International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 4, 2023

Review Article

SOLID LIPID NANOPARTILCES: MODERN PROGRESS IN NOSE-TO-BRAIN TRANSDUCTION

C. SOWMYA, SURIYA PRAKAASH K. K., ABRAR AHMED H.*

*Department of Pharmaceutics, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai-600116, India

*Corresponding author: Abrar Ahmed H.; Email: abrarabu32@gmail.com

Received: 25 Mar 2023, Revised and Accepted: 06 Jun 2023

ABSTRACT

Solid Lipid Nanoparticles (SLNs) have gained significant attention in recent years as a promising delivery system for drugs targeting the Central Nervous System (CNS) via the Nose-To-Brain (NTB) route. The unique characteristics of SLNs, such as their small particle size, high stability, and ability to encapsulate lipophilic drugs, make them suitable for crossing the Blood Brain Barrier (BBB) and achieving targeted delivery to the brain. This has led to the development of SLNs-based formulations of drugs for neurological disorders such as Alzheimer's disease and Parkinson's disease, which are being evaluated in preclinical and clinical studies. Overall, the recent advances in SLN technology have improved these nanoparticles' stability, drug loading capacity and BBB crossing ability, making them a promising delivery system for NTB drug delivery. SLNs are composed of a solid lipid core surrounded by a surfactant coating, which allows for the encapsulation of hydrophilic and hydrophobic drugs. Additionally, we will also highlight the current challenges and future perspectives of using SLNs for NTB delivery of CNS therapeutics. Overall, this review aims to provide a comprehensive overview of the current state of the art in using SLNs for NTB delivery and to encourage further research in this field.

Keywords: Solid lipid nanoparticles, Targeted drug delivery, Nose-to-brain delivery, Intra-nasal route, Methods of SLN preparation

DOI: https://dx.doi.org/10.22159/ijap.2023v15i4.47897. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The last few decades have seen researchers increasingly interested in the exciting scientific area of delivering medications to the brain. However, the Blood Brain Barrier (BBB), which creates an endothelial membrane separating the systemic circulation from the Central Nervous System (CNS), prevents drugs from reaching the brain's site of action [1]. A monolayer of tightly interconnected endothelial capillary cells makes up the BBB, which facilitates the selective entry of nutrients and hormones while preventing the passage of infections, poisons, and other foreign substances, such as medications. The therapeutic agent must first cross the BBB to reach the CNS after being administered orally or systemically. Active transport and passive diffusion (paracellular or transcellular) via endothelial cells are the primary routes through which substances reach the brain. Similar to this, tight junctions make the BBB impenetrable to big molecules and most low molecular weight (Mw) molecules, enabling only smaller and highly lipophilic molecules to get through [2, 3]. Therefore, a variety of strategies are used to target drugs to the brain, which include osmotic and biochemical disruption of BBB, drug modification like lipophilic analogues, prodrugs, chemical drug delivery, carrier-mediated delivery, and receptor/vector-mediated drug delivery, and alteration of the route of administration, including intracerebroventricular, intrathecal, and olfactory pathways (intranasal route). The intranasal route is being investigated in the current context because it offers a unique, useful, easy, and non-invasive method of breaching the BBB and minimizes systemic exposure and, ultimately, systemic unfavourable effects [4, 5]. Due to the neurological relationship between the nasal mucosa and the brain, the drug penetrates the olfactory epithelium region of the nasal mucosa after being administered intravenously, which serves as a doorway for drugs entering the CNS [6]. Solid Lipid Nanoparticles (SLNs) are made up of a colloidal solid lipid core matrix that is stabilized and emulsified in an aqueous medium by a surfactant. High drug Entrapment Efficiency (EE), smaller particle size, and huge surface area are what set them distinct [7]. Due to their ability to protect the drug from biological and/or chemical degradation and potential to prolong nasal retention time due to an occlusive effect, favourable application characteristics, and SLN's adhesion to mucous membranes, SLNs can provide advancement to conventional Nose-to-Brain (NTB) drug delivery [8].

Intranasal route (anatomy)

When creating an intranasal formulation, the anatomy, physiology, and defence systems of the nasal cavity should be taken into consideration. The nose is responsible for olfaction, regulating the temperature and humidity of the inhaled air and removing external pathogens. The nasal cavity is approximately 12–14 cm long, 5 cm tall, and has a surface area of 150–200 cm^2 and a total capacity of 15-20 ml. The nasal vestibule, the respiratory portion, and the olfactory section are the three divisions of the nasal cavity [10].

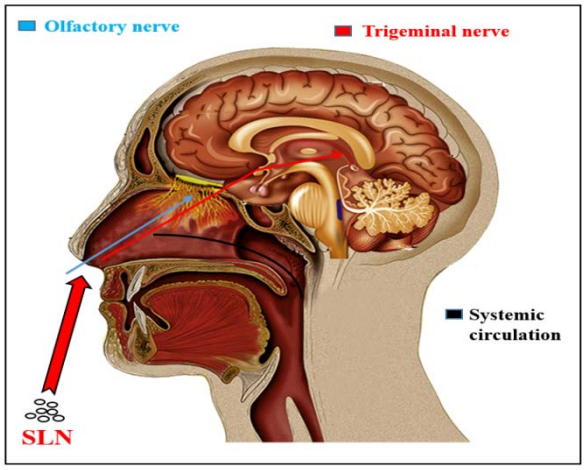

Fig. 1: Anatomical features of nose-to-brain delivery [9]

Nasal vestibule

The vestibule, which is located in the front of this cavity, serves as the body's initial line of defence against pathogen entry. Due to the low vasculature, tiny surface area (0.6 cm^2), presence of mucus, and nasal hairs (vibrissae) that filter big air particles, this area is the least permeable. A squamous epithelium that includes sweat and sebaceous glands covers this area. Studies on medication administration pay minimal attention to the nasal region.

Respiratory mucosa

The human nasal cavity's respiratory mucosa makes up about 80–90% of the total surface area and is highly vascular zed, making it an

important location for systemic drug absorption [11]. Basal cells, goblet cells, ciliated epithelial cells, and serous glands are only a few of the several cell types and glands that make up the respiratory mucosa [10,12]. In addition to helping to affix ciliated and goblet cells to the basal lamina, basal cells are progenitor cells that can develop into various cell types present within the epithelium [13]. Mucus is a fluid that is secreted by goblet cells and is made up of mucin (high molecular weight glycoprotein's), salts, water, a few proteins, and lipids [14]. The respiratory epithelium creates a coating of mucus, which acts as a first line of defence by trapping any irritants or foreign objects breathed [15]. The cilia that cover approximately 15%–20% of the respiratory cells move in rhythm and direct mucus from the front portion of the nasal cavity to the throat, where it is thereafter eliminated through the gastrointestinal tract. When dangerous exogenous compounds are retained in mucus and removed through this renewal process every 15 to 30 min, the respiratory tract is protected by a mechanism known as Mucociliary Clearance (MCC). Mucociliary clearance is the consequence of the removal of this mucus toward the nasopharynx by ciliated cells [11,16]. As a component of innate immunity, serous glands release watery fluid and other antimicrobial substances [17].

Olfactory mucosa

About 5–10% of the surface area of the human nasal cavity is taken up by the olfactory mucosa, which is situated on top of the nasal cavity. The olfactory epithelium, lamina propria, so-called Olfactory Sensory Neurons (OSN), and olfactory receptor neurons make up the olfactory mucosa [18]. The first cranial nerve to convey sensory data linked to scent is the olfactory nerve.

The olfactory region, the only area directly connecting the nasal mucosa to the brain, is situated in the upper portion of the nasal cavity, above the superior nasal turbinate of the respiratory region and beneath the cribriform plate of the skull. This location provides a direct route for drugs to enter the CNS via the olfactory bulb. Additionally, the Cerebro Spinal Fluid (CSF) has a direct conduit through this area, which has a surface area of 10 cm^2. The cribriform plate, a bone structure made up of tiny holes and neuronal bundles, permits drugs to move from the olfactory epithelium into the CNS [19].

Nose-to-brain delivery of therapeutics

It has been thoroughly studied how drugs are delivered from the nose to the brain. The medicine can enter the brain by one of three main channels, or through a combination of them, according to a large number of studies. The drug enters the systemic circulation through the nasal mucosa and is then transported to the brain through the indirect route, also known as the systemic pathway. The drug enters the brain through the direct route, passing through the trigeminal and olfactory nerves. Numerous factors, including drug solubility, formulation residence time, metabolic stability, and mucociliary clearance rate, affect the medication's capacity to permeate the nasal mucosa [20, 21].

Moreover, to prevent irritation, ciliotoxicity and tissue damage, it is crucial to assess the drug's safety and toxicity in the nasal mucosa. Also, the medication must avoid the mucociliary clearance process after being administered intravenously to reach the olfactory area. This procedure may cause some medicine to be lost before having a therapeutic effect [22].

The NTB method of drug delivery favours medications having a low oral bioavailability. The intranasal route, which offers a direct transport path into the CNS, provides several advantages over conventional drug delivery techniques. Additionally, it eliminates the negative effects of the BBB, making it an efficient delivery method.

The delivery of therapeutic compounds to the brain to treat CNS illnesses has been researched via drug transport through the olfactory mucosa. As previously mentioned, it has the considerable benefit of avoiding the BBB and lowering systemic exposure. Although the NTB delivery mechanisms are not fully known, several recent research has offered some significant potential paths. One method is the direct delivery of medications to the brain via neural pathways like the trigeminal or olfactory nerves. The brain can also cross the BBB through indirect drug delivery via the lymphatic and vascular systems. There may be several mechanisms involved in drug absorption from the nose to the brain, rather than just one unique process.

Olfactory pathway

Four groups of major drug transport mechanisms across the olfactory system may be distinguished as intra-and extra-neuronal pathways, paracellular pathways, and transcellular pathways. The NTB delivery mechanism heavily relies on olfactory neurons. OSN can endocytose therapeutic molecules, causing them to form vesicles that can then be transported along neurons, through the cribriform plate, and into the olfactory bulb. They will proceed via exocytosis and be dispersed throughout the CNS once they get to the brain [23]. One of the tiniest axons in the CNS, the human olfactory axon has a diameter of between 0.1 and 0.7 m [24].

The drug enters the olfactory cortex by intraneuronal and extraneuronal transport along the olfactory nerves, passing through the olfactory bulb on its way to the CNS, more particularly the cortex, cerebrum, and cerebellum. The medicine must travel through the axons during intraneuronal transport, which is sluggish and might take hours or even days to complete. The olfactory bulb and the CNS have reached in a matter of minutes thanks to extraneuronal transport, which is quicker and follows paracellular and transcellular transport [25].

Trigeminal pathway

The trigeminal route, or intracellular transport, is the movement through the trigeminal nerve after endocytic and axonal movement. The trigeminal nerve is the largest cranial nerve and innervates the respiratory and olfactory epithelium [26]. It has three different branches (mandibular, ophthalmic, and maxillary), which converge in the trigeminal ganglion, enter the CNS, and terminate in the brainstem. Since they link the nasal cavity to the CNS [27], the maxillary and ophthalmic branches of the trigeminal nerve are crucial for NTB transport. Drugs can enter the brainstem via the respiratory epithelium of the trigeminal nerve and go to the rostral and caudal regions of the brain via the dorsal olfactory epithelium through the cribriform plate. The maxillary and ophthalmic branches are two of those that are involved in NTB delivery. The dorsal nasal mucosa and the front of the nose are both crossed by ophthalmic branches, whereas the lateral nasal mucosa is crossed by maxillary branches.

Drug transport via the trigeminal nerve happens via several paths, much to the olfactory nerve system. Drug molecules will combine in the trigeminal ganglion and enter the brain close to the pons when they get to the trigeminal nerve branches. Drug molecules can traverse the cribriform plate and reach both the caudal and rostral parts of the brain since some trigeminal nerve segments are located close to olfactory bulbs.

Systemic pathway

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.

The systemic pathway is a diversion where drugs go to the bloodstream and lungs before travelling to the brain. To reach the brain via this route, the drugs must thus cross the BBB, which extends the time it takes to accomplish the therapeutic effect and reduces the quantity of drug that reaches the brain [28]. Moreover, the level of drugs in the brain after intranasal delivery varies across people and is subject to hepatic and renal routes of elimination.

Thus, depending primarily on the characteristics of the medicine, pharmaceuticals can enter the brain directly or through the systemic route. For instance, after being administered intravenously, several lipophilic medications enter the brain via the systemic pathway.

Advantages of SLNs for brain delivery

Biocompatibility and Biodegradability

One of the main advantages of SLNs is their biocompatibility and biodegradability. SLNs are composed of lipids that are similar to those found in the body, such as triglycerides and phospholipids. This means that they are well-tolerated by the body and have low toxicity. Additionally, SLNs are biodegradable, which means that they can be broken down into harmless byproducts and eliminated from the body through natural processes.

Enhanced drug stability

SLNs can protect drugs from degradation, as the lipid matrix can act as a barrier to external factors, such as light, heat, and moisture. This is particularly beneficial for drugs that are sensitive to degradation, such as biologics and peptides. The lipid matrix can also protect the drug from enzymatic degradation in the nasal mucosa, which can improve the bioavailability of the drug.

Controlled drug release

SLNs can provide sustained and controlled drug release, which can improve drug efficacy and reduce the frequency of dosing. The rate of drug release from SLNs can be modified by altering the lipid composition or the preparation method of the nanoparticles. For example, the use of lipids with different melting points can create a gradient of drug release over time. This can be useful for drugs that have a narrow therapeutic window or require constant drug levels to maintain efficacy.

Increased drug bioavailability

SLNs can improve the bioavailability of drugs, as they can protect them from metabolism and enhance their absorption through the nasal mucosa. The nasal mucosa has a large surface area and is highly vascularized, which allows for rapid drug absorption into the bloodstream. Additionally, the use of SLNs can reduce the dose required to achieve a therapeutic effect, which can minimize side effects and improve patient compliance.

Targeted drug delivery

SLNs can be engineered to target specific cells or tissues, such as the brain, by modifying the surface of the nanoparticles. This can enhance the accumulation of the drug at the target site while reducing off-target effects. For example, the surface of the SLNs can be coated with ligands that bind to specific receptors on the nasal epithelium or brain endothelium, which can facilitate transport across the blood-brain barrier. Additionally, SLNs can also be loaded with contrast agents, which can be used for diagnostic purposes in imaging modalities such as Magnetic Resonance Imaging (MRI).

Ease of production

SLNs can be easily produced on a large scale using various techniques, such as high-pressure homogenization, hot homogenization, and microemulsion. This makes them a cost-effective option for drug delivery. Additionally, the use of natural lipids in SLNs makes them readily available and easy to source. Furthermore, the production process is relatively simple and can be easily adapted for different drug compounds, making SLNs a versatile option for drug delivery.

Limitations of SLNs for brain delivery

Low drug loading capacity

The drug loading capacity of SLNs depends on various factors, including the solubility and stability of the drug in the lipid matrix, the size of the nanoparticles, and the preparation method used. The lipid matrix can solubilize lipophilic drugs and protect them from degradation, while hydrophilic drugs can be incorporated into the nanoparticles by using surfactants or co-solvents. However, due to the limited space available in the solid lipid matrix, only a small amount of drug can be loaded into the nanoparticles. This can be a challenge for drugs that require high doses to be effective, as the volume of the nanoparticles required to deliver a therapeutic dose may be too large. SLNs require a complex formulation process and may not be suitable for all types of drugs.

Limited drug release

The release of the drug from SLNs can be influenced by various factors, including the properties of the lipid matrix, the size of the nanoparticles, and the method of preparation. The lipid matrix can control the release of the drug by providing a barrier to its diffusion. The size of the nanoparticles can also affect the rate of drug release, with smaller nanoparticles generally releasing the drug more rapidly than larger nanoparticles. The method of preparation can also affect the drug release profile, with techniques such as hot homogenization and microemulsion producing SLNs with faster drug release rates than those produced by cold homogenization. SLNs may not be as stable as other drug delivery systems, which can impact the drug's efficacy.

Limited transport across the mucus layer

The mucus layer in the nose can act as a physical barrier to the transport of SLNs to the brain. The mucus layer consists of a complex mixture of glycoproteins, lipids, and other substances, which can entrap and clear nanoparticles. The size and surface properties of the nanoparticles can influence their ability to penetrate the mucus layer. Smaller nanoparticles may be able to diffuse through the mucus layer more easily than larger nanoparticles, while nanoparticles with a hydrophilic surface may be cleared more rapidly than those with a hydrophobic surface. To improve the transport of SLNs across the mucus layer, various strategies have been proposed, including the use of mucoadhesive agents and the modification of the nanoparticle surface to enhance their interaction with the mucus layer.

Clearance by the immune system

The immune system can recognize and clear SLNs from the body, which can limit their effectiveness for nose-to-brain drug delivery. The clearance of SLNs by the immune system can be influenced by various factors, including the size, shape, and surface properties of the nanoparticles. Larger nanoparticles may be more rapidly cleared by the immune system than smaller nanoparticles, while nanoparticles with a hydrophilic surface may be more rapidly cleared than those with a hydrophobic surface. Surface modifications of the nanoparticles can be used to decrease their recognition by the immune system, for example, by coating them with Polyethylene Glycol (PEG), which can reduce their uptake by phagocytic cells.

Stability issues

SLNs may be prone to aggregation, which can affect their stability and ability to transport the drug to the brain. Aggregation can occur due to various factors, including the interaction of the nanoparticles with biological fluids or other nanoparticles, and can lead to increased clearance by the immune system and reduced penetration through the mucus layer. To improve the stability of SLNs, various strategies have been proposed, including the use of stabilizing agents, such as surfactants, and the modification of the nanoparticle surface to reduce their interaction with other nanoparticles or biological fluids. Additionally, storage conditions can also affect the stability of SLNs, with factors such as temperature and humidity needing to be carefully controlled to ensure the long-term stability of the nanoparticles.

Challenges

Physicochemical properties that govern the NTB delivery

Several physicochemical properties can affect the NTB delivery of drugs, including molecular weight, lipophilicity, and charge.

Particle size

One of the most critical elements of the NTB delivery method is particle size. The OSN's diameter, between 0.1 and 0.7 m, as previously mentioned, restricts the particle size to the Nano range. Additionally, because mucus develops a mesh-like structure, smaller particles penetrate the mucous membrane with less resistance. The ideal nanoparticle diameter for axonal transport is less than 100 nm, according to several studies.

Molecular weight

Smaller molecules tend to be more easily transported across the nasal mucosa, as they can more easily diffuse through the membrane.

Surface charge

The charge of a molecule can also affect its transport across the nasal mucosa. Generally, molecules with a positive charge tend to be repelled by the negatively charged nasal mucosa, while those with a negative charge tend to be attracted to it. Positively charged particles are more likely to interact with the nasal mucosa by electrostatic force because the nasal mucosa membranes are often negatively charged. As a result, the nasal epithelium will experience longer residence times and bioadhesion. To boost medication bioavailability for NTB administration, various studies have employed positively charged carriers such as chitosan and its derivatives.

Lipophilicity

Lipophilic (fat-loving) molecules tend to be more easily transported across the nasal mucosa, as they can dissolve in the lipid bilayer of the membrane. As they create hydrophobic bonds with the hydrophobic domains of mucin and prolong residence duration, hydrophobic carriers are more likely to induce mucoadhesion. The hydrophobic contact between the carrier and mucin, however, prevents it from penetrating the mucus and causes MCC to remove it. A careful balance between lengthening the residency period and mucus penetration would thus be crucial. Hydrophobicity, like the charge of the nanoparticle, can influence mucoadhesion as well as the route of NTB transport and distribution in the brain.

Formulation, such as liposomes, nanoparticles, and micelle, can be used to improve the transport of drugs across the nasal mucosa and enhance NTB delivery. SLNs differ from all other Nano formulations, SLNs are composed of solid lipids, while others, such as liposomes, polymeric nanoparticles, or dendrimers, are made of different materials. The solid lipid matrix of SLNs provides a high degree of stability and reduces aggregation. SLNs can provide a prolonged release of the encapsulated drug compared to other Nano formulations, which can result in a more sustained therapeutic effect. SLNs have unique physiochemical properties, such as size, surface charge, and lipid composition, that distinguish them from others. The biocompatibility of SLNs is generally considered to be better than other Nano formulations due to their lipid-based composition. Overall, SLNs offer several advantages over other Nano formulations, making them a promising option for drug delivery applications.

Techniques of preparation of SLNs

The formulation of SLNs for NTB delivery involves several steps, including the selection of the appropriate lipid and surfactant, the preparation of the nanoparticles, and the characterization of the resulting formulation. First, the lipid and surfactant used to make the SLNs must be selected. Lipids such as tristearin, stearic acid, and cetyl palmitate are commonly used in SLN formulations due to their solid state at room temperature and biocompatibility. Surfactants such as polysorbate 80, poloxamer 188, and lecithin are also commonly used in SLN formulations due to their ability to form stable nanoparticles [29]. Next, the SLNs are prepared using techniques such as high-pressure homogenization, ultrasonication, or microemulsion. High-pressure homogenization and ultrasonication are physical methods that use mechanical energy to break down the lipid and surfactant mixture into small nanoparticles. The Microemulsion is a technique that uses a combination of surfactants and co-surfactants to create an emulsion that is then cooled to form SLNs. After preparation, the SLNs are characterized for their size, size distribution, zeta potential, drug loading, and encapsulation efficiency. The particle size and size distribution of the SLNs are important factors in determining the ability of the nanoparticles to penetrate the nasal mucosa. The zeta potential is a measure of the surface charge of the nanoparticles, which can affect their stability and ability to interact with the mucosal surface. The drug loading and encapsulation efficiency of the SLNs are important factors in determining the potential therapeutic effect of the drug. Finally, the formulated SLNs must be evaluated for their ability to target the brain following nasal administration. This can be done by measuring the levels of the drug in the brain after administration, as well as assessing the pharmacokinetics and pharmacodynamics of the drug. Additionally, the toxicology and safety of the SLN formulations must be evaluated before they can be considered for use in humans [30].

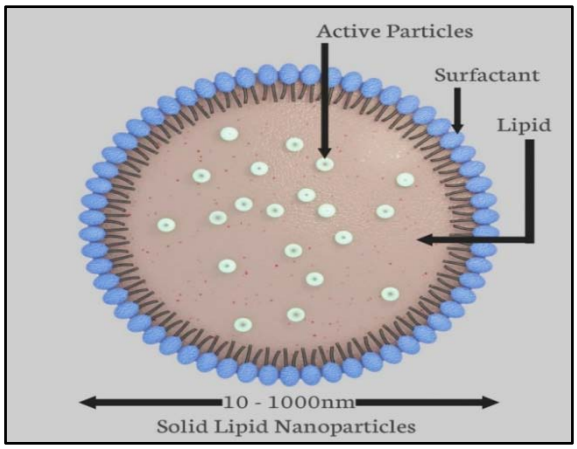

Fig. 2: Diagrammatic representation of SLNs [31]

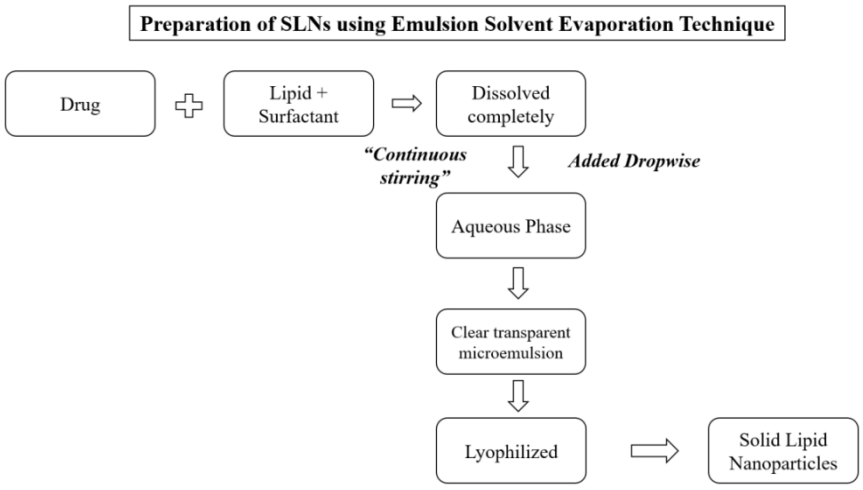

Fig. 3: Schematic representation of emulsion solvent evaporation technique [31]

Emulsion solvent evaporation

By using the process of emulsion solvent evaporation, PLGA-CN nanoparticles were formed. Briefly, 10 ml of the aqueous phase (0.5% acetic acid solution with a pH range of 4.6-4.8) containing 0.5% PVA and 0.5% CN was added after 100 mg of PLGA had been dissolved in 2.5 ml of chloroform with or without DVF (30% w/w) in 2.5 ml. The main emulsion was vortexed for 90 seconds before being sonicated on ice for 60 seconds at 50W using a probe sonicator. Under a partial vacuum, a rotary evaporator was used to extract the chloroform. By using ultracentrifugation (23,000g, 18 min at 4 °C), the nanoparticles were produced. Mannitol was used as a cryoprotectant during the freeze-drying of the concentrated nanoparticles (2.5% w/w).

Double-emulsion solvent evaporation

A modified double-emulsion solvent-evaporation method was used to create MEL-SLNs. The method by which the water-in-oil-in-water (W1/O/W2) emulsion was as follows: The oily phase was produced by dissolving either 9 mg of phosphatidylcholine in 1 ml of cyclohexane or 9 mg of cholesterol in 1 ml of ethanol using a homogenising mixer (0.5 cycles with 75% amplitude) for 1 minute. Next, 0.2 ml of meloxicam aqueous solution (15 mg/ml) was added dropwise to the oily phase. 1.6 ml of 2% poloxamer 188 aqueous solution (W2) was then added dropwise to the resultant nanoemulsion using the homogenising mixer (0.5 cycles with 75% amplitude) for an additional minute. To allow the organic solvent to evaporate and create the SLNs, the final mixture was stirred continuously throughout the night using a magnetic stirrer [32].

Solvent emulsification diffusion

By using a modified solvent emulsification-diffusion process, drug-loaded SLNs were manufactured. As the internal oil phase, accurately weighed lipid was dissolved in a 2.5 ml combination of ethanol and chloroform (1:1). The drug was dissolved in the above solution. The external aqueous phase, which was 22.5 ml of an aqueous solution of Tween 80, was then added drop by drop to this organic phase, and the mixture was homogenized for 30 min at 3000 rpm to create a primary emulsion (o/w). Pouring the above main emulsion into 75 ml of ice-cold water that included surfactant and stirring helped to properly solidify SLNs and remove the organic solvent into the continuous phase. To distribute the SLNs, the stirring was kept up for a further 2-2.5 h at 3000 rpm. To create SLN dispersions of a consistent size, the SLN dispersion was sonicated for 5 min (1 cycle, 100% amplitude). The solid lipid material containing the drug was then separated from the dispersion using a centrifuge at 18,000 rpm for 20 min. The dispersion was then repeatedly rinsed with deionized water to confirm that all organic solvents had been completely removed. To create the SLNs, this was redispersed in 1.5–1.625 percent (w/v) of an aqueous Tween 80 surfactant mixture and sonicated for 5 min. To preserve them from freezing, 5% (w/v) mannitol was added to the SLN dispersions before lyophilization [33].

Overall, the formulation and evaluation of SLNs for NTB delivery is a complex process that involves the selection of appropriate lipids and surfactants, the preparation of stable nanoparticles, and the characterization and evaluation of the resulting formulation [34].

Characterization of SLNs

Characterization of SLNs is an important step in the formulation process as it provides information about the physicochemical properties of the nanoparticles, which are critical for their efficacy and safety [35]. The following are some of the commonly used methods for SLN characterization:

Particle size and size distribution

Particle size and size distribution are critical parameters that determine the stability and efficacy of SLNs. These parameters can be determined by various methods, such as dynamic light scattering (DLS) and Malvern Zeta Sizer.

Zeta potential

Zeta potential is also an important parameter that determines the stability of the SLN suspension. It can be measured by Malvern Zeta Sizer, Electrophoretic Light Scattering (ELS) or Laser Doppler Velocimetry (LDV).

Morphology

The morphology of SLNs can be observed by Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM). These techniques provide information about the shape and size of the nanoparticles.

Drug loading and encapsulation efficiency

Drug loading and encapsulation efficiency are important parameters that determine the amount of drug that is loaded in the nanoparticles and the efficiency with which the drug is encapsulated. These parameters can be determined by various methods, such as high-performance liquid chromatography (HPLC) and UV-Vis spectroscopy [36].

Differential scanning calorimetry (DSC)

DSC is a thermal analysis technique that measures the heat flow in a sample as a function of temperature. It can be used to determine the melting point, crystallinity, and thermal stability of the lipids in the SLNs.

Table 1: Recent studies carried out on SLNs

S. No.	Disease	Drug	Size (nm)	PDI	Zeta potential (mV)	Lipids	Surfactant/co-surfactant	Conclusions	Ref
1.	HIV	Efavirenz	108	0.172	-21	Glyceryl tripalmitate	Poloxamer	150 times increase brain targeting efficiency	[28]
2.	Parkinson's disease	The conjugate of geraniol with ursodeoxycholic acid	121	0.164	-22	Compritol® ATO 888	Span® 85/Tween® 80	Induction of the prodrug permeation from nose to CSF of rats	[30]
3.	Alzheimer's	Galantamine	92.0 _ 3.51	0.380±0.16	-17.22±1.1	Compritol 888 ATO	PF-127/Tween 80	Enhanced bioavailability	[31]
4.	Depression	Agomelatine	167.70 ±0.42	0.12±0.1	-17.90±2.70	Gelucire 43/01	PVA/SDC	Enhance absolute bioavailability and brain delivery	[31]
5.	Other CNS diseases and pain	Ondansetron	299.67	0.296	-16.5	Glycerol Monostearate	Lecithin/ Poloxamer 188	Rapid action	[32]
6.	Parkinson's	Geraniol	121±8.4	0.164±0.03	-22.5±7.7	Compritol ATO 888	Span 85	Anti-inflammatory effect	[34]
7.	Parkinson's	Ropinirole	66.22-6.22	0.023-0.21	+28.19-3.02	Dynasan 114/ Stearylamine	PF 68/Soy lecithin	improve therapeutic efficacy	[35]
8.	Schizophrenia	Risperidone	148.05± 0.85	0.148±0.02 8	-25.35±0.45	Compritol 888 ATO	PF-127	brain targeting	[36]
9.	Meningitis	Levofloxacin and doxycycline	29	-0.200	-	Stearic acid/Compritol® 888 ATO	Span® 60/HPMC	Higher drug concentration in brain than drug-free solution after IN Administration	[37]

Fourier transform infrared (FTIR) spectroscopy.

FTIR spectroscopy measures the absorption or transmission of infrared light by a sample. It can be used to determine the chemical composition and structure of the lipids in the SLNs.

X-ray diffraction (XRD)

XRD is used to determine the crystal structure and crystallinity of the lipids in the SLNs.

***In vitro* drug release**

In vitro, drug release studies are conducted to determine the release profile of the drug from the SLNs. These studies can be performed by various methods, such as dialysis, ultrafiltration, or chromatography [37, 38].

CONCLUSION

In conclusion, Solid Lipid Nanoparticles have emerged as a promising platform for nose-to-brain drug delivery due to their ability to enhance drug targeting and efficacy in the brain. SLNs offer several advantages, such as improved drug solubility, enhanced drug stability, sustained release, and reduced toxicity. Moreover, the use of SLNs in nose-to-brain drug delivery offers a non-invasive and convenient route for drug administration. The modern progress in SLN research has shown that they can be used to deliver various therapeutic agents, such as anti-inflammatory agents, anti-cancer drugs, and neuroprotective agents, among others. However, there are still some challenges that need to be addressed, such as the optimization of the particle size and surface properties of SLNs, and the need for more in-depth studies on their safety and toxicity. Overall, SLNs have shown great potential in nose-to-brain drug delivery, and further research and development of this technology can lead to significant advancements in the treatment of various brain disorders.

ACKNOWLEDGEMENT

The author acknowledges to Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research for all support.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest in this article.

REFERENCES

1. Zhu Y, Liu C, Pang Z. Dendrimer-based drug delivery systems for brain targeting. Biomolecules. 2019;9(12):1-29.
2. Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. Neurotherapeutics. 2005;2(1):3-14. doi: 10.1602/neurorx.2.1.3.
3. Battaglia L, Panciani PP, Muntoni E, Capucchio MT, Biasibetti E, De Bonis P. Lipid nanoparticles for intranasal administration: application to nose-to-brain delivery. Expert Opin Drug Deliv. 2018 Apr 3;15(4):369-78. doi: 10.1080/17425247.2018.1429401.
4. Illum L. Nasal drug delivery: new developments and strategies. Drug Discov Today. 2002;7(23):1184-9. doi: 10.1016/S1359-6446(02)02529-1, PMID 12547019.
5. Mitra AK, Krishnamoorthy R. Prodrugs for nasal drug delivery. Adv Drug Deliv Rev. 1998 Jan;29(1-2):135-46. doi: 10.1016/s0169-409x(97)00065-3, PMID 10837584.
6. Haque SS, Sahni JK, Ali J, Baboota S. Development and evaluation of brain targeted intranasal alginate nanoparticles for treatment of depression. J Psychiatr Res. 2014 Jan;48(1):1–12.
7. Ahmed T, Badr Eldin S, Ahmed O, Aldawsari H. Intranasal optimized solid lipid nanoparticles loaded in situ gel for enhancing trans-mucosal delivery of simvastatin. J Drug Deliv Sci Technol. 2018 Oct 1;48.
8. Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. J Control Release. 2008 Apr;127(2):97-109. doi: 10.1016/j.jconrel.2007.12.018, PMID 18313785.
9. Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA. Nose-to-brain drug delivery: an update on clinical challenges and progress towards approval of anti-Alzheimer drugs. J Control Release. 2018;281:139-77. doi: 10.1016/j.jconrel.2018.05.011. PMID 29772289.
10. Gänger S, Schindowski K. Tailoring formulations for intranasal nose-to-brain delivery: a review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. Pharmaceutics. 2018 Aug;10(3). doi: 10.3390/pharmaceutics10030116, PMID 30081536.
11. Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. Adv Drug Deliv Rev. 2012 May;64(7):614-28. doi: 10.1016/j.addr.2011.11.002, PMID 22119441.
12. Bourganis V, Kammona O, Alexopoulos A, Kiparissides C. Recent advances in carrier-mediated nose-to-brain delivery of pharmaceutics. Eur J Pharm Biopharm. 2018;128(Feb):337-62. doi: 10.1016/j.ejpb.2018.05.009. PMID 29733950.
13. Rock JR, Randell SH, Hogan BLM. Airway basal stem cells: a perspective on their roles in epithelial homeostasis and remodeling. Dis Model Mech. 2010;3(9-10):545-56. doi: 10.1242/dmm.006031, PMID 20699479.
14. Lillehoj EP, Kato K, Lu W, Kim KC. Cellular and molecular biology of airway mucins. Int Rev Cell Mol Biol. 2013;303:139-202. doi: 10.1016/B978-0-12-407697-6.00004-0, PMID 23445810.
15. Fahy JV, Dickey BF. Airway mucus function and dysfunction. N Engl J Med. 2010 Dec;363(23):2233-47. doi: 10.1056/NEJMra0910061, PMID 21121836.
16. Md S, Mustafa G, Baboota S, Ali J. Nanoneurotherapeutics approach intended for direct nose-to-brain delivery. Drug Dev Ind Pharm. 2015;41(12):1922-34. doi: 10.3109/03639045.2015.1052081, PMID 26057769.
17. Stoeckelhuber M, Olzowy B, Ihler F, Matthias C, Scherer EQ, Babaryka G. Immunolocalization of antimicrobial and cytoskeletal components in the serous glands of human sinonasal mucosa. Histol Histopathol. 2014 Oct;29(10):1315-24. doi: 10.14670/HH-29.1315, PMID 24737387.
18. Lindsay SL, McCanney GA, Willison AG, Barnett SC. Multi-target approaches to CNS repair: olfactory mucosa-derived cells and heparan sulfates. Nat Rev Neurol. 2020 Apr;16(4):229-40. doi: 10.1038/s41582-020-0311-0, PMID 32099190.
19. Ali J, Ali M, Baboota S, Sahani JK, Ramassamy C, Dao L. Potential of nanoparticulate drug delivery systems by intranasal administration. Curr Pharm Des. 2010 May;16(14):1644-53. doi: 10.2174/138161210791164108, PMID 20210751.
20. Sabir F, Ismail R, Csoka I. Nose-to-brain delivery of anti glioblastoma drugs embedded into lipid nanocarrier systems: status quo and outlook. Drug Discov Today. 2020 Jan;25(1):185-94. doi: 10.1016/j.drudis.2019.10.005, PMID 31629966.
21. Kozlovskaya L, Abou-Kaoud M, Stepensky D. Quantitative analysis of drug delivery to the brain via nasal route. J Control Release off J Control Release Soc. 2014 Sep;189:133-40.
22. Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA. Nose-to-brain drug delivery: an update on clinical challenges and progress towards approval of anti-Alzheimer drugs. J Control Release. 2018 Jul;281:139-77. doi: 10.1016/j.jconrel.2018.05.011, PMID 29772289.
23. Bannister LH, Dodson HC. Endocytic pathways in the olfactory and vomeronasal epithelia of the mouse: ultrastructure and uptake of tracers. Microsc Res Tech. 1992 Oct;23(2):128-41. doi: 10.1002/jemt.1070230204, PMID 1421552.
24. Morrison EE, Costanzo RM. Morphology of olfactory epithelium in humans and other vertebrates. Microsc Res Tech. 1992 Oct;23(1):49-61. doi: 10.1002/jemt.1070230105, PMID 1392071.
25. Selvaraj K, Gowthamarajan K, Karri VVSR. Nose-to-brain transport pathways an overview: potential of nanostructured

lipid carriers in nose to brain targeting. Artif Cells Nanomed Biotechnol. 2018 Dec;46(8):2088-95. doi: 10.1080/21691401.2017.1420073, PMID 29282995.

26. Dhuria SV, Hanson LR, Frey WH. Intranasal delivery to the central nervous system: mechanisms and experimental considerations. J Pharm Sci. 2010 Apr;99(4):1654-73. doi: 10.1002/jps.21924, PMID 19877171.
27. Alavian F, Shams N. Shams N. Oral and intra-nasal administration of nanoparticles in the cerebral ischemia treatment in animal experiments: considering its advantages and disadvantages. Curr Clin Pharmacol. 2020;15(1):20-9. doi: 10.2174/1574884714666190704115345, PMID 31272358.
28. Gupta S, Kesarla R, Chotai N, Misra A, Omri A. Systematic approach for the formulation and optimization of solid lipid nanoparticles of efavirenz by high-pressure homogenization using design of experiments for brain targeting and enhanced bioavailability. BioMed Res Int. 2017;2017:5984014. doi: 10.1155/2017/5984014, PMID 28243600.
29. de Oliveira Junior ER, Truzzi E, Ferraro L, Fogagnolo M, Pavan B, Beggiato S. Nasal administration of nano encapsulated geraniol/ursodeoxycholic acid conjugate: towards a new approach for the management of Parkinson's disease. J Control Release. 2020 May;321:540-52. doi: 10.1016/j.jconrel.2020.02.033, PMID 32092370.
30. Misra S, Chopra K, Sinha VR, Medhi B. Galantamine-loaded solid-lipid nanoparticles for enhanced brain delivery: preparation, characterization, *in vitro* and *in vivo* evaluations. Drug Deliv. 2016 May;23(4):1434-43. doi: 10.3109/10717544.2015.1089956, PMID 26405825.
31. Lee D, Minko T. Nanotherapeutics for nose-to-brain drug delivery: an approach to bypass the blood-brain barrier. Pharmaceutics. 2021;13(12). doi: 10.3390/pharmaceutics13122049, PMID 34959331.
32. Pardeshi CV, Rajput PV, Belgamwar VS, Tekade AR, Surana SJ. Novel surface modified solid lipid nanoparticles as intranasal carriers for ropinirole hydrochloride: application of factorial design approach. Drug Deliv. 2013;20(1):47-56. doi: 10.3109/10717544.2012.752421, PMID 23311653.
33. Patel S, Chavhan S, Soni H, Babbar AK, Mathur R, Mishra AK. Brain targeting of risperidone-loaded solid lipid nanoparticles by intranasal route. J Drug Target. 2011 Jul;19(6):468-74. doi: 10.3109/1061186X.2010.523787, PMID 20958095.
34. Fatouh AM, Elshafeey AH, Abdelbary A. Intranasal agomelatine solid lipid nanoparticles to enhance brain delivery: formulation, optimization and *in vivo* pharmacokinetics. Drug Des Devel Ther. 2017;11:1815-25. doi: 10.2147/DDDT.S102500, PMID 28684900.
35. Gupta B, RS. Formulation and *in vitro* characterization of the solid lipid nanoparticles of naftopidil for enhancing oral bioavailability. Asian J Pharm Clin Res. 2023;16(2):77-82. doi: 10.22159/ajpcr.2023.v16i2.46465.
36. Parameshwar K, SKS. A review of merely polymeric nanoparticles in recent drug delivery system. Asian J Pharm Clin Res. 2022;15(4):4-12. doi: 10.22159/ajpcr.2022.v15i4.43239.
37. Charumathy AU, Ubaidulla P, Sinha GR. Recent update on liposome-based drug delivery system. Int J Curr Pharm Res. 2022;14(3):22-7. doi: 10.22159/ijcpr.2022v14i3.1991.
38. Priyanka PM, Rekha, ASD. Review on formulation and evaluation of solid lipid nanoparticles for vaginal application. Int J Pharm Pharm Sci. 2022;14(1):1-8.
39. Maghsoudi S, Hosseini SA, Ravandi S. A review on phospholipid and liposome carriers: synthetic methods and their applications in drug delivery. J Chem Res. 2022;4(4):346-63. doi: 10.22034/jcr.2022.355104.1182.
40. Joshi AS, Patel HS, Belgamwar VS, Agrawal A, Tekade AR. Solid lipid nanoparticles of ondansetron HCl for intranasal delivery: development, optimization and evaluation. J Mater Sci Mater Med. 2012 Sep;23(9):2163-75. doi: 10.1007/s10856-012-4702-7, PMID 22802103.
41. Akel H, Ismail R, Katona G, Sabir F, Ambrus R, Csoka I. A comparison study of lipid and polymeric nanoparticles in the nasal delivery of meloxicam: formulation, characterization, and *in vitro* evaluation. Int J Pharm. 2021;604(May):120724. doi: 10.1016/j.ijpharm.2021.120724, PMID 34023443.
42. Yasir M, Sara UVS. Solid lipid nanoparticles for the nose to brain delivery of haloperidol: *in vitro* drug release and pharmacokinetics evaluation. Acta Pharm Sin B. 2014;4(6):454-63. doi: 10.1016/j.apsb.2014.10.005. PMID 26579417.
43. Abdel Hady M, Sayed OM, Akl MA. Brain uptake and accumulation of new levofloxacin-doxycycline combination through the use of solid lipid nanoparticles: Formulation; optimization and *in vivo* evaluation. Colloids Surf B Biointerfaces. 2020;193:111076. doi: 10.1016/j.colsurfb.2020.111076, PMID 32408259.