oh D, Jarvinen T, Savolainen J. Prodrugs: design and clinical applications. Nature Reviews Drug Discovery 2008; 7(3):255–269.

Kreuter J. Drug delivery to the central nervous system by polymeric nanoparticles: What do we know? Advanced Drug Delivery Reviews 2014; 71:2–14.

Kreuter J. Nano particulate systems for brain delivery of drugs. Advanced Drug Delivery Reviews 2001; 47(1):65-81.

Gelperinaa S, Maksimenkoa O, Khalanskyb A, Vanchugovaa L, Shipuloa E, Abbasovac K, Berdievc R, Wohlfartd S, Chepurnovac N, Kreuter J. Drug delivery to the brain using surfactant-coated poly (lactide-co-glycolide) nanoparticles: Influence of the formulationparameters. European Journal of Pharmaceutics and Biopharmaceutics 2010; 74(2): 157-163.

Kuo YC, Chung CY. Transcytosis of CRM197-grafted polybutylcyanoacrylate nanoparticles for delivering Zidovudine across human brain-microvascular endothelial cells. Colloids and Surfaces B: Biointerfaces 2012; 91(1):242– 249.

Kuo YC, Chen HH. Effect of nanoparticulatepolybutyl cyanoacrylate and methylmethacrylate-sulfopropylmethacrylate on the permeability of Zidovudine and lamivudine across the in vitro blood-brain barrier. International Journal of Pharmaceutics 2006; 327(1-2):160-169.

Dutta T, Garg M, Jain NK, Targeting of efavirenz loaded tuftsin conjugated poly (propyleneimine) dendrimers to HIV infected macrophages in vitro. European Journal of Pharmaceutical Sciences 2008; 34(2-3):181–189.

Dutta T, Jain NK, Targeting potential and anti-HIV activity of lamivudine loaded mannosylated poly (propyleneimine) dendrimers.Biochimica et BiophysicaActa-General Subjects 2007; 1770(4):681–686.

Gajbhiye V,Ganesh N, Barve J, Jain NK. Synthesis, characterization and targeting potential of zidovudine loaded sialic acid conjugated-mannosylatedpoly (propyleneimine) dendrimers. European Journal of Pharmaceutical Sciences 2013; 48 (4-5):668–679.

Dhembre GN, Moon RS, Kshirsagar RV. A review on Polymeric Micellar Nanocarriers. International Journal of Pharma and Bio Sciences 2011; 2(2):109-116.

Batrakova EV, Li S, Alakhov VY, Miller DW, Kabanov AV. Optimal structure requirements for pluronic block copolymers in modifying P-glycoprotein drug effluxtransporter activity in bovine brain microvessel endothelial cells. The Journal of Pharmacology and Experimental Therapeutics 2003; 304(2):845-54.

Dusserre N, Lessard C, Paquette N, Perron S, Poulin L, Tremblay M, Beauchamp D, Désormeaux A, Bergeron MG. Encapsulation of foscarnet in liposomes modifies drug intracellular accumulation, in vitro anti-HIV-1 activity, tissue distribution and pharmacokinetics. AIDS 1995; 9(8):833-41.

Fresta M, Puglisi G, Giacomo CD, Russo A. Liposomes as in vivo carriers for Citicoline: effects on rat cerebral post-ischaemic reperfusion, Journal of Pharmacology and Pharmacotherapeutics 1994; 46(12):974–981.

Anda T, Yamashita H, Fujita H, Yoshiharu T, Shibata S. Basic experiment of BBB permeability of Cisplatin encapsulated in liposome by means of in vitro BBB, Drug Delivery System 1995; 10(6):425–430.

Almeida AJ, Souto E. Solid lipid nanoparticles as a drug delivery system for peptides and proteins.Advanced Drug Delivery Reviews 2007; 59(6):478–490.

Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. Journal of Controlled Release 2008; 127(2):97–109.

Allen TM, Martin FJ. Advantages of liposomal delivery systems for anthracyclines.Seminars in Oncology 2004; 31(6): 5-15.

Blasi P, Giovagnoli S, Schoubben A, Ricci M, Rossi C. Solid lipid nanoparticles for targeted brain drug delivery. Advanced Drug Delivery Reviews 2007; 59 (6):454–477.

Chattopadhyay N, Zastre J, Wong HL, Wu XY, Bendayan R.Solid lipid nanoparticles enhance the delivery of the HIV protease inhibitor, Atazanavir, by a human brain endothelial cell line.Pharmaceutical Research 2008; 25(10):2262-2271.

Singh S, Dobhal AK, Jain A, Pandit JK,Chakraborty S. Formulation and Evaluation of Solid Lipid Nanoparticles of a Water Soluble Drug: Zidovudine.Chemical and Pharmaceutical Bulletin 2010; 58(5):650—655.

Sankar V, Nareshkumar PN, Ajitkumar GN, Penmetsa SD, Hariharan S. Comparative studies of lamivudine-zidovudine nanoparticles for the selective uptake by macrophages. Current Drug Delivery 2012; 9(5):506-514.

Morsi NM, Ghorab DM, Badie HA. Brain targeted solid lipid nanoparticles for brain ischemia: preparation and in vitro characterization. Pharmaceutical Development and Technology 2013; 18(3):736–744.

Martins SM, Sarmento B, Nunes C, Lúcio M, Reis S, Ferreira DC. Brain targeting effect of Camptothecin-loaded solid lipid nanoparticles in rat after intravenous administration. European Journal of Pharmaceutics and Biopharmaceutics 2013; 85(3):488–502.

Das S, Ng WK, Tan RBH. Are nanostructured lipid carriers (NLCs) better than solid lipid nanoparticles (SLNs): Development, characterizations and comparative evaluations ofClotrimazole-loaded SLNs and NLCs? European Journal of Pharmaceutical Sciences 2012; 47(1):139–151.

Doktorovováa S, Araújob J, Garciab ML, Rakovsky´ E, Soutoa EB. Formulating fluticasone propionate in novel PEG-containing nanostructured lipid carriers (PEG-NLC). Colloids and Surfaces B: Biointerfaces 2010; 75(2):538–542.

Hu FQ, Jiang SP, Du YZ, Yuan H, Ye YQ, Zeng S. Preparation and characteristics of monostearin nanostructured lipid carriers. International Journal of Pharmaceutics 2006; 314(1):83–89.

Joshy KS, Sharma CP. Blood Compatible Nanostructured Lipid Carriers for the Enhanced Delivery of Azidothymidine to Brain. Advanced Science Letters 2012; 6(1): 47-55.

Alam T, Pandit J, Vohora D, Aqil M, Ali A, Sultana Y. Optimization of nanostructured lipid carriers of Lamotrigine for brain delivery: in vitro characterization and in vivo efficacy in epilepsy. Expert Opinion on Drug Delivery, 2014; 28:1-14.93.

Tsai MJ, Wu PC, Huang YB, Chang JS, Lin CL, Tsai YH, Fang JY. Baicalein loaded in tocol nanostructured lipid carriers (tocol NLCs) for enhanced stability and brain targeting. International Journal of Pharmaceutics 2012; 423(2):461-70.

How to cite this article:

Malay K Das, Tapas Chakraborty. Progress in Brain Delivery of Anti-Hiv Drugs. J App Pharm Sci, 2015; 5 (07): 154-164.