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A Review on Lipid Based Nanoparticles Via Nose-To-Brain Delivery

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ABSTRACT
Central nervous system disorders significantly affect the lives and health of millions of people worldwide. Despite many therapeutic drugs are available that could potentially target central nervous system disorders, their clinical utility is severely constrained by their inability to cross the blood-brain barrier (BBB). Fortunately, nanotechnology has been advanced to offers a solution to allow drugs reaching the targeted brain regions safely, efficiently, and precisely through nasal drug delivery system (NDDS), bypassing the BBB completely. This strategy can promote the drug accumulated in the targeted brain region, improve drug bioavailability, and minimal side effects and mucociliary clearance effectively. In this review, we elaborate recent advances in the use of lipid-based nanoparticles, involving liposomes, nanoemulsions, nanostructured lipid carriers, and solid lipid nanoparticles. Besides, we particularly introduced the nasal cavity physiological structure, and further summarized the nose-to-brain drug delivery pathways, including olfactory, trigeminal, and blood circulation pathway. Moreover, the mechanism and route of NDDS by various types of nanoparticles are also highlighted.

KEY WORDS:
Nanoparticles, nose-to-brain, blood-brain barrier, drug delivery, central nervous system.

I. INTRODUCTION

The human brain is considered one of the most challenging therapeutic areas for drug delivery due to its protective physiological barriers (blood-brain and blood-cerebrospinal fluid barrier) (Abbot et al. 2010). Hereof, still, nowadays, most treatments for neurodegenerative diseases (Parkinson's/Alzheimer's disease, etc.) generally result in symptom relief. In the case of brain neoplasms, the therapeutic outcomes are even poorer. The blood-brain barrier is the primary factor restricting drug transport to the brain – approximately 98% of small molecules and almost 100% of drugs cannot reach the brain parenchyma. Structurally, it comprises endothelial cells, astrocytes, and pericytes. The tight junctions and adherens junctions between the brain capillary endothelial cells are mainly responsible for its diffusion barrier role, low permeability, and high electrical resistance (≈ 500–600 higher than other body parts).

In this context, research strategies are constantly evolving to find a feasible approach to circumvent the BBB, ideally via physiological pathway mechanisms without compromising its integrity, and to deliver drugs to the brain parenchyma, thereby providing safe and effective treatment for a variety of CNS disorders. The main strategies to achieve these goals can be broadly classified into invasive and non-invasive approach Through invasive methods, the drugs can reach the brain either directly, via temporary disruption of the BBB using hyperosmotic solutions or ultrasound, or by intra-cerebral/ventricular/thecal delivery.

However, these strategies are associated with low patient compliance, technical difficulties, and, last but not least, risk of exposure of the brain to toxins or occurrence of neuropathological

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changes in case of transient BBB disruption. Great research interest provokes the non-invasive approaches, which use either an alternative route to reach the CNS – as in the case of the nose-to-brain delivery via the olfactory and trigeminal nerve pathways, or different techniques enabling drugs` transport across the BBB. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are among the most exploited platforms for brain delivery due to their superior safety profile in terms of potential cytotoxicity, biodegradability, or biocompatibility compared, for instance, to the polymeric or inorganic counterparts.

Furthermore, they are characterized by high drug-loading capability, controlled drug release, and scale-up feasibility. In addition to the excellent tolerability, their main structural constituents (lipids, in solid-state at room/physiological temperature in SLNs, and a mixture of solid and liquid lipids in case of NLCs) provide them the possibility to cross the BBB. Undoubtedly, the latter is also highly dependent on the physicochemical characteristics of the nanocarriers, primarily by their size, surface charge, shape, and, last but not least, their surface modification. Therefore, the functionalization of lipid nanoparticles (LNPs) with different ligands (e.g., proteins, peptides, antibodies, etc.) is a prerequisite for further improvement of their brain target selectivity and therapeutic outcomes.

In this regard, the impact of the physicochemical and surface properties of LNPs, along with the potential transport mechanisms and the specific characteristics of the target area – BBB's structure discussed in the paper. The review also summarizes current studies exploiting SLNs and NLCs as brain drug delivery systems.

NOSE-TO-BRAIN DELIVERY:

Conventional methods of administering drugs for brain-targeting systems, such as oral and parenteral routes, involve delivering drugs into the brain through the systemic circulation. However, the majority of administered drugs often remain in the systemic circulation due to challenges in penetrating physiological barriers, such as the BBB.

Specifically, large molecules and more than 98% of low-molecular-weight drugs face difficulties permeating the BBB, resulting in low brain bioavailability. Additionally, oral administration leads to hepatic first-pass metabolism and intestinal enzymatic degradation prior to the arrival of the drug in the brain. Parenteral administration, like intrathecal delivery, can lead to complications, such as cerebrospinal fluid leakage and meningeal issues.

On the other hand, the receptor-mediated approach has gained attention as a potentially safe and effective method for enhancing brain-targeting capability without disrupting the BBB membrane. However, this strategy carries the risk of losing therapeutic effectiveness due to the accumulation of drug carriers in unintended sites, such as the liver.

In 1989, William H. Frey II introduced intranasal administration as a non-invasive approach for nose-to-brain delivery. This approach capitalizes on the direct connection between the olfactory nerve and the frontal region of the brain, facilitated by the olfactory bulb, as well as the entry of the trigeminal nerve through the trigeminal ganglion and pons. These connections provide opportunities for bypassing the BBB, evading hepatic first-pass effects, and preventing intestinal enzyme degradation. Nose-to- brain delivery also boasts high patient compliance and affordability, and it eliminates the need for expert interventions. General information regarding oral, parenteral, and intranasal administration routes.[6]

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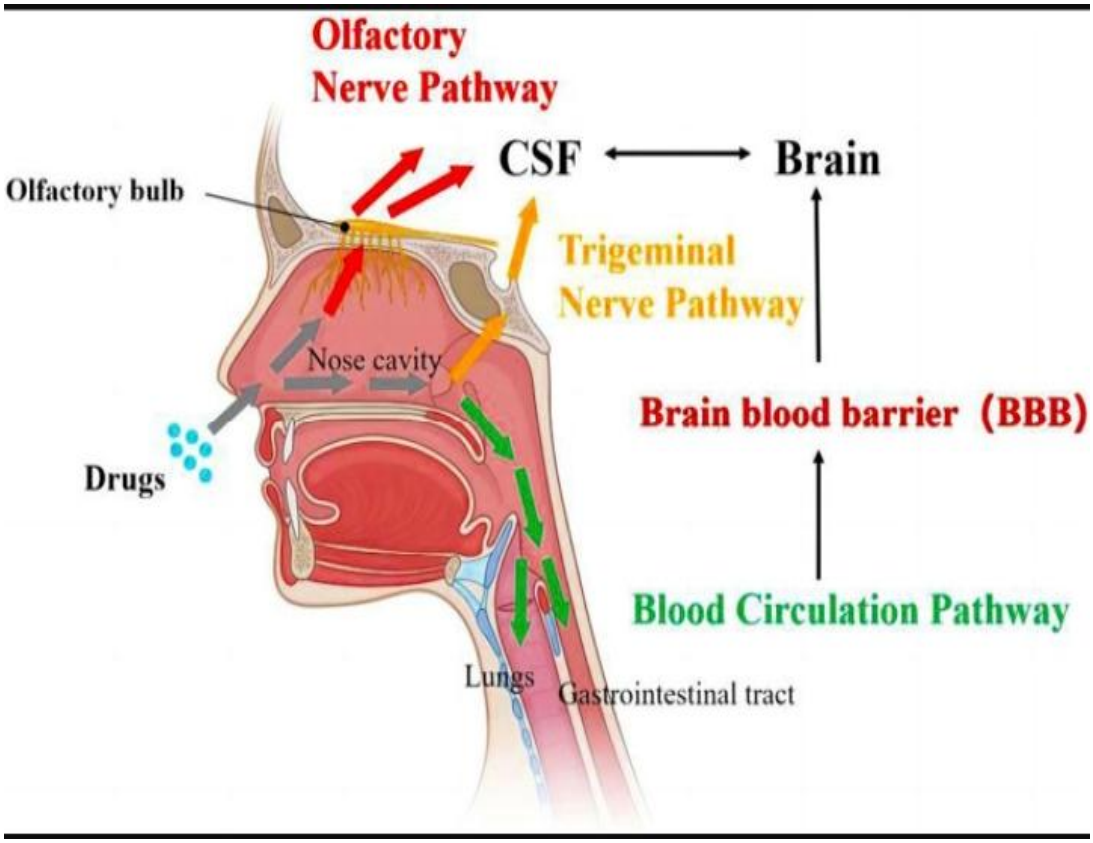

NOSE-TO-BRAIN DELIVERY

PATHWAYS OF INTRANASAL TRAANSPORT TO THE BRAIN:

The motivation for developing intranasal drug administration stems from the challenge of delivering drugs to the brain while overcoming the Blood-Brain Barrier (BBB).13 Two primary delivery pathways in intranasal administration, the olfactory and trigeminal nerve pathways, provide direct routes to the brain. However, not all drugs administered intranasally are confined to these pathways. Some drugs may enter systemic or lymphatic circulations, where crossing the BBB is necessary to reach the brain. In such cases, the quantity of the drug that successfully penetrates the BBB and reaches the brain is often limited.

In the respiratory system, drugs are transported to the brain via the trigeminal nerve pathway. The trigeminal nerve is the fifth cranial nerve and it is innervated with ophthalmic, maxillary, and mandibular nerve branches, which gather in the trigeminal ganglion. The trigeminal nerve originates from the pons of the brainstem, allowing it to be a potential target nerve for drug transport to the CNS. In particular, drugs absorbed in the maxillary and ophthalmic nerve branches can be delivered.

The olfactory region of the nasal cavity remains directly connected to the frontal cortex; especially olfactory bulb of the brain via olfactory nerves. The middle and the largest region of the nasal cavity (the respiratory region) remain supplied with the trigeminal sensory neurons and blood vessels. When the drug is administered into the nasal cavity, the drug has to travel to the olfactory mucosa to undergo mucociliary clearance in the vestibular region.

Olfactory mucosa contains olfactory receptor neurons responsible for the transduction in olfactory receptors on the cilia which is the end of the olfactory receptor neurons. The drug molecules reach the olfactory receptor neurons by paracellular or transcellular mechanism. Moreover, the drug molecules reach to the internal portion of the nasal cavity, thereby comes in contact with the blood vessels (respiratory epithelium) and neuronal network (olfactory and respiratory epithelium).[6]

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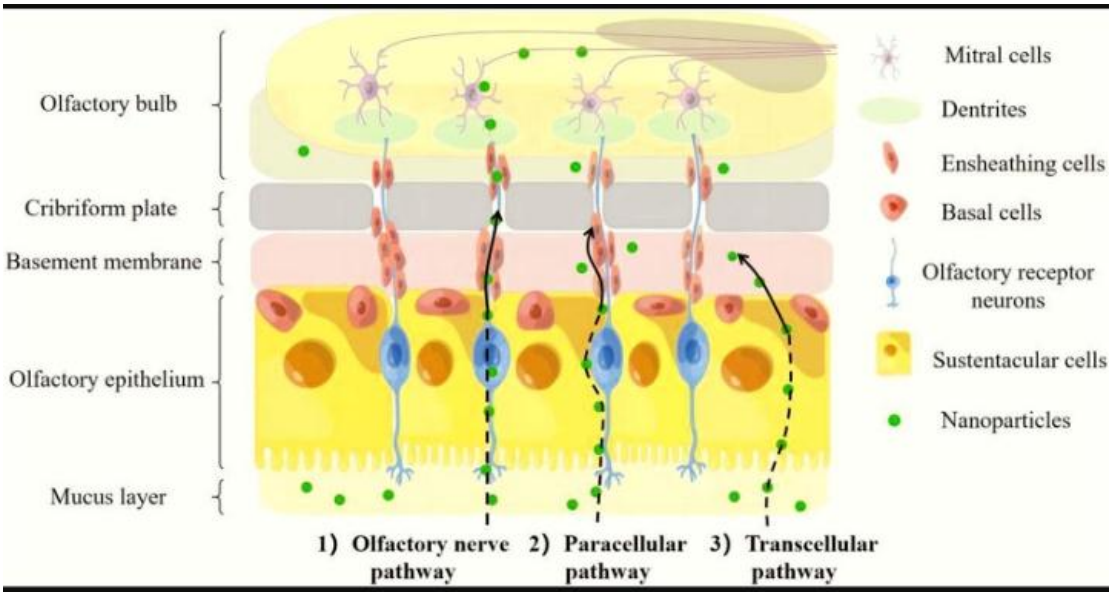

PATHWAYS OF INTRANASAL TRANSPORT TO THE BRAIN

Inhaled drug transport to the brain can happen indirectly through the respiratory epithelium through lymphatic and systemic circulation. The respiratory epithelium is highly vascularized and provides access to blood circulation as a result of a continuous and fenestrated endothelium. The BBB is the rate-limiting barrier between these drugs and the CNS; thus crossing it is necessary. Small and lipophilic compounds often go through the systemic channel to penetrate the BBB transcellularly.

SALIENT FEATURES OF LIPID BASED NANOPARTICLES

- It provides information about the physicochemical properties of the nano particles, which are critical for their efficacy and safety.
- Particle size and shape distribution are critical parameters that determine the stability and efficacy of SLNs.
- Zeta potential is also an important parameter that determines the stability of the SLNs.
- Different scanning calorimetry [DSC] is a thermal analysis technique that measures the heat flow in a sample as a function of temparature. It can be determined the melting point, crystallinity and thermal stability of the lipids in the SLNs
- The morphology of SLNs can be observed by transmission electron microscopy [TEM] or scanning electron microscopy [SEM].[3]

ADVANTAGES OF LIPID BASED NANOPARTICLES:

The benefits of various colloidal systems including liposomes, nanoemulsions, and polymeric nanoparticles are all combined in SLNs. The following succinctly describes the main benefits of SLNs:

- SLNs have no bio toxicity because the lipids utilised are biocompatible and biodegradable materials.
- SLNs have no bio toxicity because the lipids utilised are biocompatible and biodegradable materials.
- It is possible to make SLNs without employing organic solvents.
- The physical stability of SLNs is high.
- SLNs can be used to achieve both drug targeting and controlled drug release.
- Incorporating active compounds into SLNs can boost their stability.
- Lipophilic and hydrophilic medications may be encapsulated in SLNs.
- It is simple to produce SLNs on a big scale.
- SLNs are sterilizable.[4]

DISADVANTAGES OF LIPID BASED NANOPARTICLE:

- Lipid dispersion have high water content.
- Limited transdermal medication delivery.
- Hydrophilic drug loading capacity is constrained.
- Polymeric changes.
- Lipid dispersion gelation.
- Increase the particles size while being stored.[5]

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II. APPLICATIONS OF LIPID BASED NANOPARTICLES

Development of solid lipid-based nanoparticles is one of the emerging fields of lipid nanotechnology with several potential applications in drug delivery, clinical maedicine and research, as well as in other disciplines. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics.

The conventional approaches such as use of permeation enhancers, surface modification, prodrug synthesis, complex formation and colloidal lipid carrier-based strategies have been developed for the delivery of drugs to intestinal lymphatics. In addition, polymeric nanoparticles, self-emulsifying delivery systems, liposomes, microemulsion, micellar solutions and recently solid lipid nanoparticles (SLN) have been exploited as probable possibilities as carriers for oral intestinal lymphatic delivery.

In modern medicine, the intranasal drug delivery is emerging as a non-invasive option for various neurological dysfunctions with minimal peripheral side effects. Therefore, this method facilitates the delivery of compounds such as growth factors, hormones, neuropeptides, and therapeutics including insulin, oxytocin, orexin, stem cells for the treatment of various neurological disorders.[8]

III. TYPES OF FORMULATIONS USEDIN LIPID BASED NANOPARTICLES [7]

1.LIPOSOMES FOR NOSE- TO- BRAIN DELIVERY:

Liposomal formulations have gained tremendous popularity as they are biocompatible, non-toxic, and deliver both hydrophilic and hydrophobic molecules. Liposomes, as adaptable lipid-based nano particle, have the potential to enhance medication transport from the nose to the brain. This is attributed to their compatibility with biological systems, capacity to encapsulate diverse medicines, and ability to target particular areas of the brain. The brain levels of lipophilic and amphiphilic drugs were notably higher compared to hydrophilic drug molecules when administered via the nasal route in liposomal formulations. This is attributed to their efficient absorption through both direct and indirect transport pathways to the brain

Rats treated with liposomal formulations of donepezil exhibited higher AUC and C_{max} levels in both plasma and the brain, alongside a prolonged half-life, indicating enhanced systemic and brain bioavailability. Quetiapine fumarate administered intranasally via liposomal formulations exhibited markedly higher brain levels for an extended period compared to the free drug, possibly attributable to increased brain uptake via endocytosis. These studies collectively underscore the efficacy of liposomal formulations in delivering drug molecules from the nose to the brain, encompassing both hydrophilic and hydrophobic compounds. However, it is essential molecules.

2.SOLID LIPID NANOPARTICLES FOR NOSE -TO- BRAIN:

SLNs are being increasingly studied for their potential to deliver drugs through various routes including the nose-to-brain route. This is because SLNs are known for their stability, biocompatibility, and ability to effectively encapsulate a wide range of pharmaceuticals. The feasibility of SLNs to deliver actives to the brain via the nose-to-brain route was demonstrated using sumatriptan. The prepared SLNs exhibited spherical morphology and sustained drug release up to 12 h. Ex vivo studies indicated quick permeation across nasal mucosa, while histopathology studies confirmed the integrity of the nasal mucosa after treatment. SLNs provide ameans to enhance the transportation of drugs to the brain, therefore addressing the issue of drug delivering for the treatment of Alzheimer's disease. In one study, asiatic acid-loaded SLN was developed with the objective of improving the bioavailability through the intranasal route. The study discovered that learning and memory impairments brought on by amyloid-β_{1-42} were alleviated by the intranasal therapy of drug-loaded SLNs.

They also demonstrated successful brain targeting, indicating the potential of this approach for enhancing the therapeutic efficacy of agomelatine. Similarly, the SLNs were investigated as a drug-delivery system to enhance the brain-targeting efficiency of rosmarinic acid via intranasal administration. In a rat model of Huntington's disease, the SLN treatment significantly improved behavioral abnormalities and attenuated oxidative stress. Indeed, the nasal delivery of SLN showed significant therapeutic effects compared to intravenous administration, with a brain drug concentration of 5.69 µg and favorable pharmacokinetic parameters. Another drug, haloperidol, was delivered to the brain through the nasal route. Results of in vitro release studies demonstrated sustained release, while pharmacokinetic studies in rats revealed significantly higher brain concentrations of

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haloperidol with SLNs compared to other administration routes.

3.NANOSTRUCTURED LIPID CARRIERS FOR NOSE- TO- BRAIN:

NLCs are a sophisticated kind of lipid-based nanoparticle that have garnered interest for their enhanced drug-loading capacity and stability in the context of nose-to-brain drug administration. NLCs are made to meet all industrial requirements, including quantification, scalability, inexpensiveness, and basic technology. The use of biocompatible and biodegradable lipids and surfactants in NLCs has also made them suitable from a regulatory standpoint. Owing to their lipophilic properties, NLCs exhibit a superior ability to partition into the lipid bilayer of nasal epithelial cell membranes compared to free drugs. Additionally, nanosized particles with ample lipophilicity can easily traverse intercellular spaces between olfactory cells.

Various categories of drugs including agomelatine, aripiprazole, artesunate, asenapine, astaxanthin, diazepam, efavirenz, nicergoline, olanzapine rivastigmine, sumatriptan, etc., have been developed into NLCs to be delivered into the brain through nasal application for targeting CNS disorders. Quetiapine, an antipsychotic medicine, has difficulties in effectively reaching the brain and has adverse effects on the whole body.

Intranasal delivery of asenapine using glycol chitosan-coated NLCs showed promising results, with increased systemic and brain bioavailability compared to asenapine solution. The developed NLCs demonstrated good biocompatibility and could be a potential carrier for intranasal drug delivery, offering improved pharmacokinetics and 6safety. The potential of NLCs in delivering astaxanthin, a potent antioxidant with anti-inflammatory and neuroprotective effects, to the brain was assessed in rats. It was noticed that the intranasal administration of the developed NLCs significantly reduced oxidative stress, neuroinflammation, and apoptosis while improving cholinergic neurotransmission. Similar studies were also reported by other researchers wherein the NLCs have demonstrated their potential in delivering different actives to the brain via nose-to-brain delivery.

4.NANOPARTICULATE FORMULATIONS:

Nano formulations/ Nanoparticulate formulations Drug targeting to human brain has always been challenging for formulators due to the presence of strong barriers such as blood brain barrier and blood cerebrospinal fluid barrier as discussed earlier. After intensive research, intranasal route has been found as a potential route for drug transport directly to brain. Drug delivery through nasal route is considered as non-invasive route.1 The ability of nasal mucosal layer to transport the small sized molecules has also been explored widely. Various drug delivery technologies has been emerged, amongst them nanoparticulate system is fascinating part for formulation and a major area of interest due to its potential benefits like ease of preparation, long term stability, achieving desired therapeutic concentration at the site of action, potent drugs can encapsulated and protection from environmental degradation.

5.SURFACTANTS:

Surfactants are the substances that have a major role in fabrication of all the pharmaceutical formulation. Surfactants contribute by decreasing the surface tension between hydrophilic and lipophilic components and thereby providing a stable formulation. Surfactants possess various functional groups, having solubility in either aqueous phase or oil phase. Thus, surfactants with hydrophobic group have affinity towards lipophilic phase and surfactants with hydrophilic group have affinity towards aqueous phase.

6.STABILISERS, PRESERVATIVES:

Stabilizers play important role to keep the formulation stable for long duration of time without any particulate aggregation due to surface charge builtup on it. Generally major phase in SLN constitutes of aqueous phase. This can lead to microbial growth during long storage. Hence for the prevention of microbial growth, preservatives are added (eg: Benzalkonium chloride).

IV. METHODS OF PREPARATIONS OF LIPID BASED NANO PARTICLES[4]

SLNs are prepared from lipid, emulsifier and water/solvent by using different methods and are discussed below.

Methods of preparation of solid lipid nanoparticles:

1. High pressure homogenization
   a. Hot homogenization
   b. Cold homogenization.
2. Ultrasonication/high speed homogenization
   a. Probe ultrasonication
   b. Bath ultrasonication
3. Solvent evaporation method
4. Solvent emulsification-diffusion method
5. Supercritical fluid method

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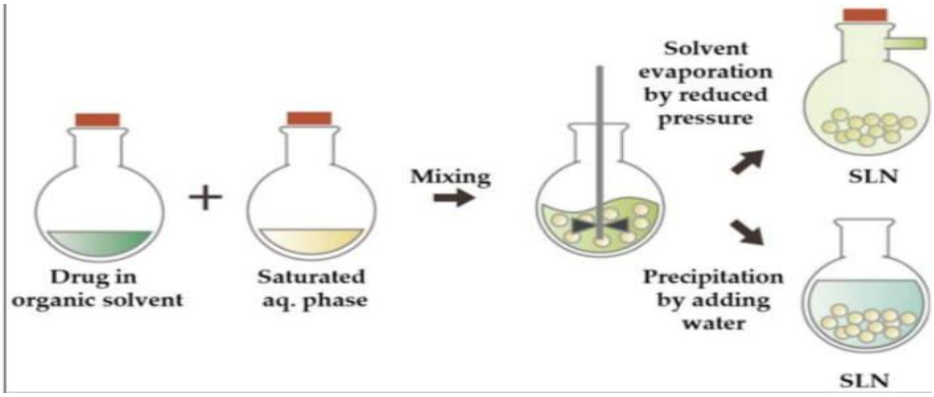
6. Microemulsion based method
7. Spray drying method
8. Double emulsion method
9. Precipitation technique
10. Film-ultrasound dispersion.[4]

1.SOLVENT EVAPORATION METHOD:

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 (40-60mbar). Nanoparticles of 25 nm size range are formed by this method.[4]



SOLVENT EVAPORATION METHOD

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 (100-2000bar) 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.[4]

3.HOT HOMOGENIGSTION METHOD:

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.[4]

4.COLD HOMOGENIGATION METHOD:

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 pre-suspension 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), coemulsifiers (e.g. Butanol) and water. This mixture is stirred at 65-70˚C.The hot microemulsion is dispersed in cold water (23˚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.[4]

5.ULTRA 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

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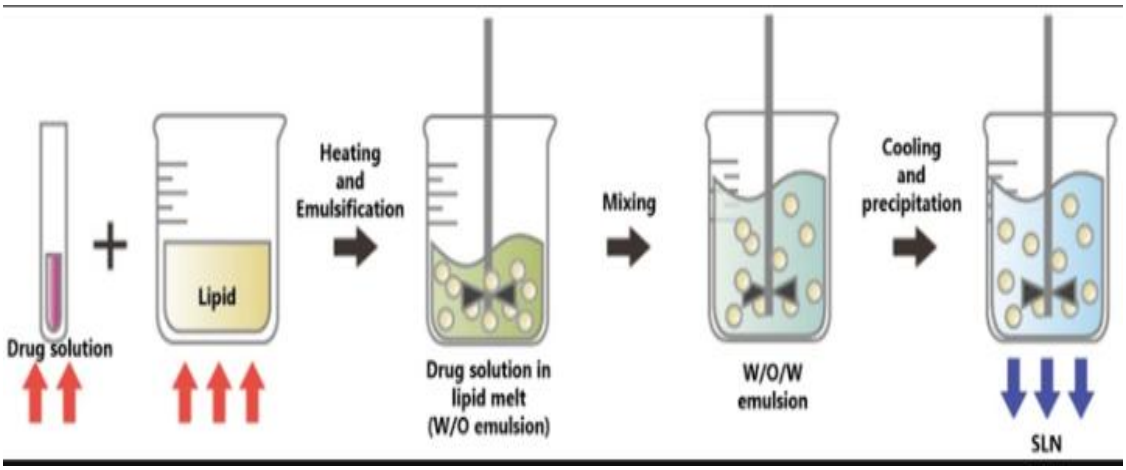
dichloromethane at 50˚C and with constant sirring. This emulsion produced is subjected to sonication for appropriate time and finally cooled in ice bath to get solidify lipid nanoparticles.[4]



ULTRA SOLVENT EMULSIFICATION TECHNIQUE

6.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.[4]

7.PRECIPITATION METHOD:

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

8.FILM ULTRA- SOUND 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.[4]

9.PHASE INVERSIONTEMPERATURE METHOD:

The PIT method is based on the use of non-ionic polyoxyethylated surfactants that have temperature-dependent properties. The ethoxy groups are highly hydrated at low temperatures, and, thus, the surfactants have a high hydrophilic-lipophilic-balance (HLB) value. At high temperatures, the ethoxy groups are dehydrated, which decreases the HLB value of the surfactants and increases their lipophilicity. PIT is the temperature at which the surfactants have an equal affinity for aqueous and lipid phases. The PIT method includes three steps: (i) heating, (ii) cooling, and (iii) the precipitation of lipids. In the first step, drugs, lipids, water, and surfactant are heated to a temperature > PIT, to form a water/oil emulsion. In the second step, the water/oil emulsion is rapidly cooled, to induce the formation of an oil/water nanoemulsion. The heating and cooling process can be carried out for several cycles (e.g., three cycles between 60 and 90 C). The third step is to cool the oil/water nanoemulsion, to precipitate lipids and form SLNs. The PIT method is solvent-free and requires little energy input. However, the nanoemulsion has low stability.[9]

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Volume 4, Issue 5, Sep.-Oct., 2024, pp: 248-257 ISSN: 3048-6874
www.ijhssm.org

V. EVALUATION OF LIPID BASED NANOPARTICLES [4]

1.*Invitro* 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.

2.Reverse dialysis:

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

3.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.

4.Ex vivo for permeability testing:

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

Analytical Characterization of SLN:[4]

1.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 covers a size range from a few nanometers to about few nanometers to about 3micron.

2.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.

3.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.

4.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.

VI. CONCLUSION

Since there is a long list of drugs that have been developed for the treatment of CNS related disorders but due to its inability for drug substances to cross the BBB, many of them were discarded. Most of the drugs that are presently being used for brain diseases use the IV route of administration due to its rapid onset of action, however, its side effects are more pronounced as compared to other routes. Over the last several decades, majority of research and development projects are actively pursuing the development of novel nasal drug-delivery systems that are capable to pass through BBB. A number of studies on both animals and human subjects have also demonstrated that intranasal delivery of various types of drug molecules can produce salubrious effects on the brain. Although the exact mechanism of nose to brain drug delivery remains subtle, the olfactory and trigeminal nerve pathways have been found to play a vital role in circumventing the traditional barriers of brain targeting. The present outlook for patients suffering from CNS related diseases may appear feeble, but recent developments in drug delivery techniques has provided a reasonable hope in overcoming those formidable barriers.

Recently, it has been found that intranasal drug delivery has potential relevance for future clinical trials in the settings of preventing disease transmission and treatment of SARS-CoV-2 and other viral diseases. The strategy is still under investigations with various research studies and surplus challenges to get better insight for the development of successful nose to brain targeted therapy before reaching the pharmacy counter. This article summarizes the current knowledge regarding intranasal drug delivery and its potential applications in combating several CNS disorders and viral pandemics like SARS-CoV-2.

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