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Solid lipid nanoparticle a complete tool for brain targeted drug delivery

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ABSTRACT

The current review focuses on the potential of solid lipid nanoparticulate systems for effective targeted delivery to the brain. The challenges in delivering the drug to the brain are discussed, as are brain targeting strategies and possible mechanisms. The benefits of using solid lipid nanoparticles as carriers to deliver the drug into the brain are also addressed. Furthermore, the physical and chemical properties of solid lipid nanoparticles are considered with regard to solving the important challenges raised in developing the appropriate brain targeting formulations. The authors conclude that a thorough examination of the technology's potential use concerning the current state of brain medication research is urgently required.

INTRODUCTION

Central Nervous System (CNS) disorders such as brain tumors, neurodegenerative diseases and cerebrovascular diseases are serious social issues. The Blood-Brain Barrier (BBB) is the main hurdle for delivering drugs to the brain, and most of the existing drugs for treating cerebral diseases are inefficient [1]. Despite the extensive research in this field, the mortality rate due to various CNS disorders is more than the mortality caused by various cancers and heart diseases [2]. However, the design of appropriate drug delivery systems can increase BBB penetration, alter drug biodistribution and pharmacokinetics, and improve efficacy while decreasing adverse effects.

The BBB is a practically impenetrable, selective and vibrant protective system for endothelial cells within the brain. It secures the brain from pathogens and poisonous chemicals while enabling the supply of nutrients [3-5]. Although the BBB protects the brain parenchyma from blood-borne chemicals, it also acts as a substantial barrier to the entrance of medicines and other exogenous substances into the CNS [6]. It is extensively understood that passive diffusion is possible through small lipid-soluble particles of less than 400 daltons. Still, the variety of medications that can permeate the CNS is about 2% of all possible drug prospects [7].

Traditional drug delivery methods that deliver medication into the blood circulation face difficulties in efficiently transporting medicine to the brain. Hence, it is crucial to establish and create methods that mainly target the brain in a much better and more efficient way [8,9].Solid lipid nanoparticles (SLNs) are considered exceptionally efficient nanocarriers. These naturally degradable and biocompatible round particles are made up of lipids (solid), with melting temperature levels more significant than the body's temperature [10]. As a result, lipid-nano particulates have excellent potential in brain medicine. Indeed, SLNs have been shown to have a strong ability to penetrate the BBB due to their lipophilic nature and small size [11].

SLN applications are unquestionably concentrated on the peroral route. By way of SLN delivery, poorly soluble medicines should become more accessible, and oral absorption should be less food-dependent. Dermal application is now the second-largest field of use of SLNs and will likely be the most significant. SLNs may be formulated as semisolids or mixed with other semisolid topical solutions. SLNs may function as medicine delivery vehicles (such as retinoids or steroids) or as sunscreens. Intravenous administration of medicines in the SLN form has also been investigated. For intravenous administration, sterility and tolerability must be excellent, and formulations of SLNs should be compatible with the physiological pH range, as well as be isotonic and non-hemolytic (Mader, 2014).

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Surface-modified nanocarrier systems would help deliver drugs efficiently to the brain [12]. However, because of the BBB's selective role, drug delivery and targeting of brain tumors are particularly difficult [13]. Four possible transport pathways for carrying solute particles through the BBB membrane are described below (Figure 1) [14].

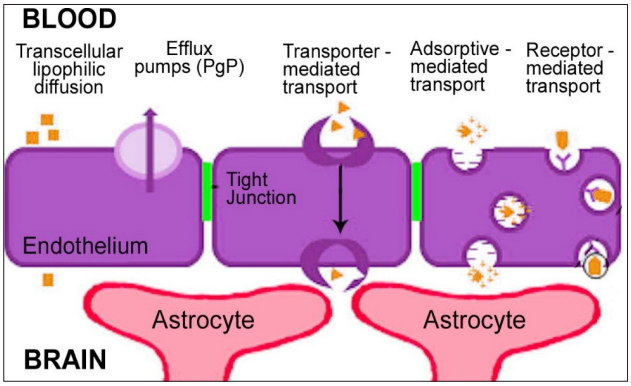

Figure 1. Schematic representation of transport pathways across the BBB

Paracellular Transport

Paracellular movement is the molecular transit between neighboring epithelial cells. Transportation over the tight junction is a rate-controlling phase in this process. The tight junction is hence the main factor of paracellular penetration. Firstly, it is passive and utterly reliant on local gradients of concentration (an unchanging feature of paracellular transport). Secondly, there are no tight junctions and epithelial barriers [15].

Transcellular Transport

Transcellular movement occurs when a tissue's cells use a transport mechanism within the cell. In contrast, paracellular transport occurs when something moves across extracellular gaps due to free passage or a physical consequence. Passive transport refers to the movement of molecules downstream along a concentration gradient. At the same time, active transport is upwards and carries molecules against gradient concentration [16].

Carrier-Mediated Transport

Several transport carriers are present in the albuminate and luminal sides of the endothelial cell membranes. Such carriers either passively or actively transport specific molecules in both directions. However, a carrier molecule is required to transport the drug or an endogenic chemical in the brain with regard to movement along the carrier-mediated transport route. For a range of endogenous substances, transporters such as glucose, amino acid, adenosine, monocarboxylic acid and other carrier moieties have been identified in the membranes of the BBB [16].

Receptor-Mediated Transport

Gupta *et al*. explain that larger molecules can be carried into the brain via this pathway. For example, certain proteins and peptides are known to overcome the BBB [17]. As a component of this pathway, the molecule ligand binds to particular receptors on the membranes of vascular endothelial cells (ECs). As a result, endocytic vesicles form, which are absorbed by the BBB and released into the cytoplasm under the supervision of lysosome enzymes. This transport depends on differences in energy levels and in the interaction between the ligand and the receptor. Several receptors are present or overexposed on the endothelial cell membranes (in some pathological circumstances).

Current drug delivery strategies for brain

Invasive and noninvasive procedures are utilized today to deliver medications to the brain. The following approaches are employed as invasive procedures: Disruption of the blood-brain barrier, intraventricular infusion and intracerebral implants. This method has substantial drawbacks. It is not patient-friendly, and it may compromise the integrity of the BBB and neurobiological function, resulting in the accumulation of neurotoxic, xenobiotic and exogenous substances that may be harmful to the CNN [18]. The majority of noninvasive approaches are pharmacological tactics that can change medications to enable them to cross the BBB. The fundamental noninvasive approaches are: a. chemical-prodrugs, drug conjugates; b. Biological-monoclonal antibodies, peptides, receptor/vector-mediated; c. colloidal-liposome, nanoparticles; d. miscellaneous-intranasal delivery and iontophoretic delivery [19]. These strategies aim to improve drug bioavailability, enhance targeting efficiency, and minimize systemic side effects.

Nanoparticles as BBB-crossing vehicles

Nanoparticles, micelles and liposomes are colloidal drug carriers that can deliver medications to the CNN [20] by way of crossing the BBB and avoiding the related defense mechanisms. Colloidal drug carriers are molecular aggregates with sizes ranging from 1 to 1000 nm. Nanocarriers based on lipids have demonstrated improved stability and circulatory system transport of poorly soluble medicines [20]. The chemistry, architecture and characteristics of the Nanoparticles dictate the possible way, and nanoparticle-based drugs can be readily transported across the BBB [21].

In outlining the different processes by which nanoparticles may bypass the BBB, it must be noted that the reticuloendothelial system's rapid clearance of nanoparticles from the bloodstream is the bottleneck in their systemic use [22]. Herein, surface charge, particle size and surface characters are clearance determinants. In terms of surface charge, nanoparticles with neutral or slightly negative surface charge had better brain penetration than positively charged untargeted nanoparticles, while colloidal systems with varying surface characters are coated with particular plasma constituents like opsonins, albumin and immunoglobulins, then rapidly removed from the bloodstream by phagocytes [23,24].

Solid Lipid Nanoparticles as a drug delivery system

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are two stable lipid matrix nanoparticles that have recently gained popularity in the field of controlled drug delivery [25]. SLNs have mean photon correlation spectroscopy diameters ranging from 50 to 1000 nm [26]. These are composed of lipid matrices (waxes, glycerides

and fatty acids) and are stabilized by suitable emulsifiers such as polyvinyl alcohol, bile salts, phospholipids, tween, etc. [27]. Because of their low toxicity, lipids utilized in the production of nanoparticles are probably in a solid state at ambient temperature. The majority of the lipids are Generally Recognized as Safe (GRAS) [28]. The procedures for synthesizing SLNs are easy because no complex apparatus is required. SLNs can be produced by various procedures using homogenizers, agitators, etc. [29].

With regard to LDCs (lipid drug conjugates) and NLCs (nanostructured lipid carriers), a mixture of the two is used to make up the core of the nanostructured lipid carrier of liquid and solid lipids. Reports on SLN/NLC delivery effectiveness are based on the experimental delivery of drugs with no therapeutic indications such as curcumin, rhein and quercetin. There are presently several encapsulated, well-performing medicinal components with low related costs that have been investigated.

SLNs are popularly suggested as potential drug delivery carriers for various CNS-targeted drugs [30]. Even though a significant body of experimental results has been reported, there is no specific tool for determining their true capability for drug delivery to the brain. Still, according to a thorough review of existing literature information, several drugs with varying biochemical characteristics have been enclosed with SLNs to improve their brain permeability [31].

Because of the variety of encapsulated molecules and the many models employed for the BBB so as to evaluate drug penetration, there are sometimes contradicting results about the real effectiveness of the nanoparticle system, particularly concerning permeation. To explain these contentious issues, researchers have attempted to categorize the chemicals transported to the CNS via SLN into distinct groups based on the rationale for their encapsulation. Specifically, SLN can be used to:

1. Physiochemically or biologically stabilize a molecule (for example, in the blood circulation).
2. Enhance a drug's tissue distribution and pharmacokinetic properties by developing an extended-release preparation with a prolonged half-life in the blood circulation.
3. Stimulate BBB endothelial cells to increase drug penetration.

Despite these benefits, SLNs have certain drawbacks, including an unanticipated inclination to gel, low encapsulation efficiency (EE) and unpredictable ejection of the integrated medicine owing to solid lipid recrystallization, making it difficult to keep the drug trapped inside [32].

There are various lipid based formulations that have been approved by the USFDA for different diseases. Among these are the use of liposomes in medical applications, and 21 liposomal products have been sanctioned that incorporate various small macromolecular drugs. The FDA has also given the nod to numerous additional nanodrugs due to the clinical trial success of Doxil®, including Depocyt®, Inflexal V®, Myocet®, AmBisome®, DaunoXome® and Myocet®, etc. Of note, it has been discovered that these liposomal formulations are useful not only in treating cancer, but also in the treatment of fungal infections and discomfort. Overall, the clinical use of liposomes has proven considerable promise for the creation of novel treatment choices [31,33].

SLNs fabrication techniques

Solvent-emulsification diffusion technique

The lipid is dissolved in a water-saturated organic solvent, and the resultant solution is emulsified with water and enriched with organic solvent while under continuous stirring. Lipid nanoparticles are created by adding water to the emulsion and enabling the organic phase to permeate into the continuous phase. It is possible to purify the SLN dispersion by employing ultrafiltration and a dialysis membrane to remove residual organic solvents, unencapsulated drug, and other impurities, ensuring a stable and purified nanoparticle formulation. [34,35].

High-pressure homogenization technique

High-pressure homogenization is a method where a liquid or dispersion is pushed through a gap of a few micrometers under high pressure (100 to 2000 bar) to develop submicron-sized particles. Intense shear stress and cavitational forces break down the particles, causing a reduction in particle size. High-pressure homogenization can occur at either high or low temperatures (referred to as 'hot-high pressure homogenization' or 'cold-high pressure homogenization', respectively) [35]. The drug products and lipids are heated to approximately 5-10°C higher than the melting temperature of the lipid in the first phase of both operations so that the drug is dissolved or dispersed in the melted lipid [36]. The usual lipid content ranges from 5% to 20% w/v. In the second stage of the high-pressure homogenization process, the amphiphile-containing aqueous phase is delivered to the lipid phase (at the same temperature as the lipid melting), and the hot pre-emulsion is formed using a high-speed stirring device. Based on the formulation and required product, the lipid supplied for homogenization is forced at high pressure through a small region 3-5 times. The drug is dispersed or dissolved in the lipid melt before homogenization. This technique, however, has several drawbacks, which are as follows: (1) It cannot be used for heat-sensitive medicines owing to degradation; and (2) a rise in the number of revolutions or pressure of homogeneity typically induces an increase in particle size [37]. These limitations can be circumvented by preparing SLNs with cold-HPH. As previously explained, the first stage is to create a suspension of melting lipids and drug product, which is then rapidly cooled in dry ice and liquid nitrogen. Milling is used in the third phase to transform the powder into micro-particles. The microparticles are then dissolved in a cold aqueous surfactant solution. The last step is generally 5 cycles of homogenization at 500 bars [38].

Microemulsion method

Microemulsions are transparent, thermodynamically stable formulations composed of oil, water and surfactant, often in conjunction with a cosurfactant. Direct (O/W), reversed (W/O), and multiple (W/O/W and O/W/O) are the three fundamental forms of microemulsions. To produce SLNs by way of this method, an optically clear combination

of a low-melting lipid, a surfactant, co-emulsifiers and water are mixed at 65-70°C to produce a hot microemulsion. To decrease particle size, the heated microemulsion is dispersed in cold water at 2-10°C accompanied by continuous stirring. The typical volume ratio of hot microemulsion to cold water is between 1:25 and 1:50. The microemulsion's composition significantly affects the dilution procedure [35]. The formation of SLNs via microemulsion technique is exemplified in Figure 2.

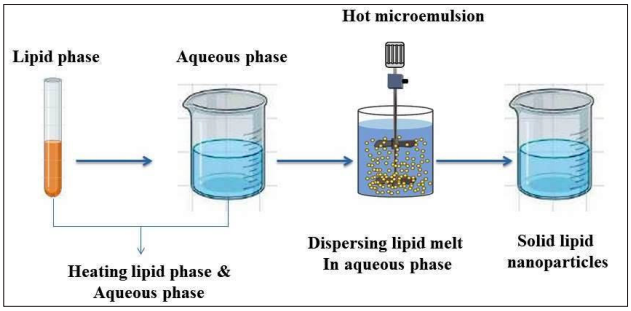

Figure 2. Schematic diagram of SLN production – microemulsion technique

Solvent injection technique

This technique involves dissolving the lipids in an organic solvent that is miscible with water and then injecting the solution, with or without a surfactant, into an aqueous phase under continuous stirring. Considerations in this nanoparticle production method include the injectable solvent type, lipid %, injected volume of lipid solution, viscosity, and diffusion of the lipid solvent phase into the aqueous phase [35,39].

Double emulsion method

This method is often used to create SLNs incorporating hydrophilic drugs and biological molecules such as peptides and insulin. The solvent in the water emulsion diffusion method is used to synthesize SLNs from w/o/w multiple emulsions in which medication is dissolved in the inner acidic phase of the w/o/w multiple emulsion, and lipids are solubilized in the water-miscible organic phase. SLNs are then synthesized by diluting the w/o/w emulsion in water. The organic solvent diffuses into the aqueous phase, causing the SLNs to settle. The type of solvent used and the interaction between hydrophilic drug with the solvent and excipients all have an effect on the production process using this method [35,40].

Ultrasonication

This approach works on the premise of particle size reduction through the use of sound waves. This approach employs high-pressure homogenization and ultrasonication to create SLNs with sizes ranging from 80-800 nm [35,40]. SLN Preparation via ultrasonication is shown in Figure 3.

Membrane Contractor Technique

In this method, a membrane contactor is utilized to create SLNs in which lipids are heated over their melting point in a pressurized vessel and allowed to press through the membrane holes (*eg*. Kerasep ceramic membrane with 0.1, 0.2, 0.45 μm pore size). At the same time, water flows tangentially through the pores and mixes with the melted

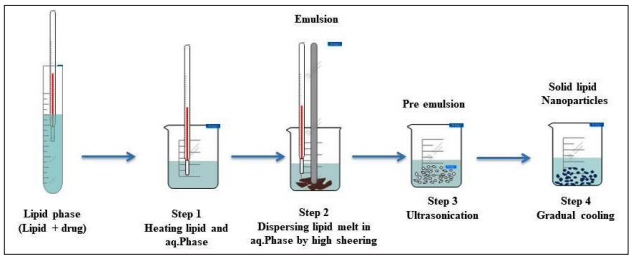

Figure 3. Schematic diagram – the Ultrasonication method

lipid droplets, which are then cooled to room temperature. The process parameters control the particle size [35,41].

Super Critical Fluid Technique

Supercritical carbon dioxide dissolves lipophilic medicines and, when paired with the ultrasonication process, can be utilized to prepare SLNs. Xionggui-loaded SLNs are created utilizing supercritical carbon dioxide fluid extraction and ultrasonication (35,42). This is achieved above the critical point of the fluid such that solubility may be controlled by a very modest pressure change. The four primary SCF techniques used to create nano- or microparticles are as follows: RESS – Rapid Expansion of Supercritical Solutions; GAS – Gas Anti-Solvent method; PGSS – Particles from Gas-Saturated Solutions/Suspensions; SFEE – Emulsion Supercritical Fluid Extraction. The supercritical fluid technique for SLN preparation is illustrated in Figure 4.

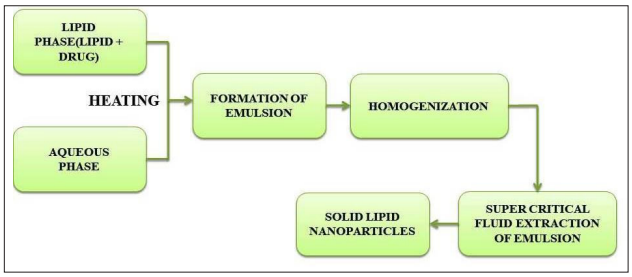

Figure 4. Flow diagram – Supercritical fluid technique

Electrospray technique

Electrodynamic atomization is a revolutionary new approach for creating SLNs. This manufactures narrowly scattered spherical SLNs smaller than 1m. SLNs are obtained directly in powder form using this approach [35,43]. In this method (generally), a syringe contains a solution of the mixture (which comprises the nanoparticles), while a metallic needle attached to a high-voltage power supply serves as the electrode. As a counter electrode, a metal foil collector is inserted across the needle. Because of the surface tension, the droplets coming out of the nozzle are not round. By making the electrical field stronger, the hemispherical drops can change into conical drops, which break up into highly charged droplets. Afterwards, the solvents are evaporated and particles are formed. Lab-created SLN preparations are listed in Table 1.

Importance of lipids and surfactants in the SLN formulation

Biological lipids are used to make lipid nanocarriers. According to their variety and nature, these are widely

Table 1. Examples of different SLN formulations intended for various applications

Name of the Drug	Name of the Surfactant	Name of the Lipid	Size (nm)	Method for Preparation of SLNs	Application	Ref
BuspironeHCl	Pluronic F68, Tween 80	Cetyl alcohol, Spermaceti	86-123	Ultrasonication and emulsification-evaporation	Amplification of nose-to-brain efficacy	[44]
Baclofen	Epikuron 200 (92% phosphatidylcholine)	Stearic acid	161	Multiple emulsion and warm microemulsion	CNS targetting	[45]
Carvedilol	Gelucire 44/14	Precirol ATO5	20-58	Homogenization/ Ultra-Sonication	CNS targetting	[46]
Clozapine	Pluronic F68	Trimyristin, tripalmitin, tristearin, soy phosphatidylcholine	96±3 to 163	Ultrasonication technique	To improve oral bioavailability	[47]
Cyclosporine A	Tagat®S, sodium cholate	Imwitor® 900	199	high-pressure homogenization	To enhance oral drug absorption	[48]
Doxorubicin HCL	Polyethylene glycol, hydrox-ystearate (Solutol®HS15)	Glycerylcaprate	199	Ultrasonication	To deliver lipophilic anticancer drugs	[49]
Ibuprofen	Pluronic®F127, sodium taurocholate	Trilaurin, tripalmitin, stearic acid	111±6 (empty SLN) 175±10 (loaded sample)	Solvent-free high-pressure homogenization	To increase drug solubility	[50]
Lovastatin	Pluronic F68	Triglyceride, and phosphatidylcholine 95%	60-119	Hot homogenization ultrasonication	Drug carrier for lipophilic drugs	[51]
Curcumin	Tween 80	Compritol 888 ATO	9	Microemulsion and ultrasonication techniques	Diagnostic radiopharmaceutical agent in nuclear medicine	[52]
Tacrolimus	Polysorbate 80 and sorbitan monooleate	stearic acid	439 to 669	solvent evaporation method	For improved topical applications	[53]
Fluvastatin	Kolliphor P188	Glyceryl Monostearate	153 to 354	Hot homogenization ultrasonication	To enhance the bioavailability	[54]
Neomycin sulfate	Pluronic F68	Glyceryl Monostearate	196	Modified solvent injection approach	Enhance the antimicrobial activity	[55]
Dapagliflozin	Poloxamer-188	stearic acid	100 to 399	Hot homogenization ultrasonication	Oral hypoglycemic medication	[56]
Clarithromycin	Tween 80	Glyceryl Monostearate	100 to 200	High-speed stirring and ultra-sonication	For Bacterial endophthalmitis	[57]
Naloxone	PluronicF127, Tween 80	Glyceryl Monostearate	99 to 452	Solvent evaporation	For the management of opioid overdose	[58]
Tacrolimus	Poloxamer-188	soybean lecithin	152.±4 and 143±7	Emulsification and low-temperature solidification	To improve penetration and retention	[59]

classified as glycerides and fatty (acids, alcohols and esters). Surface modification of SLNs can be done using surfactants and other therapeutic molecules. Moreover, it helps to maintain the stability of colloid systems. Such substances are occasionally paired with co-surfactants [60]. Some of the investigators have described the usage of waxes for the production of lipid nanocarriers [61]. Lipids are the primary component of lipid nanocarriers, impacting their characteristics (among others, drug-loading efficiency, durability and extended release). The manufacturing method for SLNs is not responsible for any chemical instabilities. However, the lipid concentration utilized may be a unique aspect that affects the stability. It is essential to select suitable lipids before their usage in the manufacture of dispersions [62]. Even though no precise standards exist, scientific evidence, such as the drug's solubility in lipids, has been presented as a relevant factor in selecting optimal lipids [63]. The drug's solubility in the lipid matrix is crucial as it affects its entrapment efficiency and loading capacity, following the benefits of lipid nanocarriers in delivering a drug. Although lipid nanocarriers made by waxes are more structurally constant, their higher crystal structure causes substantial drug ejection [64].

Another crucial element of lipid nanoparticulate preparation is the type of surfactant utilized. Surfactants are amphiphile in nature. Such state minimizes the free energy of the Surface and subsequently lowers the interfacial stress between the two stages [65]. The HLB values reflect the ratios of these two components. Surfactants employed for producing lipid nanoparticulate formulations serve two unique and critical functions. (ie 1. During manufacturing, surfactants scatter all lipid melts in the organic phase; 2. After cooling, surfactants stabilize the lipid nano particulates in dispersions). Based on their Charge, surfactants are widely classified as amphoteric, ionic or non-ionic. Besides surfactants and lipids, surface modifiers such as anionic polymers or natural anions can be used in the entrapment of cationic polar drugs [66]. For example, "stealthy" SLNs have been intensively investigated regarding efficacy and selectiveness for targeting tumor cells [67]. A list of surfactants and lipids used for SLN preparation is provided in Table 2.

Table 2. Commonly used lipids and surfactants for SLN preparation

Category	Example and Charge in physiological pH	Reference No
Surfactants	"Soybean lecithin (-) Charge	[68]
	Polyvinyl alcohol (+) Charge	[69]
	Sodium cholate (-) Charge	[70]
	Sodium glycocholate (+) Charge	[71]
	Sodium taurocholate (-) Charge	[72]
	Sorbitan trioleate" (-) Charge	[73]
Lipids	"Glycerol monostearate	[74]
	Glycerol palmitostearate	[75]
	Palmitic acid	[76]
	Stearic acid	[76]
	Precirol ATO 5	[77]
	Oleic acid"	[78]
Phospholipids	Phosphatidylcholine	[79]
	Glycerolipids	[80]
	Monoolein	[81]
	N-G Phosphatidylethanolamine A	[82]

Lipid drug solubility

Monoglycerides, diglycerides and triglycerides (of varying hydrocarbon chain lengths), fatty esters, carboxylic fatty acids and fatty alcohols are the most often utilized oily solvents in lipid-based medicinal products. Medium-chain glycerides have the best properties for drug solubilization and the production of microemulsion, while Long-chain glycerides with elevated melting temperatures are required for SLN production. Commonly, the drug content soluble in the lipid formulation may be much higher than the solubility estimated in the lipid alone. The higher solubility of medication in the entire formula brings about the requirement that medicine must not lose their effectiveness at the interface of a lipid setup. Herein, the surface area provides

a particular anisotropic setting that can provide the hydrophobic groups with a water-poor zone. The drug is more soluble in the melted lipid than in the solid lipid, and this is an essential characteristic that determines loading capacities and encapsulation efficiency [83]. The existence of diglycerides and monoglycerides as polymer composites in the lipid increases the solubility of drugs [84].

Surface modification in solid lipid nanoparticles

Newer methods and polymers have been described for altering the surfaces of SLN with active targeting molecules, enhancing biocompatibility, durability and targetability. Arana *et al*. altered SLN with PE-PEG and noticed that doing so enhanced target capabilities in the cell lines of oral adenocarcinoma. They also found that the alteration of a surface with PE-PEG enhanced the effectiveness and differentiated the circulation of the SLN loaded medication, in contrast to un-coated SLN [85]. Cho *et al*., in turn, designed TPGS1000-emulsified tristearin-based and Tween80-emulsified lipid nanoparticles and compared both formulations. They asserted that TPGS1000-emulsified SLN further increased absorption (intestinal) and oral bioavailability in rats as compared to the effect gained through Tween80-emulsified SLN. This outcome was likely due to improved drug efflux inhibition with TPGS1000 with regard to intestinal lymphatic absorption [86]. In another study, Meiling *et al*. created hyaluronic acid-coated SLNs of prednisolone, these were administered I.V in mice with collagen-induced arthritis with the result that particles alone accumulated in damaged connective tissues. Thus, hyaluronic acid-coated SLN of prednisolone has demonstrated improved circulatory, bone and cartilage preservation, and the outcome was better than free medication or encapsulated drug in HA-free SLNs. Such positive results indicate that the encapsulation of prednisolone in Hyaluronic acid-coated SLNs can be ideal transporters for treating inflammatory diseases [87]. Some examples of Surface-modified solid lipid nanoparticles are listed in Table 3.

Characterization of SLN

SLN characterization is a significant difficulty due to particle size, complexity and the dynamic nature of the delivery mechanism. Particle size, zeta potential, degree of crystallinity, drug release, entrapment efficiency (% EE) and surface morphology are all essential criteria to consider when evaluating SLNs. Dynamic light scattering and quasi-elastic light scattering are used to assess polydispersity index, particle size and charge analysis [95]. The key benefits of these methods are that they are quick and have a high sensitivity [27]. The differential scanning calorimetric technique can determine the crystallinity of lipid or polymorphism changes [96]. The function of the glass and melting point temperature as related to the enthalpies are used to calculate the crystallinity inside nanoparticles. Nanoparticle size and qualitative nature may also be determined using nuclear magnetic resonance. Accordingly, chemical shift changes are connected to molecular dynamics, which offer information about the physicochemical state of the nanoparticle components. Electron microscopy is a sophisticated technology that may provide a direct view of nanoparticles. Transmission electron microscopy and Scanning electron microscopy can further analyze the surface topography, size, stability and structural changes of SLNs over time [97]. To measure SLN entrapment, SLNs are centrifuged at high speeds, and the quantity of free chemicals in the clear supernatant is measured using UV-Visible spectroscopy or

Table 3. Examples of surface modified solid lipid nanoparticles

Name of the drug	Lipid names	Size (nm)	Surface modifying agents	Reviews	Application	Reference No
Paclitaxel	Glyceryl Monostearate	160.6±2	Hyaluronic acid	In cancer stem cells, CD44 receptors are found, which bind to Hyaluronic acid specifically	Antitumor activity	[87]
Prednisolone	Glyceryl Monostearate	147.8	Hyaluronic acid	CD44 receptor is found on synovial lymphocytes in arthritis, and can be used to target them	Targeted,glucocorticoid-based treatment of RA	[88]
Ifosfamide	Glyceryl Monooleate	222±12	Crosslinked with sodium tripolyphosphate	Ifosfamide is degraded in the acid media, pH-dependent on decreasing drug degradation, and it is crosslinked and coated with tripolyphosphate	Enhancing permeability of the drug across Caco-2 cell	[89]
Curcumin	Cholesterol	243±15 to 513±71	N-trimethyl Chitosan	There are leaky structures of tumor and inflammatory tissues that also differentiate acidic pH from normal vasculature in that location. The sensitive coat is made to regulate the drug release behavior of the pH medication	They were used as carrier particles to improve curcumin's oral bioavailability and brain distribution	[90]
Triamcinolone acetonide	Tripalmitin glyceride	165 and 97	Phosphatidylethanolamine	Leaky vasculature structures can be found in tumours and inflamed tissues, and the acidic pH in these areas differs from that of normal vasculature. A delicate coat is crafted in order to manage the drug's pH release behaviour	Target delivery for potent lipophilic anticancer drugs and anti-inflammatory agents	[91]
Docetaxel	Glyceryl Monostearate	-	Hydroxypropyl trimethylammonium chloride chitosan	Docetaxel SLN is intended to improve solubility and decrease first-pass metabolism. A positively charged chitosan coating is applied to the negatively charged SLNs to minimize electrostatic repulsion, which is a barrier to drug absorption caused by the SLNs' attraction to the cell membrane	To improve the oral absorption of docetaxel	[92]
Resveratrol	Precirol ATO5	100±13 and 258±18	N-trimethyl chitosan-g-palmitic acid	Due to its low water solubility, photosensitivity, poor absorption qualities, and quick first-pass metabolism, resveratrol's potential uses are constrained. It is thus covered in N-trimethyl chitosangpalmitic acid so as to resolve the issues	Drug delivery carriers to improve the oral bioavailability of resveratrol	[93]
Retinyl palmitate	Precirol ATO5	Smaller than 100	Diacetyl phosphate	The Surface of dialkyl phosphate is negatively charged. DCP is viewed as a secure excipient to employ in a topical medication and is known to impact the delivery efficacy of modified carriers	Useful for the development of anti-wrinkle preparations	[94]

high-performance liquid chromatography to determine the entrapment efficiency and quantify the unencapsulated drug or active compound. [98,99].

Intra-Nasal route for brain targeting

Because of the larger surface area and porous epithelium layers, the nasal route is a suitable alternate route for systemic drug administration when the I.V. route is restricted [100]. The intranasal route for drug delivery is successful for the following reasons: (i) drug absorption in the nose is enhanced by the presence of microvilli which increase the cell surface area; (ii) the nasal mucosa's subepithelial layer is highly vascularized, allowing blood to flow straight from the nose to the systemic circulation [101]. The technique is illustrated by the work of MD *et al*., who developed bromocriptine-loaded chitosan nanoparticles for nose-to-brain transport. Their findings suggest that direct nose-to-brain transfer bypasses the BBB when compared with bromocriptine solutions administered intravenously and intranasally. [102]. Abbas *et al*., in turn, delivered clonazepam to the brain via the intranasal olfactory mucosa using nano lipid carriers co-loaded with superparamagnetic iron oxide nanoparticles for nanocarrier guidance and holding in an external magnetic field. In this procedure, the nano lipid carriers are insitu in thermosensitive mucoadhesive gels, improving clonazepam administration. This work provides insight into a novel intranasal epilepsy treatment that reduces clonazepam's peripherally damaging effects [103]. Pathways for nose-to-brain drug delivery are shown in Figure 5.

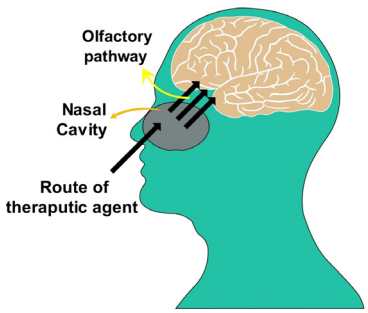

Figure 5. Schematic representation of Nose to Brain drug delivery

SLN in Brain Cancer

Because of their appealing characteristics, solid lipid nanoparticles have been utilized to treat various brain disorders, most notably brain cancer. The papers published in recent years in this field of study include the production of cationic SLN functionalized with an anti- epithelial growth factor receptor so as to target malignant glioma cells [104]. In another work, SLNs made of Precirol or Compritol were produced using ultrasonic homogenization technology and the hot melt homogenization method. The SLNs were loaded with edelfosine, a first-model anticancer agent. These nanoparticles, which were slightly larger than 100 nm in size, were found to aggregate readily in brain tissues, which was ascribed to the P-glycoprotein interaction with surfactant Tween80. These findings revealed an antiproliferative impact as well as a substantial decrease in tumor development [105]. However, the fabricated SLNs' instability and poor drug loading made them unsuitable for clinical use. In related work, cytarabine-loaded NLCs have been developed to target meningeal leukemia. Invitro results showed a rapid release (about 16%) in 1st hour, but a gradual and continuous release throughout the next 72 hours (106). It is not surprising therefore, that, like other forms of lipid formulations, the SLN technique offers effective methods for drug transport to the brain and other regions of the body. Table 4 provides formulations of lipid-based nanoparticles undergoing clinical testing.

In vivo imaging through SLN photoluminescence tracking

The creation of nanoparticles that emit fluorescent or luminescent light has made it possible to detect individual particles inside biological systems. One such method is known as 'SLN photoluminescence tracking'. This method entails labeling the SLNs with a fluorescent or luminous dye and then using imaging tools in order to monitor their distribution and accumulation *in vivo*. This method may have useful implications in the study of medication delivery since it enables researchers to monitor what happens to the SLNs and to evaluate how successful they are at delivering pharmaceuticals to certain tissues or organs. In addition, SLN photoluminescence tracking may be used to assist in the optimization of SLN formulation. This enables researchers to fine-tune the characteristics of the particles in order to achieve the highest possible rate of drug delivery. In general, SLN photoluminescence tracking is a potential technology that may be used in the development and improvement of SLN-based drug delivery systems [107,108].

Table 4. Different lipid based nanoparticles under clinical trials

Therapeutic Agent	Phase	Identifier	Route of administration	Targeted Disease	Origin country
BNT162b2	Phase IV	NCT05057182	IM injection	COVID 19	Hong Kong
CAMB	Phase II	NCT02971007	Oral	Vulvovaginal candidiasis	-
Oxiconazole	Phase I	NCT03823040	SLNs loaded gel for topical application	Tinea pedis/tinea versicolor/ tinea circinate	Egypt
ARCT-810	Phase I	NCT04416126	IV infusion	OTC deficiency	New Zealand
mRNA-2416	Phase 1 Phase 2	NCT03323398	Intratumoural	Solid tumors/ Lymphoma/ Ovarian Cancer	United States
Paclitaxel	Phase II Phase III	NCT04148833	IV injection	Aortic and coronary atherosclerotic disease	Brazil
TKM-080301	Phase I	NCT01437007	Hepatic arterial infusion	Primary liver carcinoma	United States

Source: www.clinicaltrials.gov

Regulatory Issues of SLN for Brain targeted drug delivery

Solid lipid nanoparticles (SLNs) are monitored by regulators when they are used to deliver drugs to the brain. In order for these nanoparticles to be developed and approved, there are a number of regulatory factors that need to be taken into account. The use of SLNs for brain-targeted medication delivery raises concerns about the potential for harmful effects on the CNS, which is why safety is the primary concern of regulatory agencies. Before SLN-based

therapeutic products can be licensed for use in humans, they must first undergo an exhaustive series of safety checks. In addition, SLNs need to show that they are effective in clinical trials. The efficacy of SLNs is dependent on a variety of factors, such as the characteristics of the drug, the size and surface characteristics of the nanoparticles, and the ability of the nanoparticles to penetrate the BBB and specifically target cells in the brain. Clearance of SLNs from the body is an essential problem that affects the pharmacokinetics and toxicity of the medication. Another key regulatory concern is the potential for toxicity that is linked with the use of SLNs. For the purposes of research and assessment, appropriate clinical models are required, since it is possible that animal models may not adequately represent the human reaction. The manufacturing of pharmaceutical products containing SLN has to conform with GMP requirements, and producers have to demonstrate that their products are stable under a variety of storage circumstances [109-111]. Additional concerns, such as intellectual property, the design of clinical trials, obtaining regulatory clearance and reimbursement, always need careful consideration as well. In general, the development and regulatory approval of SLN-based drug products for brain-targeted drug delivery requires a comprehensive analysis of safety, efficacy, toxicity, excretion, appropriate clinical models, manufacturing and other regulatory issues in order to ensure the successful commercialization of these products.

CONCLUSION

To different extents, SLNs may become effective in the mechanism of brain absorption of medications, as produced items have been shown to stabilize drugs from chemical breakdown in body fluids and improve blood circulation perpetuation. Although basic SLNs have previously been utilized as carriers to allow medications to cross the BBB, recent investigation is now focusing on utilizing tailored SLN to increase the selection of NP-endothelial cell interactions.

The technique of introducing low aqueous soluble medicines into solid lipid matrices has been claimed to provide enhanced bioavailability and prevention of sensitive drugs from external factors such as light and water so as to control drug release. Moreover, research has demonstrated that SLNs may carry lipid-soluble, as well as aqueous soluble products more cheaply than polymeric carriers. Due to their limitations, SLNs, however, must undergo development so as to become suitable CNS drug-delivery methods for treating the broadest possible range of neurological illnesses. Although current SLN approaches have failed to treat neurological illnesses effectively, recent technical developments and more profound knowledge of the BBB transport pathway offer renewed optimism for fine-tuning this revolutionary therapeutic approach.

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The authors declare that there are no competing interests.

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