**ABSTRACT**

The brain is a delicate organ and nature has very efficiently protected it. Brain is protected by presence of two barrier systems BBB (Blood Brain Barrier) and BCSFB (Blood Cerebrospinal Fluid Barrier). Blood brain barrier (BBB) is one such barrier which separates but not isolates brain from all other body components. The decades of research in the development of drugs delivery for brain disease, crossing of BBB is a key obstacle. So the BBB is a life-saving supporting media that protect brain against the toxic substance that circulate in the blood stream, its existence is a severe limitation to the delivery of most of the drugs to the brain because they do not cross the BBB in sufficient amounts. Many serious CNS disorders of the brain such as Alzheimer disease, stroke/neuroprotection, brain and spinal cord injury, brain cancer, HIV infection of the brain, amyotrophic lateral sclerosis (ALS), Huntington disease and childhood inborn genetic errors affecting the brain, Parkinson disease and multiple sclerosis (MS), To reach the therapeutic drug level in the brain, a novel delivery system such as Nano particulate system as drug carriers with high loading capacity and small particle size, which bypass the Reticiule Endothelial System (RES), are considered as suitable delivery system.\(^1\) CNS Drug Delivery through Novel Carriers, Colloidal Drug Carriers, Polymeric Micelles and Micro emulsions, Solid lipid nanoparticles (SLN), liposomes. It is noteworthy that only liposomes and Nanoparticles have been largely exploited for brain drug delivery. Solid lipid nanoparticles (SLNs) which consist of spherical solid lipid nanoparticles in the nanometre range, which are dispersed in water or in aqueous surfactant solution may be a suitable option for drug delivery to the brain after considering the success of the nanoparticles to pass through the BBB and their limitations such as toxicity and stability. The SLNs has the potential to carry both lipophilic and hydrophilic drugs.\(^2\,3\,4\)

**Blood Brain Barrier (BBB)**

The term “blood brain barrier” was first coined in 1900 by Lewadowsky, while studying the limited penetration of potassium Ferrocyanate into the brain\(^5\). The BBB is complex and highly regulated and screens the biochemical, physicochemical and structural features of solutes resulting in passage of only selective molecules into the brain parenchyma\(^6\). The brain is shielded against potentially toxic substances by the presence of two barrier systems: the blood brain barrier (BBB) and the blood cerebrospinal fluid barrier (BCSFB)\(^6\) the structure of the BBB is subdivided into two components: the endothelial or capillary barrier and the ependymal barrier. The BBB is considered to be the major route for the uptake of serum ligands since its surface area is approximately 5000-fold greater than that of BCSFB. The BBB is formed by a complex cellular system of endothelial cells, astroglia, pericytes, perivascular macrophages and a basal lamina (Figure 1)\(^7\).

**Functions of Pericytes and Astrocytes in the brain**

Pericytes do release and synthesis of different components of basal membrane as extracellular matrix such as glucosaminoglycocan, collagen, etc. and regulation of blood flow. Astrocytes are the brain glad cells which are responsible for the homeostasis an ion regulation in the brain\(^8,9\).

**Factors Affecting Drug Transport across BBB**

Concentration gradient of drug/polymer, Molecular weight of the drug, Lipophilicity of the drug, Sequestration by other cells, Affinity for efflux proteins, Pathological status, Flexibility, conformation of drug/polymer, Molecular charge, Affinity for receptors or carriers, Cerebral blood flow, Systemic enzymatic stability, Metabolism by other tissues, Clearance rate of drug/polymer, Cellular enzymatic stability\(^10,11\).
Approaches for Drug Delivery to the Brain

- Invasive Approach: Disruption of the BBB, Osmotic disruption, MRI-guided focused ultrasound BBB disruption technique, Application of bradykinin-analogue, Intra- cerebro- ventricular (IVC) infusion, Convection-enhanced delivery (CED), Intra-cerebral injection or use of implants
- Non-invasive approach: I. Physiological approach: Transporter – mediated delivery, Receptor mediated transcytosis, Transferrin receptor, Insulin receptor, Chemical approach: Pro-drugs and Drug conjugates, II. Biological approach: Monoclonal /cationic antibodies conjugate, Receptor /vector mediated, Aprotinin/chimeric peptide as a carrier, III. Colloidal carrier systems: Vesicular systems- Liposomes, Niosomes, Nano carrier systems- Nanoparticles, Nano suspension, Lipid based drug delivery systems, Self-micro emulsifying/ Nano emulsifying drug delivery systems (SMEDDS/SNEDDS), Solid Lipid Nanoparticle’s (SLNs), Emulsions Macro/Micro/Multiple/Nano emulsions, IV. Miscellaneous technique: Intranasal delivery and Iontophoretic delivery. Colloidal carriers can easily enter the brain capillaries if, the surface of these colloids are modified in a proper way (i.e. by PEG or PS-80). These surface modified colloidal particles enhance entering across the BBB due to prolonged blood circulation, thus colloidal carriers may be helpful for the treatment of brain diseases, because they offer clinical benefits such as reduced drug dose, decreased side effects, increased drug viability, non-invasive routes of administration and improved quality of life to patient.

Solid Lipid Nanoparticles- A Colloidal Carrier

**Definition**
Solid lipid nanoparticle are tiny colloidal carriers composed of biocompatible or biodegradable lipid matrix that is solid at body temperature and exhibit size range in between 100-1000 nm. Lipids can either be highly purified triglycerides, complex glyceride mixtures or even waxes. In addition to the lipid and drug, it contains surfactants as stabilizers. The excipients are of accepted GRAS status, where a wide variety of substances can be used for formulating purposes. SLNs are solid lipid particles with 50-1000 nm in diameter, which are dispersed in solution of aqueous surfactant made up of solid core having hydrophobic nature and prepared of a monolayer of phospholipid coating. Solid core possesses drug dissolved or dispersed in lipid matrix. They have potential to carry lipophilic or hydrophilic drugs. The SLN are dispersed in an aqueous outer or water phase and stabilized by surfactants, e.g., Tween 80, sodium dodecyl sulphate (SDS), lecithin. Alternatively, they can be produced surfactant free using steric stabilizers (e.g. poloxamer 180) or an outer of increased viscosity (e.g. ethyl cellulose solution). SLN can also be produced in no aqueous media, e.g., PEG-600 or oils like Miglyol 812. SLN can be transformed to a dry product by spray during or lyophilisation. (Figure 2 and 3)

**Ideal Properties of solid lipid Nanoparticles for Brain Drug Delivery**
Nontoxic, biodegradable and biocompatible, Particle diameter between 10- 100 nm, Physical stability *in vivo* and *in vitro*, Avoidance from RES (Reticulo-endothelial system) leads toprolonged blood circulation time, CNS targeted delivery via receptor-mediated transcytosis acrossbrain capillary endothelial cells, Scalable and cost-effective manufacturing process, Amenable to small molecules, peptides, proteins or nucleicacids, Formulation stability, minimal nanoparticle excipient-induceddrug alteration (chemical degradation/ alteration, proteindenaturation), Controlled-drug release profiles

**Advantages of solid lipid nanoparticle**
SLNs are superior to polymeric nanoparticles, fat emulsions and liposomes. The advantages of SLNs are Controlled release of the incorporated drug can be achieved up to several weeks. There is also a scope for drug targeting by coating or attaching with the ligands, SLNs in the range of 120-200 nm bypass the liver and spleen filtration as they are not taken up readily by RES (Reticulo Endothelial System), Very high long term stability, for even three year. High drug pay load, It has an excellent reproducibility with cost effective, Feasible large scale production and sterilization, Can be freeze dried to form powder formulation.

**Disadvantage of solid lipid nanoparticle**
Drug expulsion after polymeric transition during storage and Relative high water content of the dispersion

**Mechanism of Nanoparticle Transport across the Blood Brain Barrier**
The mechanism of the drug transport across the brain barrier with the nanoparticles can either by endocytosis uptake by the brain capillary endothelial cells followed either by release of the drugs in these cells and diffusion into the brain or by transcytosis, or by inhibition of P-gp efflux mechanism or solubilisation of endothelial cell membrane lipids thus, enhance drug permeability across the blood brain barrier. One of the proposemechanism of polysorbate 80 coated with NP brain uptake, Adsorption of Apo on the surface of the surface of the coated SNP, NP binds to the LDL receptor and interacts with it. Passage of SLN across the BBB by endocytosis or transcytosis, Release of the drug takes from SNP.

**Formulation of SLN**
In production of SLN various ingredients used as surfactant, Co-surfactant and aqueous phase; SLNs prepared from glyceryl esters provide good drug inclusion. Of these materials better consistency will be found intrapalmitate, whereas fewer consistencies is in glycerlymonoesterate which is not stable and in few time of span globulesare aggregated out because of presence of higher amount of monoglycerides. As hard fats are melt at body temperature not suitable for controlled release formulations. Drug diffusion velocity is altered by selection of method of preparation. (Figure 4)

**Methods of preparation of solid lipid nanoparticles**

- High pressure homogenization
  A. Hot method
  B. Cold method
- Ultra sonic/high speed homogenization
  A. Probe ultra-sonication
  B. Bath ultra-sonication
- Method solvent evaporation
- Method of Solvent emulsification-diffusion
- Method of Supercritical fluid
- Method of micro-emulsion
Evaluation of Solid Lipid Nanoparticles
It is necessary to evaluate a number of parameters of SLNs for its quality control. The important parameters which need to be evaluated for the SLNs are,

1. Particle size, Poly Dispersity Index
2. Atomic force microscopy (AFM)
3. Photon correlation spectroscopy (PCS)
4. Static light scattering/Fraunhofer diffraction
5. Nuclear Magnetic Resonance (NMR)
6. Electron Microscopy
7. X-ray diffraction (powder X-ray diffraction) and differential scanning calorimetry (DSC)

2. Zeta potential
3. Determination of incorporated drug or Entrapment efficiency
4. In-vitro and ex-vivo methods for the assessment of drug release from SLN
   5. In-vitro drug release
   6. Ex-vivo model for determining permeability across the gut
5. Sterilization of SLN
6. Measurement of crystallinity and lipid
7. Storage stability

Therapeutic Use
Solid lipid Nanoparticles possesses a better stability and ease of upgradability for large scale preparations as compared to liposomes. SLNs form the basis of colloidal drug delivery systems, which are biodegradable and capable of being stored for at least one year. They can deliver drugs to the liver in-vivo and in-vitro to cells which are actively phagocytic. This property may be very important for many modes of targeting. There are several potential applications of SLNs some of which are given below.

Targeted brain via SLNs
Ability of the drug to penetrate through the blood-brain barrier can be improved by SLNs and so is a committing drug targeting system for the treatment of disorders and diseases related to central nervous system. After intravenous injection of SLN, first interesting accumulations in the brain were reported with camptothecin and 3, 5-dioctanoyl-5-fluoro-20-deoxouridine (DO-Fud R). That show in principle the potential of SLN to deliver drugs to the brain. SLNs are made of biodegradable and biocompatible lipids and show better in-vivo tolerability. SLNs are a committing sustained and drug targeting system for lipophilic antitumor drugs, reduces dose so decrease in adverse effects. SLNs are helpful in targeting of chemotherapy in mitosis when drug concentrations in tumour tissue were required to maintain for long period.

SLNs brain anti retroviral drugs delivery
In AIDS ART fails as because cannot cross BBB and BCSBF so fail to reduce HIV viral load in the brain but various studies have shown that SLN can be successful in achieving to reduce viral load in brain.

Gene vector Vehicle
SLN can be used in the gene vector formulation. In one work, the gene transfer was optimized by incorporation of a diatomic HIV-1 HAT peptide (TAT 2) into SLN gene vector. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids [Hayes et al., 2004]. The lipid nucleic acid nanoparticles were prepared from a lipid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously sized lipid-nucleic acid nanoparticle (70-100 nm) were formed. It’s called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.

Targeted anticancer carrier drug
SLNs have been reported to be useful as drug carriers to treat neoplasms. Tamoxifen, an anticancer drug incorporated in SLN to prolong release of drug after i.v. administration in breast cancer and to enhance the permeability and retention effect. Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate and camptothecin.
Figure (1): Blood Brain Barrier comprised of specialized endothelial cells, astrocytes foot processes and pericytes. Endothelial Cells in Blood Brain Barrier possess tight junction in between endothelial cells. Transport of essential ingredients from abdominal luminal site, occurs by different mechanisms as (a) lipid soluble agents can diffuse through endothelium by Trans cellular diffusion (b) Some of Hydrophilic molecules can through Blood Brain Barrier by specialized diffusion, (c) In absorptive mediated endocytosis as per its surface charges, (d) Receptor mediated Endocytosis occurs in certain polypeptides like insulin, (e) Specific Transport Carrier of Glucose, amino acids, purine bases, nucleosides, choline and other ingredients transport through endothelium
CONCLUSION

As reviewed above nearly 98% of therapeutics for treatment of neurological disorders available in the market is not ideal for transport across the BBB. CNS drugs molecule difficult transport across the BBB, There for various novel drug delivery methodologies used for transport drug in to brain. However, need idea that drugs reach the right site in the body, at the right time, at right concentration. It should not exert side effects, neither on its way to the therapeutic target, nor at the target site, nor during the clearance process. The SLNs have the potential to achieve, at least partially, these broad objectives. Numerous study on SLNs as carrier system had been made and concluded that SLN are rational approach in various systems where to input active compounds or therapeutically difficult molecules such as proteins, peptides, hormones, genes, DNA, RNA or viral vectors for targeting to get their related merits. The appropriate characterization of the complex surfactant/lipid dispersions SLN requires several analytical methods in addition to the determination of the particle size. The kinetic Aspects are taken into account. SLN administration to various organs and tissues as brain, nasal route has been providing new path for fewer indiscriminate bio distribution and increase the bioavailability of hydrophobic molecules in specific sites in body. SLNs provide a new approach for an effective delivery of various drug moieties as analgesics, anti-TB, Chemotherapeutics, anti-aging, antiepileptic, neuroleptics, antibiotics, antiviral agents etc. into the brain. Safety parameters and biodegradability property shows the SLN technology as strong tool which will provide and carve best among other conventional delivery systems for next coming era.

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Cite this article as:

Source of support: Nil, Conflict of interest: None Declared