Available online on 30.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-18, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited

Open Access Review Article

Solid Lipid Nanoparticles for Brain Targeting

Hangargekar Sachin Raosaheb*, Pradeepkumar Mohanty, Ashish Jain

LNCT, University, Bhopal- 462042, MP, India

ABSTRACT

Brain is considered to be highly impermeable barrier, possessing different obstacles like presence of enzymes, presence of tight junctions that limit the entry for most of the drugs. The presence of these obstacles, possess a challenge for administration of the drugs. The conventional means of drug delivery in form of emulsions, fail to overcome these obstacles, and hence there is a need for newer drug delivery approach, that will cross these barriers of the brain. So, these nanoparticles can be an alternative to other conventional systems. They offer several advantages such as improved bioavailability and solubility that are composed of macromolecular materials like lipids and polymers possess low cytotoxicity, high drug loading capability, and good scalability these are the most effective colloidal carriers that have the ability to incorporate drugs into nanocarriers and used as drug targeting to specific area. Thus, this article will emphasise on properties of Blood Brain Barrier, strategies to overcome the blood–brain barrier, literature regarding the use of SLNs in various neurological disease states, production methods of SLN and its evaluation. Hence, these solid lipid formulations can be a new form and one of the promising approach for drug delivery system in future, that have remarkable possibility to cross the BBB.

Keywords: Solid lipid nanoparticles, Nanocarriers, Blood–brain barrier

Article Info: Received 07 July 2019; Review Completed 11 Aug 2019; Accepted 19 Aug 2019; Available online 30 Aug 2019

Cite this article as:

Hangargekar SR, Pradeepkumar M, Ashish J, Solid Lipid Nanoparticles for Brain Targeting, Journal of Drug Delivery and Therapeutics. 2019; 9(4-A):911-915 http://dx.doi.org/10.22270/jddt.v9i6-s.3783

***Address for Correspondence:**

Hangargekar Sachin Raosaheb, LNCT, University, Bhopal- 462042, MP, India

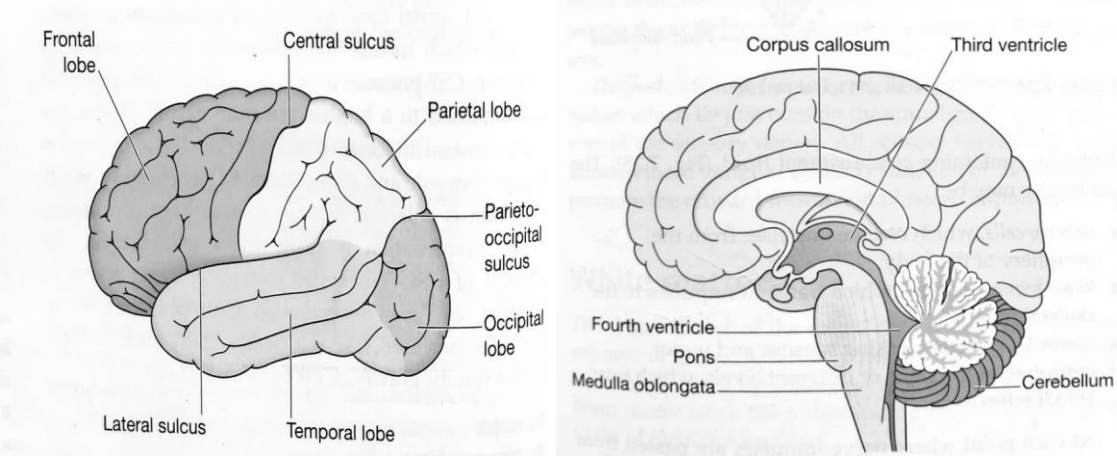
INTRODUCTION:

Brain being one the toughest barrier for the delivery of drugs, due to the presence of the blood brain barrier (BBB). Delivery of drugs to blood brain barrier has been achieved through prodrug approach. Delivery of drugs, through nanoparticulates has been a drug delivery of choice, that can bypass the RES[1-3]. Solid lipid nanoparticles, are specific successful nanoparticles, that overcome the limitations and toxicity of nanoparticles. These range in nanoscale that has the capacity to enclose both hydrophilic and lipophilic drugs [4-6].

The human brain is divided into 3 main parts on the basis of their function and location[7-8] - Fore Brain Mid Brain and Hind Brain. Fore Brain is the anterior part of the brain. It is responsible for controlling the voluntary actions. It collects sensory information from various organs such as ears, skin, tongue, eyes. Fore brain has 3 parts namely Cerebrum, Thalamus, Limbic system. Cerebrum is considered as biggest part of the brain. Higher brain functions such as thinking and action are associated with cerebrum. It is divided into 2 halves called cerebral hemisphere. Right hemisphere related to creativity and left hemisphere links to logic abilities. They communicate via corpus collosum. Cerebral cortex is outer region of cerebrum. cerebral cortex is again divided into four lobes Frontal lobe, Parietal lobe, Occipital lobe, Temporal lobe functions of cerebrum are sensory processing, determines the intelligence of the being, helpful for the movement. Thalamus is a small structure which is situated within brain. It is located above the brain stem and between the cerebral cortex and mid brain. It is responsible for carrying the sensory information from body to cerebrum and the limbic system. Limbic system is arc shaped structure between thalamus and cerebrum. It consists of hypothalamus, the hippocampus, the amygdala and other nearby areas. It is also known as paleo mammalin cortex. Functions of limbic system are management of hunger, fear, thirst, anger, and sexual response.

Mid brain is located below the cerebral cortex and above the hind brain. It is also called mesencephalon. Midbrain consists of 4 principal regions Tectum, Cerebral aqueduct, Tegmentum, Cerebral penducles. It control reflex movement of the body and hearing reflexes.

Hind brain is present at the backside of the brain. It is also called as rhombencephalon. Hind brain is connecting link between the spinal cord and rest of the brain. It consist of Cerebellum, Pons, Medulla oblongata.



(a) **(b)**

Figure 1: (a) – The lobes and sulci of cerebrum (b) – The cerebellum and its associated structures. Regenerated from source [8]

There is more research going in the areas of brain targeting, for treatment of neurological disorders. Most of the economy is taken into consideration, for treatment of brain disorders like, brain tumour, drugs that will help repair damage, help growth of brain cell etc. But these efforts still remain a challenge, due to the presence of the obstacles, of the BBB.

However, obstacles to effective therapy delivery remain, and one of the most notable obstacles for drugs to penetrate the brain effectively is the BBB[9-10].

BLOOD BRAIN BARRIER (BBB)

Basal membrane and brain cells, such as pericytes and astrocytes, surrounding the endothelial cells further form and maintain an enzymatic and physical barrier known as the blood–brain barrier (BBB).

Structure:

Although brain capillaries are morphologically similar to those found in other tissues, brain vessels are functionally bound to the other cells of the brain parenchyma. BBB consists of blood vessels built up by specialized endothelial cells (ECs), astrocytes, pericytes, and neuronal terminations.

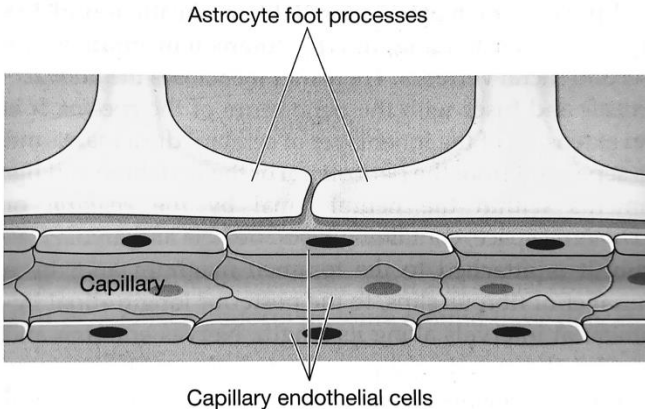


Figure 2: Blood–brain barrier (BBB) - Regenerated from source[8].

Astrocytes lay their end-feet over the continuous basal lamina and form a very restrictive barrier Pericytes, a type of mesenchymal cell, occupy the perivascular space, between the capillary wall and astrocytes end-feet, except in the large vessels where smooth muscle cells replace them. Pericytes play a regulatory role in vasculature tone, stability, repairment and angiogenesis as well as they can modulate astroglial function. Neurons are also active participants in structure of BBB.

BBB tight junctions are formed between endothelial cells in brain capillaries, thus preventing paracellular transport of molecules into the brain. Micro-vessels small in diameter and thin walls compared to vessels in other organs make up an estimated 95% of the total surface area of the BBB, and represent the principal route by which chemicals enter the brain.. Therefore, only lipid-soluble solutes that can freely diffuse through the capillary endothelial membrane may passively cross the BBB[11] .

BLOOD-CEREBROSPINAL FLUID BARRIER (BCSFB)

BCSFB act as barrier to drugs entering the CNS. It is formed by the plexus epithelial cells. The epithelial cells have an arrangement in such a manner that it prevents the entry of molecules. Due to the presence of inconsistency between the interstitial fluid and CSF, put forward the occurrence of CSF-brain barrier.

The BBB is constituted of polarized endothelial cells that are linked by tight junctions. and presence of these, is responsible for low permeability, limiting the drug delivery to central nervous system (CNS). Different types of cells like pericytes, neurons, astrocytes regulate the BBB functionality[12,13].

Strategies to evade the blood–brain barrier?

Depending on the properties of BBB, there are number of strategies, that include pharmacological line, invasive methods and physiological [14-16]. Pharmacological method include modification of drug, that will help to cross the BBB. But these modifications, affect the biological activity of the drug.[17]. While the invasive involves use of techniques as interruption of BBB, use of polymers, use of catheters etc. As these are invasive, may lead to damage to brain tissues, toxic conditions, infection chances. This is not cost effective method [18].The physiological way is considered to be better approach as compared to the two methods, as it takes the advantage of transport receptors, that help to cross the BBB barrier. These all three methods, suffer from the disadvantage of limited success rate for treatment of neural diseases. Due to the limitations of these methods, research has advanced for the use of nanotechnology, for effective

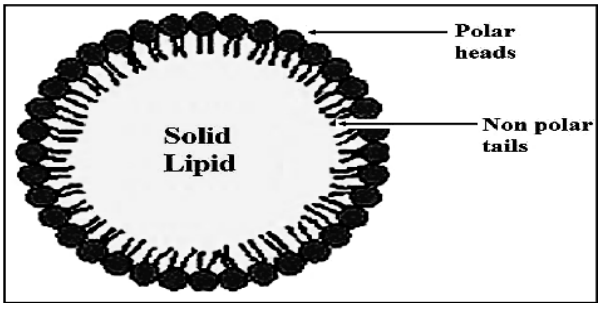
delivery of the drugs across the BBB. Nanoparticles have played an important role for brain drug delivery [19-20].

So, in this review, we are focusing on the most promising approach of solid lipid nanoparticles for drug brain targeting and delivery.

NOVEL DRUG DELIVERY SYSTEMS FOR BRAIN DRUG DELIVERY

There are numerous colloidal delivery systems tried by many investigators to overcome, the barriers of brain. These systems include lipid microspheres, microspheres, liposomes, niosomes, nanoparticles, and solid lipid nanoparticles (SLNs). As per the study of Chen et al. polymeric nanoparticles are suitable for drug delivery to the brain [21] .As per their study the uptake of the drug by brain is through different mechanisms like nanoparticles help in opening of the tight junctions, retention of drug in blood brain capillaries and transcytosis of these through the endothelium. The coating of these polymeric nanoparticles by polysorbates help in improvement of bioavailability. The mechanism of this includes – the polysorbates help in solubilization of lipids and membrane fluidization, Inhibition of efflux system, P-gp and endocytosis [22]. But, they possess certain limitations as use of organic solvents, polymer aggregation, toxic degradation products etc.[23-24]. Though nanoparticles have the advantage of crossing the BBB, but due to its disadvantages, good alternative to it is SLN.

SLNs are sub-micron colloidal carriers which are ranging from 50 to 1000 nm. SLN introduced in 1991 as an alternative to tradition colloidal carriers such as emulsions, liposomes and polymeric-micro and nanoparticles. SLN is composed of physiological lipid which is dispersed in water or aqueous surfactant solution.[25] SLNs are made up of solid core with a monolayer phospholipid shell. Protection to chemically labile drugs and prolongation of drug release is provided by the solid state of the Nanoparticulate matrix.[26].



ADVANTAGES OF SOLID LIPID NANOPARTICLES [27-28]

1. Controlled release kinetics can be achieved with solid lipid nanoparticles
2. SLNs improved bioavailability of poorly water soluble molecules or protection of drugs which undergoes gastro-intestinal degradation
3. Better stability as compared to liposomes
4. Lyophilisation is possible
5. Toxic metabolites are not produced
6. SLNs are easy to manufacture than bio polymeric nanoparticles
7. No special solvent is required
8. Both hydrophilic and lipophilic drugs can be encapsulated

DISADVANTAGES OF SOLID LIPID NANOPARTICLES

1. During storage drug expulsion after polymeric transition may occur
2. Drug loading capacity is poor
3. Water contents of dispersion are relatively high (70-99.9%)
4. Gelating tendency is unpredictable in nature
5. Growth of particles can occur

RATIONAL FOR PREPARATION OF SOLID LIPID NANO PARTICLES [29]

1. Use of organic solvent may avoided
2. Drug stability may increase
3. Controlled drug release may possible
4. Drug loading capacity is high
5. Hydrophilic and lipophilic drug can be incorporate

Archives regarding the use of SLNs in various neurological disease states

As per the literature, SLNs have the ability of the drug to penetrate through the blood-brain barrier (BBB). Abbas et al. studied the use of clonazepam for targeting to the brain via intranasal olfactory mucosa utilizing nanolipid carriers. These were co-loaded with iron oxide nanoparticles (SPIONs). These nanolipid carriers were incorporated in situ in thermosensitive mucoadhesive gels, that resulted in the enhanced delivery of clonazepam[30]. Goppert and Muller prepared polysorbate 80 SLNS for brain targeting. The coating of high apoE/apoCII ratio had been absorbed absorbed on the particles to achieve brain targeting [31]. As per the study conducted by Bhargava s et al, nifedipine loaded solid lipid nanoparticles (SLN) were established for CNS targeting. The results depicted in-vitro & in-vivo studies results showed The Dementia blocking activity on brain cells were shown by DNA Fragmentation & Cell Viability studies [32].

In one study, haloperidol (HP)-loaded solid lipid nanoparticles (SLNs) were formulated for enhancement of HP to brain via intranasal (i.n.) delivery. The highest entrapment efficiency (2362.43%) and direct transport percentage (95.77%) was found with HP-SLNs as compared to the other formulations. Higher DTE (%) and DTP (%) suggest that HP-SLNs have better brain targeting efficiency as compared to other formulations [33]. In one report, DOX-SLN were prepared by solvent evaporation method that had an average particle size close to 200 nm and polydispersity index (PDI) <0.3. The cytotoxicity studies showed the higher toxicity of DOX-SLN than plain DOX on U87MG cell lines. The cellular uptake studies also confirmed the internalization of the DOX-SLN inside brain cancer cells. The study confirmed that the development of a SLN as potential carrier for brain cancer with enhanced ability to cross the BBB [34].

As per the study of Morsi N et al, formulated solid lipid nanoparticles (SLNs) of Vinpocetine (VIN) for brain targeted sustained drug-delivery system. VIN SLNs were prepared by modified high shear homogenization followed by ultrasonication technique. The effect of different lipids at different concentrations of various surfactants was studied. Their Formula (F32) of 5% glyceryl monostearate (GMS) with 2% surfactant mixture [Tween 80, Pluronic F 68 (1:1)] was the utmost suitable formula for brain delivery having EE% of 89.09% ± 1.49, zero-order release kinetics with cumulative released percent of 72.12% after 96 h, zeta-potential of −11.3 ± 0.97 mV. Thus, zero-order sustained release profile was achieved and met the requirement for a brain targeted . Brain targeted solid lipid nanoparticles for brain ischemia: preparation and in vitro characterization [35].

Wang et al. merged 3', 5'-dioctanoyl-5-fluoro-2'-deoxyuridine into the solid lipid nanoparticles. The i.v administration of SLN and drug solution was determined and

AUC values obtained. The results showed the values obtained by SLN were two folds than that by injecting plain drug solution [36].

METHODS OF PREPARATION OF SLN [37]:

Solvent Emulsification and Evaporation:

In this method Solid Lipid nanoparticles are prepared by precipitation of lipids from emulsions. Lipids are dissolved in organic solvents like cyclohexane and then emulsified in aqueous phase by high pressure homogenization. Nanoparticles dispersion is formed by precipitation of the lipid in aqueous medium and evaporation of solvent from emulsion under reduced pressure (40-60 mbar). Nanoparticles of 25 nm size range are formed by this method.

High Pressure Homogenization:

Solid lipid nanoparticles can be produced by most reliable and powerful High Pressure Homogenization technique. In this technique liquid push through narrow gap with high pressure (100-2000 bar) using High Pressure Homogenizer. The fluid accelerates with very high velocity (1000km/hr) to a very short distance. Very high shear stress and cavitation forces causes disruption of particles down to submicron range.

a) **Hot Homogenization**

In Hot Homogenization lipid is melted above the temperature of its melting point and pre-emulsion of drug in melted lipid and aqueous phase (hot surfactant mixture) is formed by high shear mixing device. Due to higher temperature viscosity is decreased and small size particles are formed. But High temperature may result into degradation of drug and carrier and increased homogenization pressure may lead to increase in particle size due increased kinetic energy of particles.

b) **Cold Homogenization**

Various problems of hot homogenization like temperature induced drug degradation, drug distribution into aqueous phase during homogenization can be overcome by cold homogenization. In this technique drug containing lipid melt is cooled, the solid lipid ground to lipid micro particles. Then presuspension is prepared by dispersing these lipid microparticles into cold surfactant solution and then homogenized at or below room temperature .due gravitation force lipid microparticles directly break into solid lipid nanoparticles.

Microemulsion Based Method

This method involves dilution of microemulsions. Microemulsions are composed of low melting fatty acids (e.g. Stearic acid) , an emulsifier (eg. Polysorbate 20), co-emulsifiers (e.g. Butanol) and water. This mixture is stirred at 65-70˚C.The hot microemulsion is dispersed in cold water (2-3˚C) with stirring. Due to high temperature gradients rapid lipid crystallisation occurs and aggregation is prevented. Due to Dilution step lipid contents are lower than HPH based formulations.

Ultrasonic Solvent Emulsification Technique :

This method involves the dissolution of lipid phase into organic solvent such as dichloromethane by heating upto 50˚C. Aqueous phase containing mixture of surfactant and emulsifiers is heated upto same temperature and added to organic phase after partial evaporation of dichloromethane at 50˚C and with constant sirring. This emulsion produced is subjected to sonication for appropriate time and finally cooled in ice bath to get solidify lipid nanoparticles.

Spray Drying Method

Lipids with melting point > 70˚C are recommended for use in spray drying technique. Due to high temperature, shear forces and partial melting of particles aggregation may occur. By using SLN concentration of 1% in a solution of trehalos in water or 20% Trehalose in ethanol-water mixtures (10/90 v/v) best results can be obtained.

Double Emulsion Method

Drug and stabilizer are encapsulated to prevent the partitioning of drug into external water phase during solvent evaporation in external water phase of w/o/w double emulsion.

Precipitation Method

This method involves emulsification of aqueous phase and glycerides dissolved in organic solvent like chloroform. The lipid will precipitated forming nanoparticles after evaporation of organic solvent.

Film – Ultrasound Dispersion

Lipid and drug are mixed with suitable organic solvent. Thin lipid film is formed after decompression, rotation and evaporation of organic solvent. Then aqueous solution which includes emulsion is added. By using ultrasound with probe to diffuser at last, solid lipid nanoparticles are produced.

EVALUATION PARAMETERS [38]

In Vitro Drug Release:

Dialysis tubing: In vitro drug release is greatly explained by dialysis tubing .In this method SLN dispersion was placed in the previously washed dialysis tubing which can be sealed. The dialysis sac then dialyzed against the specific dissolution medium at room Tem. Then sample is removed from dissolution medium at suitable time period, centrifuged and analyzed for particular amount of drug content by using the suitable analytical method.

Reverse dialysis: In this method different type of small dialysis sac which may containing dissolution medium are placed in the SLN dispersion. then SLNs are then displaced into the medium.

Franz diffusion cell: In the franz diffusion cell presence of the Donor chamber in which the SLN dispersion is placed with a cellophane membrane. The dispersion is then analyzed against the suitable dissolution medium; then sample is removed from dissolution medium at suitable time period and analyzed the drug content by using suitable method like spectroscopy and HPLC method.

Ex Vivo for permeability testing

The rat jejunum (20-30cmdistal from the pyloric sphincter) is excised from the rats after scanning the animal used for the study.

Analytical Characterization of SLN

Particle size and Zeta potential: For the measurement of the particle size photon correlation spectroscopy (pcs) and laser diffraction (LD) are the most powerful technique for the measurement of particle size. This method cover a size range from a few nanometer to about few nanometer to about 3 micron.

Measurement of crystallinity and lipid modification: Lipid crystallization modification may appear due to the small size of particle and presence of emulsifier. The DSC and

X-ray scattering are widely used to determine the presence of lipid.

Co-existence of additional structure: The magnetic resonance technique ,nuclear magnetic resonance(NMR) and electron spin resonance (ESR) are mostly used to determine dynamic phenomenon and presence of Nano-compartment in the colloidal lipid dispersion

Determination of Incorporated drug: For determination of drug content the drug and solid lipid particles are separated by ultracentrifugation, centrifugation filtration, or gel permeation chromatography. Then drug content can be determined by using spectrophotometer, HPLC or Liquid Scintillation counting.

CONCLUSION

SLN comprise an effective drug delivery to brain. The advantages of SLNs like controlled release kinetics, improved bioavailability, avoid gastric degradation, physical stability and no special solvent required make them a choice for drug delivery to the brain . SLNs thus open new channels for delivery of drug to brain like antitubercular, antianxiety, antibiotics ,neuroleptics etc. SLN are good formulations as targeted drug delivery system.SLN bears the properties of good patient compliance and economical for delivery of drugs.

REFERENCES

1. Bummer PM, Physical chemical considerations of lipid based oral drug delivery — solid lipid nanoparticles, Critical Reviews™ in Therapeutic Drug Carrier System, 2004; 21: 1–20.
2. Muller RH., Keck CM. Challenges and solutions for the delivery of biotech drugs — a review of drug nanocrystal technology and lipid nanoparticles, Journal of Biotechnology, 2004; 113 (1–3):151–170.
3. Begley DJ. Delivery of therapeutic agents to the central nervous system: the problems and the possibilities, Pharmaceutical. Therapeutics, 2004; 104 (1): 29–45.
4. Fundaro A, Cavalli R, Bagoni A, Vighetto D, Zara G.P, Gasco M.R, Non-stealth and stealth solid lipid nanoparticles (SLN) carrying doxorubicin: pharmacokinetic and tissue distribution after i.v. administration to rats, Pharmaceutical Research, 2000; 42 (4): 337–343.
5. Chen D, Yang T, Liang W, Zhang Q. In vitro and in vivo study of two types of long circulating solid lipid nanoparticles containing Paclitaxel, Chemical and Pharmaceutical Bulletin ,2001; 49: 1444–1447.
6. Reddy JS, Venkateshwarlu V. Novel delivery systems for drug targeting to the brain, Drugs of Future, 2004; 29 (1): 63–83.
7. Tortora G, Derrickson B. Principles of Anatomy and Physiology. 15th ed. John Wiley and Sons; 2017. P.477-501.
8. Waugh A, Grant A. anatomy and Physiology. 9th edition. Churchill Livingstone; 2001,P. 171-189.
9. Lesniak MS, Brem H. Targeted therapy for brain tumours. Nature Reviews Drug Discovery, 2004; 3:499–508.
10. Stenehjem DD, Hartz AM, Bauer B, Anderson GW. Novel and emerging strategies in drug delivery for overcoming the blood-brain barrier. Future Medicinal Chemistry, 2009,1:1623–1641.
11. Parle P, Aggarwal G, Kumar S. Brain Targeted Drug Delivery System: A Review. World Journal of Pharmacy and Pharmaceutical Sciences, 2016; 5(6): 398-414.
12. Pardridge WM. Blood-brain barrier delivery. Drug Discovery Today, 2007; 12:54–61.
13. Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nature Reviews Neuroscience, 2006; 7:41–53.
14. Pavan B, Dalpiaz A, Ciliberti N, Biondi C, Manfredini S, Vertuani S. Progress in drug delivery to the central nervous system by the prodrug approach. Molecules. 2008; 13: 1035–1065.
15. Gabathuler R. Approaches to transport therapeutic drugs across the blood-brain barrier to treat brain diseases. Neurobiology of Disease, 2010; 37: 48–57.
16. Banks WA, From blood-brain barrier to blood-brain interface: new opportunities for CNS drug delivery. Nature Reviews Drug Discovery, 2016; 15: 275–292.
17. King A, Breaking through the barrier. Chem World. 2011; 8:36–39.
18. Barua NU, Gill SS, Love S. Convection-Enhanced drug delivery to the brain: therapeutic potential and neuropathological considerations. Brain Pathology, 2014; 24:117–127.
19. Vlieghe P, Khrestchatisky M, Medicinal chemistry based approaches and nanotechnology-based systems to improve CNS drug targeting and delivery. Medicinal Research Reviews, 2013; 33:457–516.
20. Bhaskar S, Tian F, Stoeger T, et al. Multifunctional nanocarriers for diagnostics, drug delivery and targeted treatment across blood-brain barrier: perspectives on tracking and neuroimaging. Part Fibre Toxicology, 2010 : 7:3.
21. Chen Y, Dalwadi G, Benson H, Drug delivery across the blood–brain barrier, Current Drug Delivery, 2004; 1: 361–376.
22. Kreuter J, Nanoparticles system for brain delivery of drugs, Advanced Drug Delivery. Reviews, 2001; 47: 65–81.
23. Kante B, Dubois-Krack G, Meester C, Toxicity of polyalkylcyanoacrylate nanoparticles, Journal Pharmaceutical Sciences,1982; 71 :786–789.
24. Limayem I, Fessi H, Purification of nanoparticle suspension by a concentration/diafiltration process, Pure Technology, 2004; 38 : 1–9.
25. Ekambaram P, Priyanka K, Sathali A, Solid Lipid Nanoparticles: A Review. Scientific Reviews And Chemical Communications, 2012; 2(1): 80-102.
26. Bagul U, Pisal V, Solanki N, Current Status of Solid Lipid Nanoparticles: A Review. Modern Applications of bioequivalence & bioavailability, 2018; 3(4) : 1-2.
27. Yasir M, Sara U. Solid lipid nanoparticles for nose to brain delivery of haloperidol: in vivo drug release and pharmacokinetics evaluation. Acta Pharmaceutica Sinica B, 2014; 4 (6) : 455.
28. Mishra M, Bansal K, Verma A. Solid lipid nanoparticles: Emerging colloidal nano drug delivery systems. Pharmaceutics, 2018; 10(19): 1-21.
29. Garud A, Singh D, Garud N. Solid lipid nanoparticles (SLN): Method, Characterization and Applications. International Current Pharmaceutical Journal, 2012; 1(11): 384-393.
30. Abbas H, Refai H, Sayed N,. Superparamagnetic Iron Oxide-Loaded Lipid Nanocarriers Incorporated in Thermosensitive In Situ Gel for Magnetic Brain Targeting of Clonazepam. Journal Pharmaceutical Science, 2018; 107(8):2119-2127.
31. Goppert T, Muller R, Polysorbate-stabilized solid lipid nanoparticles as colloidal carriers for intravenous targeting of drugs to the brain: comparison of plasma protein adsorption patterns, Journal of Drug Targeting, 2005; 13 (3): 179–187.
32. Bhargava S, Bhargava V, Surface Modified Solid Lipid Nanoparticles for the targeted delivery to brain: Management of HIV-1 Associated Dementia, 2018, International Congress. 880.
33. Yasira B, Solid lipid nanoparticles for nose to brain delivery of haloperidol: in vitro drug release and pharmacokinetics evaluation, Acta Pharmaceutica Sinica B, 2014; 4(6):454–463.
34. Jain P, Pandey V, Soni V.Surface Modified Solid Lipid Nanoparticles for Brain Cancer Treatment, Asian Journal of Pharmaceutics, 2019; 13 (2) : 119 – 124.
35. Morsi N, Dalia M. Ghorab A, Brain targeted solid lipid nanoparticles for brain ischemia: preparation and in vitro characterization Pharmaceutical Development and Technology, 2013; 18(3) : 736-744.
36. Wang JX, Sun X, Zhang ZR, Enhanced brain targeting by synthesis of 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine and incorporation into solid lipid nanoparticles, European Journal of. Pharmaceutics and Biopharmaceutics, 2002; 54 (3) : 285–290.
37. Swathi G, Prasanthi NL, Manikiran SS, Ramarao N, Solid lipid nanoparticles: colloidal lipid carrier system for drug delivery. International Journal of Pharmaceutical Sciences and Research, 2010; 1(12): 1-16.
38. Pallerla S, Prabhakar B, A Review on Solid Lipid Nanoparticles. International Journal of Pharmaceutical Sciences Review and Research, 2013; 20(2): 196-206.