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Review Article

Nose-to-Brain Drug Delivery: A Novel Approach Through Solid Lipid Nanoparticles

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ABSTRACT

Solid Lipid Nanoparticles (SLNs) are now a state-of-the-art substrate allowing delivering medications to CNS, especially when utilizing a nose-to-brain administration method. This thorough analysis summarizes the advancements in SLN composition, emphasizing how they can enhance medication absorption and get over the BBB. The creation of SLNs that can encapsulate both hydrophilic and hydrophobic medicinal compounds has been made easier by developments in fatty membrane choosing, nanoparticle technology, as well as surface activation. By utilizing the sensory and trigeminal neural routes, the inhalation method minimizes broad clearance and side effects thus enabling easy and efficient medication delivery to the cerebral cortex. The physical and chemical factors that affect SLN effectiveness, such as particle size, stability, and releasing kinetics, are examined in this paper. The investigation also highlights the possibility of SLNs to transform therapy approaches for brain cancer, Parkinson's disease, as well as other CNS ailments by discussing recent therapeutic and preclinical trials. Issues with prospective safety, approval procedures, and composition flexibility are included as well. The prospects for non-invasive, targeted brain therapies are presented by the combination of nanostructures and sophisticated administration techniques, which could revolutionize the way that CNS methods for delivering drugs are currently limited. All things considered; it is evident from these observations that SLNs represent a significant breakthrough in contemporary nanotechnology that aims to enhance clinical results.

INTRODUCTION

Nanomedicine The goal of nanotechnology was to accurately identify illnesses while manage those who have fewer opposite reactions. The efficacy for enclosing or connecting medications along with other biological agents into nanoparticles allows further precise and regulated delivery of

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these substances to specific cells, which is why nanotechnologies is increasing in prominence[1]. With Substances now vary in dimension across the micro- to nanoscale because of technological advancements over the past 20 years. Substances' total dimension rises by various orders magnitudes to be the diameter of particles is reduced at the nanoscale. Nanoparticle were molecules that fall between 1 and 1000 nm in diameter. Although the term "nano" has many applications, it is readily described[2]. Solid lipid nanoparticles are shown as a means of transporting both correcting reactive medicine and water-soluble medicines. Nanotechnology were colloidal substances with a dimension range of 10–1000 nm. These originate using synthetic distinctive plastics while are ideal for improving drug delivery and reducing toxicity[3]. Considering the extensive knowledge acquired in the diverse sectors of biology, medicine, including nanotechnologies, the area of novel drug delivery systems is developing on a rapid pace. Nanotechnology, simply the development of small components including the API, is used in a lot of the latest manufacturing techniques. According to the National Nanotechnology Initiative (NNI), nanostructures involve the investigation and utilization of components that are approximately between 1 and 100 nm in dimension[4]. Medications either hydrophilic or hydrophobic might be carried by SLNs, which contain solid cores lipid tiny carriers. These are among the best options for delivering drugs because it may be composed of biodegradable components. Adjustments that alter SLNs' membrane can give such special qualities including mucoadhesiveness or targeted ability[5]. Colloidal transporters known as SLNs were created in the last ten years as a substitute for the conventional transporters currently now in use, such as polymeric nanoparticles, emulsions, and liposomes. These are a novel class of lipid fluids that are small in dimension and in which a rigid lipid was developed used in place for the fluid lipid (oil). Due to the possibility to enhance the efficacy of medications, nutrients, additional substances, SLN have appeal due to their special qualities, which include small dimensions, large surface area, higher dosage, and process interactions across interfaces[6]. Alternate particle drug delivery mechanisms, referred to as lipospheres, nanospheres or SLNs, were created throughout over 20 years to accommodate formulations with lipophilic frequently insoluble medications manufactured using synthetic or organic hard lipids[7]. SLN are among pharmaceutical delivery technologies that have greatly advanced the therapy of many illnesses. Colloidal medication transport devices are known as SLNs. Despite having different lipid compositions, they behave remarkably similar to nano emulsions. With SLN, the lipid solids at low temperatures, such as high-melting range waxes or glycerides, takes over for of the fluid lipid utilized in formulations. Their importance as substitute carrier substances for polymeric nanoparticles is growing. regulated delivery of medicines, improved cell redistribution and therapy employing SLN, plus greater absorption of encapsulated pharmaceuticals through changes in dissolution kinetics[8]. When viewed alongside alternative ways of distribution, nanotechnology provide a number of benefits due to their unique features, which include a high surface area, tiny particle dimensions and the capacity to modify their outside features. Parenteral, oral, cutaneous, ophthalmic, pulmonary, and rectal SLN preparations were created as well as extensively studied both in vitro to in vivo[9]. The advantages of SLNs are combined with the disadvantages of some colloidal particles of its class, such as rigidity, controlled dissolution, good tolerance, and certainty of combined unstable medicines from safety or decomposition. Both in vitro and in vivo, SLN compositions for the intravenous, oral, cutaneous, ocular,

respiratory, and colonic modes of administration were created and extensively studied[10]. There are numerous main features, such as good biocompatibility, minimal risk, as well as the ability of solid lipid nanoparticles to deliver lipophilic drugs more effectively. The structure is also physically strong[11]. Due to their exceptionally broad spectrum of characteristics, SLNs can be used for topical, respiratory, cutaneous, and injectable administration of pharmaceuticals. These solutions were created to improve the efficacy of treatments and lessen the adverse reactions of the very effective medications they contain[12]. Additionally, they have shown promise in the dietary supplement, cosmetics, and genetic transfer industries. The overall number of items available in the marketplace remains constrained, nevertheless, due to the aforementioned restrictions as well as challenges[13].

Basic Points:

Solid Lipid Nanoparticles (SLN):

Considering the extensive knowledge acquired in the diverse sectors of biological sciences, medical science, and nanotechnologies, the science of novel drug delivery systems is developing at a rapid pace[14]. Nanotechnology, or the development of small size nanostructures carrying the active ingredient, is used throughout several of the current contemporary formulating techniques. According to the National Nanotechnology Initiative (NNI), nanotechnologies involve the investigation and utilization of structures that are approximately between 1 nm and 100 nm in scale[15]. The overarching objective of nanotechnologies is similar to that of medication: to use a regulated and targeted medication method of administration for diagnosis as correctly as promptly as feasible and then cure as efficiently as feasible having any adverse reactions. Among the significant drug delivery systems created with the basic concepts of nanotechnologies are SLN, nanoparticles, nanosuspensions, nano-emulsions, and microcrystals[16]. The primary subject of this paper is Solid Lipid Nanoparticles (SLNs). Discovered around 1991, SLNs are a superior and alternate transport technology to established colloidal mediums such as polymeric micro and nanoformulations, and liposomes[17].

Solid lipid nanoparticles (SLNs) are shown for a means of delivering hydrophilic and correcting reactive medications. The suspended components, known as nanoparticles, ranged in size from 10 to 1000 nm. These can improve drug delivery and reduce toxicity because they are made from synthetic distinctive polymers[18]. Important characteristics of SLN include its small size, large surface area, maximum medicine organizing, and the ability to communicate across phases at the interfaces. It is also attractive due to its capacity to improve pharmacological implementation. The fluid dispersions of colloids known as solid lipid nanoparticles (SLN) have stable soluble fluids as their backing material[19].

These are the distinguishing qualities which make SLN a compelling carrier:

1. Because biologically suitable cholesterol is used, there is an improvement in body/tissue endurance with a relaxation of regulatory constraints.
2. The capacity to capture polar and nonpolar medications employing a variety of manufacturing processes.
3. The medium used is not biotoxic.
4. It was successfully demonstrated that unstable molecules, such as retinal, coenzyme Q-10, fatty acids and are protected towards molecular destruction.
5. According to the needs, drug absorption can be modulated based on the form of SLN. While SLN that has a drug-enriched

core results in prolonged absorption, SLN has a drug-enriched core that exhibits rapid absorption properties.

6. The potential for medication-targeted and regulated medication administration[20].

CNS targeting:

The blood-brain barrier makes it extremely difficult to introduce medications into the brain. Especially during specific instances such as if the prodrugs are used has effective passage over the blood-brain barrier (BBB) been accomplished[21]. Nanoparticulate structures, that include drugs that have relatively small particles and an adequate loading capacity to avoid the Reticulo Endothelial System (RES system), have been investigated as potential delivery approaches to achieve effective doses in the nervous system[22]. Solid lipid nanoparticles (SLNs) are an additional viable choice for introducing medications into the nervous system, given the effectiveness of such nanoparticles in crossing the blood-brain barrier and their drawbacks, particularly concerning safety and stability[23].

Drugs must be delivered into the brain to treat conditions affecting the Central Nervous System (CNS), including schizophrenia, meningitis, migraine, Parkinson's disease, and Alzheimer's disease[24]. The Blood–Blood Barrier (BBB), an impermeable endothelium layer that separates the circulatory systems from the brain circulatory system, makes this transfer difficult, particularly for hydrophobic and high atomic weight medicines[25].

Macromolecular medications, often known as "biologics," which include protein and peptide chains, are simply too big and hydrophilic to cross the blood-brain barrier through the circulatory system. If administered by mouth, they will be quickly broken down through the liver's cytochromes or digestive enzymes[26]. Consumers are interested in a non-invasive treatment, especially for conditions like dementia which ask for long-term dosage. Research on both humans and animals has demonstrated that one possible way to get over the blood-brain barrier is to carry external molecules straight through the nose to the brain[27]. The olfactory or trigeminal nervous systems, which begin in the cerebral cortex and conclude in the olfactory neuroepithelium or respiration epithelial tissue as well, in the nose space, are involved along this pathway. Since these are the only regions of the central nervous system that are available to the outside, these offer a most straightforward non-invasive way to enter the brain[28].

Administering medications encased by particulates carriers (such artificial nanoparticles) on the olfactory epithelium may enhance the immediate transport of medications, particularly biological products, to the central nervous system[29]. In order to further the science of nanotechnology, this article is going to evaluate the scientific proof of nose-to-brain delivery, including a particular emphasis on nanoparticulate drug carriers, and offer future possible approaches[30].

History of SLN:

In 1990s, solid lipid nanoparticles (SLN) emerged for a substitute of conventional transports currently already into use, including polymeric nanoparticles, emulsions, and liposomes. Solid lipid nanoparticles (SLN), that are becoming more and more popular as fluid drug carriers, originate from physiologically fats or lipid compounds that have a track record for acceptable application to biological healthcare[31].

Utilizing biological lipids, avoiding chemical solvents, having a possibly broad range of uses

(cutaneous, parenteral), and using homogenization under high pressure as a proven synthesis technique were all benefits of SLN[32]. Furthermore, there was believed that adding water-insoluble medications to the solid lipid substrate would increase accessibility, shield delicate compounds against surroundings (light, moisture), and possibly provide controlled dissolution properties[33].

Aim of SLN:

- The potential for regulated medication administration.
- A higher level of medicinal product endurance.
- A large dose of drugs.
- The medium is not biotoxic.
- organic solvents are avoided.
- The use of hydrophilic and lipophilic medications[34].

Why SLN:

Lipids were originally proposed to serve as alternate transport to get around the drawbacks of nanoparticles of polymers, especially for lipophilic medications. These small particles are referred to as solid lipid nanoparticles (SLNs), and creators from all over the globe take notice[35]. Granular transporters known as SLNs were created under the past ten years as a substitute for the conventional transporters that are now in use, such as polymeric nanoparticles, emulsions, and liposomes. This is a new type of lipid fluid where are very tiny and employ a solid lipid instead of a fluid (oil)[36]. Because of its ability to enhance the efficiency of medicines, supplements, as well as other substances, SLN is appealing because to its special qualities, which include small dimensions, big surface area, maximum drug absorption, plus process interactions across surfaces[37].

SLN For Nose to Brain Drug Delivery System:

Pharmaceutical problems getting through the blood-brain barrier (BBB) are a root of the frequent failures with noticeably extended lifespans of these medications. The intricacy within the CNS, the BBB, plus the physical as well as pharmacological obstacle also contribute to the low conversion of CNS study drugs onto authorized medications[38]. For preventing the entry of poisons as well as infections, the blood-brain barrier (BBB), a very intricate contact among the brain parenchyma with blood from capillaries system, specifically safeguards brain tissue. It safeguards the transmission of substances through bloodstream into the brain[39].

Providing a substitute for comprehensive immunization, plus medication delivery that targets the nervous system, intranasal (IN) delivery became popular in the past few years. IN represents a non-invasive therapy alternative within the realm with developing medications over the therapy induced neurological illnesses. Numerous neurological conditions, including pathogens of the nerve cells, multiple sclerosis (MS), seizures, Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), and strokes, must be managed by medications that enter the brain[40]. The present article tries to carefully characterize the physiological foundation that underlies the nasal-brain connection within accordance with the earlier described data. Additionally, we look at different N2B product methods of delivery that emphasize that review authorized medications over intranasal administration with CNS diseases as well as existing product delivery systems[41].

Composition of SLN:

In general, the elements of SLN formulation include water, active compounds, surfactants, and

solid lipids. The beginning ingredients utilized are generally regarded as safe (GRAS)[42].

1. **Lipid:** The primary matrices element which is essential for defining the characteristics for the aqueous structure using theirs is lipids. Approximately 70 percent of regularly used lipids are classified as free fatty acids, fatty alcohols, or glycerol esters. Stearic acid, glyceryl behenate, tripalmitin, cetyl palmitate, tristearin, and glyceryl monostearate are a few instances of those lipids[43].

2. **Surfactant:** SLN compositions frequently include lubricants to lower the electric field within the lipid as well as water state while nanoparticle production is underway. To maintain the structural integrity of any dispersal systems throughout archiving, lubricants have a tendency to aggregate near the contact point that form a film over the fragments[44]. For one investigation, the effectiveness of detergents in lowering aggregating brought about by the inclusion of ions was examined and published. Their study revealed that stearate antagonism acts as a useful means of keeping SLN stable while being suspended[45].

3. **Additional components:** Thus, preserved SLN compositions use cryoprotectants such as sorbitol, fructose, and glucose. Chitosan is also used for the coating substance and parabens have been employed as the preservatives[46].

4. **Active molecules embedded in SLN:** Lipid systems have been utilized to incorporate multiple active molecules, either independently or as a component of a codelivery approach. Several drugs are potential candidates for nanoparticle integration since their hydrophobic characteristics and poor water solubility. Those drugs respectively categorized as anaesthetics, antipyretics, antibiotics, antiparasitic, analgesics, antiretrovirals, anticancer, and antihypertensive agents[47].

Types of SLN:

Cylindrical nanotechnology having a rigid lipid centre which holds medication is referred to as solid lipid nanoparticles (SLNs). The advantages of both polymeric nanoparticles and liposomes are incorporated into new devices for drug delivery known as SLNs. These evolved to maintain the medication's absorption description, which lessens the requirement fer frequent administering of drugs[48]. Additionally, the selection of the SLNs' many constituents, particularly the lipid and surfactants elements, influences their purity overall ultimate physical features, including drug concentration and size of particle. Furthermore, variations in compositions, manufacturing conditions, other ways of preparing can lead SLNs to possess distinct characteristics[49]. Currently, three drug trapping phases exist:

1. **Phase I: Solid Solution Model (Homogeneous Matrix Model):** The solid solution model of SLNs is generated through cold homogenization, in which a solid drug and lipid solution are employed in the absence of a surfactant, and the drug molecules are spread throughout the matrix. They are ground in a homogeneous matrix during the solidification of the solid drug components. Surfactants maintain the drug in the core, and drug availability is boosted by a combination of processes, including direct gastrointestinal absorption and the capacity to stimulate the lymphatic transport system[50].

2. **Phase II: Core-Shell Model (Drug-Enriched Shell):** According with this hypothesis, the drug molecules is enclosed with an inner casing that is enriched of the pharmaceutical ingredient and is made via thermal homogenization. Using this procedure, the medication was re-partitioned into the lipid layer because of the formation of a lipid centre during the recrystallization point of cooling within the resulting distribution[51].

3. **Phase III: Core-Shell Model (Drug Enriched Core):** The process from distributing drugs within melted lipid and then cool then leads to supersaturation having the medicine absorbed within the lipid, creating this core-shell structure that has a pharmaceutical-enriched centre. That drug-rich centre is surrounded by thick membrane-like layer when lipid recrystallizes[52].

Mechanism of action:

We examined how manufacturing circumstances plus formulation variables affected this SLN releasing pattern. They studied their release pattern about their manufacturing humidity, over instance. The bulk of the time, the alternating mechanism appears, with a protracted release after a brief flow[53]. When doxorubicin is encapsulated, this became apparent how much packing could be affected by both similar drug: lipid ratios also a DMSO: lipid ratios. Greater lipid concentrations led to greater encapsulating effectiveness, whereas a smaller amount of DMSO had a similar impact[54].

Particle dimensions (stearic acid created bigger nanoparticles), dispersion, along zeta potential were also impacted by this heating procedure. Tetradecanoic acid-SLN, palmitic acid-SLN, and stearic acid-SLN all showed improved absorption within rodent studies, with increases of about 6.79, 3.56, and 2.39-fold, correspondingly[55]. Whenever low homogenization was employed, however, alternating releasing characteristics were absent. settings of releasing (sinking versus non-sink settings, releasing medium, etc.) may directly affect the overall velocity of releasing. Another important factor for bursting releases may be the quantity of surfactants[56].

Drug Release Kinetics from the Solid Lipid Nanoparticles:

When developing, improving, plus evaluating new medication transport structures, medication absorption as well as releasing experiments constituted an important essential resource. This lipid matrix's interface deterioration, degradation, plus pharmaceutical particle diffusion releases various medicines incorporated within SLN. This location for its medication is its main indicator for its release within this SLN[57]. This position among medication particles often causes rapid absorption since this medication accumulates along their nanoparticle appearance, plus since their medication was located within its lipid structure. Thus, by controlling that drug's stability within its aqueous phase which can be influenced via that heating plus surfactant quantity used it could be done may control the quantity of bursting releasing throughout manufacturing[58].

Stealth Nanoparticles:

Those offer another new as well as different way to administer drugs while avoiding immunity's rapid elimination. Medications that targeting particular tissues including indicator substances are being used to effectively evaluate Stealth SLNs using rodent studies. Research using stealth lipobodies labelled using antibodies has demonstrated improved distribution into targeted tissues under reachable locations[59].

Formulation and optimization of SLN:

LNPs were produced using wide variety about methods, including spray drying, solvent emulsification/evaporation, high-pressure homogenization (HPH), ultrasonication or high-speed mixing, including supercritical fluid extractor from emulsions (SFEE). Both HPH procedures are established: its heating procedure as well as its cold procedure[60].

Preparation methods of solid lipid nanoparticles:

Overall preparation method, that has an effect upon its atom's size, actual medication's ability can control, its releasing, its stability, etc., is largely responsible for overall accomplishment of SLNs. Concentrations of highly separated lipid nanoparticles can be made via many numbers of ways[61].

Among various preparing techniques are:

1. **SLN preparation with homogenization at high pressure**: Solid lipid nanoparticles (SLN) being identified via photon correlation spectroscopy (PCS) for having some average size between 50 and 1000 nm. Hydration solid lipids, as well as surfactants, are examples of typical components. Lipid was a very generic term that includes hormones (including cholesterol), waxes (including cetyl palmitate), fatty acids (like stearic acid), triglycerides (like tristearin), including unfinished glycerides[62]. In terms of charges as well as molecular mass, surfactant creates is intended to settle lipid dispersion. This SLN were developed towards its close when this previous decade that is thought towards have a useful drug delivery method, especially for providing one steady distribution pattern for their active ingredients. Drug movement was lower with solid lipids versus fluid oils when compared with liquid lipid forms including nanoemulsions[63].

2. **SLN Formulated with Micro Emulsion Technology**: Often consisting either the lipophilic phase (like lipid), another co-surfactant, as well as surfactant, plus liquid, micro emulsions were simple but slightly light-coloured mixtures. This term "micro emulsion" seems controversial. Micro emulsions were now thought of for their fundamental structure rather than an authentic emulsion that contains large particles[64]. This microemulsions exhibit both their qualities associated with a true structure (substances, over instance, exhibit micro emulsion involvement dissolvability as well as lack this flow value similar to macro emulsions) along with those qualities about true macro emulsions (such instance, how minimal molecular amounts can be determined through bright releasing of lasers)[65]. During Gasco's SLN production procedure, that effect occurs. Something higher than this lipid's melting point is needed to be reached so as to create the microemulsion containing a lipid that is stable under room temperature. After the lipids (unsaturated fats along with glycerides) then liquefied, a mixture with water plus one or more co-surfactants will be placed onto top of the liquid lipid while being gently mixed[66].

3. **Lipid nano pellets and lipospheres**: Speiser created as well as manufactured these lipid nano pellets with delivery via mouth. sonication involves shaking via dispersing a fluid lipid into the presence of surfactants. The width caused by the stirring pressure indicates the dimension within the atoms that were extracted[67]. In every case, a mixture of microparticles as well as nanoparticles will result. This surfactant also gets bonded with

total lipid processes throughout the generation of lipid nanoparticles; more surfactant that is accessible, absolutely better it becomes solidified, leading to this reduction among the crystallinity of lipid molecules that advances ahead of lipid solubilization[68].

Characterization of SLN:

These SLNs must be adequately as well as correctly characterized in order to be utilized in quality control. fortunately, since of the microscopic shape of this atom and this intricate with dynamic structure with its transport mechanism, characterizing SLN represents also significant difficulty. Particle size, zeta potential, polymorphism, coexistence of various colloidal buildings (miscellas, liposomes, extremely cooled melts, medication small particles), duration of circulation procedures, dosage, in-vitro drug absorption, along with exterior characteristics are among their significant elements assessed regarding SLNs[69].

1. **Particle size and Zeta potential**: The particle dimension with SLNs affects its material strength. These two strongest methods with determining particle size were laser diffraction (LD) while photon correlation spectroscopy (PCS). The amount that the reflected light fluctuates due to nanoparticle motion, and PCS (sometimes called dynamic light scattering) quantifies this variation. The particulate 387 size range is detected via photon correlation spectroscopy (PCS) between 3 nm to 3 µm along with laser diffraction between 100 nm to 180 µm. Despite being a useful technique towards characterizing nanoparticles, PCS may also identify bigger small particles[70].

2. **Electron microscopy**: Nanotechnology might be seen up close using transmission electron microscopy (TEM) with scanning electron microscopy (SEM). During morphological evaluation, SEM becomes superior. TEM's detection range is modest[71].

3. **Atomic force microscopy (AFM):** The approach generates the topological mapping using the loads acting among its tip along with the substrate by rastering an instrument point having atomic-scale accuracy throughout an element. To differentiate between all these sub-techniques, the specific kind within pressure used determines whether the tool moves along the specimen (contacting mode) as well as left hovering slightly above it (non-contact mode)[72].

4. **Dynamic light scattering (DLS):** During a microsecond timing scales, DLS, sometimes referred as PCS and quasi-elastic light dispersion (QELS), captures variations in dispersed illumination. The variance is determined via compiling a self-correlating functional that occurs via the reflections with light dispersed via specific particles beneath an impact about Brownian motion. This technique's benefits include its susceptibility towards submicrometer particulates, rapidity for examination, plus absence of necessary validation[73].

5. **Static light scattering (SLS)/Fraunhofer diffraction:** With such approach, their structure of rays dispersed via an electron solution can be obtained as well as fitted to basic electromagnetism formulas where size constitutes an essential factor. Although this serves as a quick as well as reliable procedure, it necessitates greater purity compared to DLS plus a deeper understanding regarding this optical characteristic for each particle[74].

6. **Differential scanning calorimetry (DSC):** In order to determine the amount with crystallinity from each particles variation, DSC plus powder X-ray diffractometry (PXRD) is employed. A relationship between the melting enthalpy/g within the dispersed and overall melting enthalpy/g to that main substance serves to assess their progress to crystallinity employing DSC[75].

7. **Acoustic methods:** By solving physiologically applicable formulas, acoustical spectroscopy, a different ensembles strategy, determines volume by measuring the absorption the vibrations. Additional data about surface charges might be gathered by detecting a rotating electrical field produced via its motion for charged atoms beneath this effect on acoustics[76].

8. **Nuclear magnetic resonance (NMR**): Particles' size plus qualitative makeup might be ascertained via NMR. This sensitivities towards molecular motion are enhanced via the flexibility provided via chemical shift, which offers insights into particle physicochemical state of each nanoparticle's constituent parts[77].

Evaluation of SLN:

1. **Particle size:** Particle dimension determines the physical consistency for SLNs. Laser diffraction (LD) and photon correlation spectroscopy (PCS) were particularly effective methods that figuring out particle dimension. Molecule mobility causes the degree from scattered light to fluctuate. Particle dimensions between 3 nm and 3 m can be detected by photon correlation spectroscopy (PCS), while particle dimensions between 100 nm and 180 m can be detected by laser diffraction[78].

2. **Zeta potential:** Zeta potential might be measured with the zeta meter or zeta potential analyzer. preceding measuring, SLN concentrations were diluted 50 times via this initial distribution planning media over dimensions description while zeta potential. This occurs to ensure that there are no additional variables present, including hydrophilic surface appendages or steric stabilizers, just like a higher zeta potential could cause particles separation. Zeta potential data might be used for storage estimates. stability of colloidal dispersion[79].

3. **Surface morphology:** Utilizing scanning electron microscopy (SEM), which offers three-dimensional pictures of particles along with their superficial development, in addition to transmission electron microscopy (TEM), which offers data regarding the dimension, shape, and internal structure about each particle, electrons microscopes confirm the morphological characteristics of SLN[80].

4. **Degree of crystallinity:** Lipid nanoparticles' level of crystallization might be assessed by differential scanning calorimetry (DSC). Utilizing lipid energy, this thermal analysis offers an affordable but precise way to assess the level in crystalline arrangement in lipids. Another non-destructive method for characterizing crystallized substances as well as analyzing the microscopic arrangement of SLN was powdered X-ray diffractometry (PXRD)[81].

5. **Nuclear magnetic resonance (NMR):** Nanoparticle dimensions as well as quality might be assessed using NMR. This produced Solid Lipid Nanoparticles (SLN) were examined using 1H NMR spectrometry. The 1H NMR Spectroscopy version Avance-II

(Bruker, Germany) was used for measuring the nanoconjugates over 300 MHz after they had been dispersed in D2O. A number of changes but maxima have been noticed but each team's interpretation varied[82].

6. **Atomic force microscopy (AFM):** To establish that topological mapping using the interactions among the edge as well as this substrate, some microscopic-sharp probe point is snapped over a specimen. AFM was an effective instrument because of its ultra-high resolution and ability to image an object using characteristics beyond dimensions, including resistant displacement or colloidal adhesion[83].

7. **Entrapment efficiency:** The effectiveness capacity capture for their medication was determined by its amount within their dispersion solution itself. Centrisart, with a membrane filtrate (cellular mass cutoff 20,000 Da) in the bottom about their material collection space, was chosen during ultracentrifugation. When the liquid phase reaches its sample-collecting room, both SLNs plus encapsulating medicine remain inside of the outside container[84].

8. **In vitro drug release:**

1. **Dialysis tubing**: In vitro drug distribution might be accomplished via dialysis tubes. This nanoparticle's solid lipid distribution is placed into pre-washed, tightly closed haemodialysis tubes. After dialyzing the dialysis container with an adequate dissolving environment at room temperature, samples are taken from the dissolution media at scheduled times, centrifuged, and examined for the presence of pharmaceuticals utilizing a proper analytic technique[85].

2. **Reverse dialysis:** The process involves inserting an assortment of little dialysis sacs with 1 millilitre of dissolution media into SLN distribution. These SLNs were then moved inside the fluid[86].

3. **Stability testing:** Preservation stability studies showed that simple SLN plus linked SLN compositions stored at 41°C last longer when stored at room temperature. It was shown that nanoparticles typical size increases with preservation, possibly associated with particle formation during different storage conditions[87].

In vitro and in vivo studies:

In vitro drug release studies: The primary purposes with in vitro drug release investigations include quality assurance and in vivo kinetics predictions. Regretfully, the amount of release seen in vivo may vary significantly compared to the releasing measured in a buffer solution since their nanoparticles' extremely tiny diameter. In vitro release studies are still highly helpful, nevertheless, for quality assurance and assessing whether process factors affect the frequency at which chemical substances are released[88]. SLNs' in vitro drug release characteristics might be assessed using a variety of laboratory techniques. releasing drug profiles could be performed with or without dialysis tubing. Before being sealed tightly, prewashed dialysis lubricant is mixed with SLN. Under a consistent degree and while mixing constantly, this dialysis sac was processed by the dissolving liquid[89].

Via the dialysis membranes, this discharged medication diffuses. Materials were extracted into the dissolving media during specific intervals, centrifuged, then their pharmaceutical concentration measured[90]. It is necessary for maintaining specific sink conditions throughout

releasing examines. alleged stated because SLN fragments weren't immediately dissolved into the dissolving substrate, proper sink conditions fail to be maintained throughout releasing investigations. Consequently, the quantity gradient among the constant state within the SLN dispersion with the dissolving media is what determines the frequency for medication presence within this dissolution media instead of the actual flow rate for the medication[91]. Such approach may have its disadvantage about lacking "sensitive" adequate for describing a drug's quick dissolution through the colloidal transport. Nonetheless, this technique might be applied to their study in the in vitro releasing pattern form colloidal particles when the medication breaks down for a duration of time which is significantly beyond one hour[92].

Toxicity and Status of Excipients:

One of the main problems with using a means of delivery was toxicology along with this condition about the ingredients used. The prediction was possible to establish a highly advanced means of delivery, however getting within the healthcare along with pharmaceuticals marketplace is going severely hampered that toxicology studies are required[93]. Thus, necessary for discussion about various excipients' condition with SLN with regard to its modes for delivery. There are no excipient-related issues concerning the topical along with oral delivery with SLN[94]. Additionally, lipids plus surfactants that food industry can be used. Naturally, its usage in medical devices isn't immediately permitted by its application within the restaurant business. Nonetheless, this is a rather simple issue because toxicology data for food products might be submitted by the pharmaceutical's regulatory bodies[95]. For parenteral delivery, these circumstances were a little unique. As of this moment, no parenterally administered medications in offer include solid lipid nanoparticles. Thus, a toxicology assessment may be required. Toxicology research including the injectable novel medication must also be conducted regardless, thus the lipid simply may not add much into the overall expenses for the necessary investigation[96]. This suggests to concentrate on those so-called approved surfactants (such as sodium glycocholate, lecithin, Tween 80, and Poloxamer 188) using intravenous injections. Research conducted both in vitro and in vivo have shown SLN's moderate tolerance. During cultured cells, polyester nanoparticles (PLA, PLA/GA) and SLN was contrasted. With 0.5% PLA/GA nanoparticles, every cell killed; at 10% SLN into the tissue suspension, about 80% for these cells were still viable[97].

Safety Concern:

The total number of biological organizations which should be examined within the medication discovering pipeline prior to among gets to consumers exceeds 10,000. Within 1990 and 2002, an extremely elevated loss rate (42%) during potential medicines occurred, with toxicology testing being an important factor within this elevated inability percentage, making up half of these instances[98]. Additionally, several medications accepted by USFDA possess significant adverse reactions within the wider patients. Depending on how severe those side effects are, this medication may occasionally need to be withdrawn. The cyclooxygenase 2 inhibitor rofecoxib (Vioxx®), which was authorized with FDA for use around 1999 for treating osteoarthritis, severe pain, and dysmenorrhea, is an excellent instance[99]. The drug was pulled off shelves around 2004 owing to its intolerably high danger for heart adverse reactions, like arrhythmia, myocardial infarction, along with stroke. According to research, around 3% of all pharmaceutical drugs which was authorized

during 1975 and 1999 eventually went off market. Six significant medications were taken off marketplaces between 2000 and 2006 because of health risks[100]. The quantity of major problems with medications recorded towards this FDA have steadily increased throughout 1998. Approximately 90,000 cases about harmful medication reactions have been reported within 2005, with 15,000 for those cases ending with death[101].

The primary pharmacological ingredient in a medication frequently represents responsible for its toxicology, however occasionally its carrier may also be a contributing factor. Each medication utilized for medical treatment has a risk for unfavourable, occasionally lethal side effects[102]. Its unspecific characteristics of medication metabolism within the bloodstream using standard preparations increase this potential of harm. This accumulative doxorubicin dosage permitted within cancer therapy patients has been reduced to prevent permanent cardiotoxicity due to instance, their unspecific biodistribution as well as absorption about doxorubicin through heart cells causes increased myofilament dissolution, reduction in cardiac proteins, as well as myocardial cell division[103]. That heart disease about doxorubicin is reduced by lipid-based formulations of their drug, outlined within such paper's passively targeted subsection. Similarly, non-specific in vivo circulation of numerous antitumor chemotherapeutic drugs frequently causes substantial medicine buildup into bone marrow, resulting in serious myelosuppression, additional frequent dose-limiting complications with this category of drugs[104].

An alternate paclitaxel formulation called Abraxane® was created with hopes toward addressing such issues. This composition reduces carrier-related concerns as well as employs protein rather than Cremophor EL®-based carrier. Nevertheless, there is evidence linking the application developing Abraxane® to a higher incidence developing the condition[105]. As a result, this appears additional development remains necessary to boost the effectiveness of therapy as well as decrease poisoning. Numerous negative responses have recently been linked to polysorbate, a kind within non-ionized surfactants that is frequently used for a medical additive for dissolving hydrophobic medicines. Polysorbate 80 caused intense hypersensitivity responses comparable to those caused by Cremophor EL® in Taxol® after it was employed to make docetaxel, an unable to be cytotoxic taxane medication that is comparable to paclitaxel[106]. Additionally, it was hypothesized that such surface-active chemical was partially responsible over this water retaining problems that occurred while using that docetaxel preparation. A rise within overall occurrence from antibody-mediated purified red cells aplasia (PRCA) was caused by the usage with polysorbate 80 within Eprex®, a regenerated people erythropoietin manufacturing, within a separate incident, which resulted within a medicine recalling[107].

Considering such instances, it becomes clear how the excipients towards this composition have a significant role towards the medicinal good's all-around characteristics. Since lipids are organic but generally harmless, they are a viable substitute with water-insoluble medications[108].

Sterilization of SLN:

When administering SLN parenterally through breathing, sterility was a concern. This was demonstrated whether autoclaving works with lecithin-stabilized SLN. When autoclaved, the SLN melts, while cooled, it recrystallizes. meanwhile something specific can be added via the SLN under regulated conditions via modifying

its manufacturing elements, autoclaving becomes feasible[109]. Once elements melted repeatedly within the autoclaving process then reassemble within an uncontrolled manner, their unique composition that produced the goal regulated releasing pattern will be gone. Sterile stabilization polymers, such as poloxamer series 17–23, can't be autoclaved at 121°C[110]. Around all times, the polymeric absorption barrier may gradually disintegrate from particular autoclaving frequency being very near these polymeric' critical flocculation temperature (CFT), which results with inadequate stability with particulate aggregating. Through lowering that autoclaving frequency (for example, from 121°C to 110°C) and increasing overall autoclaving duration, it might be prevented. essentially impossible for extrapolation about its chemical stability while autoclaving since it greatly relies upon the SLN formulation's component[111].

Consequently, it remains possible to view both sentences before just approximate guidelines. Like intravenous nutrition formulations, SLN fragments may be sterilization via filtering. Filtration during its natural stage has significance because it enables the filtration for materials much bigger that the filter's openings. Applying the method into SLN was simple but popular via parenteral formulations[112].

Advantages:

1. Compared to liposomes, SLNs were simpler to make more stable.
2. Because physiological lipid makes up this lipid structure in SLNs, there is less risk for short and long-term damage.
3. Exceptionally stable over time.
4. It is simpler to produce that nanostructures of biopolymers.
5. Greater command upon the encapsulating compound's releasing rates[113].
6. This bioavailability for encapsulated bioactive could be improved by SLNs.
7. Molecular defense of the integrated labile substance.
8. The initial components needed are identical as those needed for emulsified.
9. Manufacturing upon a huge scale is feasible.
10. It is possible to get substantial amounts of useful compounds.
11. The possibility of lyophilization[114].

Disadvantages:

1. Limited ability to load drugs.
2. Pharmaceutical ejection during preservation following the polymeric transformation.
3. This dispersion has a comparatively high-water content (70–99.9%).
4. A restricted capacity of loading hydrophilic medications because of production-related partition effects[115].

Clinical Applications of SLNs in CNS Disorders:

The administration from drug-loaded SLNs over their therapy about a variety with CNS problems, such as AD, PD, HD, multiple sclerosis, brain tumors as well as cancer, epilepsy, ischemic stroke, and some neurodegenerative conditions has become the subject of numerous released while continuing investigations recently[116].

1 Drug-Loaded SLNs for Alzheimer's Disease:

Elderly people are most affected by AD, a neurodegenerative disease that worsens with time. Repeated intellectual damage, including memory loss, plus recurrent behavioural changes that result with deaths are its defining characteristics. Cholinesterase drugs, which tackle cholinergic dysfunction, form a basis for these therapies.

Among acetylcholinesterase inhibitors, such FDA-approved medications donepezil, galantamine, and rivastigmine serve for different degrees with AD[117]. Yet, among those medications' main drawbacks lies in a sufficient dosage isn't attained within the brain location. That was mostly caused by their medications' incapacity can penetrate that blood-brain barrier, which reduces their pharmaceutical efficacy. To improve neuroprotection, greater medication levels have to attained. Being a cutting-edge method for medicine administration, SLNs were employed to prepare new medications, enhancing their bioavailability along with efficiency for the management of AD[118]. The outcomes from the in vitro investigation shown that donepezil, an anti-Alzheimer's medication, had improved medication absorption via a favourable releasing pattern using CMEC/D3 brain endothelium tissues while adult SH-SY5Y neurons if customized with ApoE-targeted and SLN-based preparations. Galantamine hydrobromide-loaded SLNs belong to the greatest effective anti-AD medications[119].

2. Drug Loaded SLNs for Parkinson's Disease:

Besides Alzheimer's disease, Parkinson's disease (PD) was the next leading neurological illness. It includes signs of sadness, tremors, bradykinesia with ageing, and psychiatric issues. Protein misfolding, oxidative stress, and mitochondrial dysfunction all contribute to this pathogenic mechanism's slow depletion of dopaminergic neurons. As of right now, levodopa remains an effective medication treating Parkinson's disease that targets its dopaminergic receptor[120]. Levodopa is being encapsulated using its most current SLN drug distribution method, which was invented using the microemulsion technology, to get without restrictions. One preferred medication was bromocriptine, which is inserted into SLNs via ultrasonication and homogenization. These SLNs have a mean diameter of 197.5 nm, a PDI of 0.22, and great stability over six months. Also found that these SLNs had a higher CNS dosage and half-life while used for Parkinson's disease[121].

SLN Versus Other Colloidal Carriers:

Several factors demonstrate that SLN is an improved transport method over traditional o/w emulsion. if the medicine must be protected toward chemical degradation[122]. Compared with the oily interior part of emulsions and liposomes, the integration by the medicine into a solid lipid structure undoubtedly provides a superior level of security. A sustained absorption of the medication through an emulsion isn't possible, but this might be somewhat accomplished using SLN[123]. Several factors show that SLNs are a superior transporter over polymeric nanoparticles:

- Lower Reduced cytotoxicity as a result from the chemicals' elimination.
- Reduced ingredient costs.
- The straightforward method for high-pressure homogenization enables large-scale manufacturing[124].

FUTURE DIRECTIONS:

This SLN was a desirable technology that transporting colloidal pharmaceuticals because of its superior physical characteristics, possible incorporation with active chemicals, and associated advantages. The goal for this overview was to raise the general understanding for the application for nanotechnology within medicine delivery along with the background for the rise of various forms of literature that concentrated on the development and operation for solid lipid nanoparticles, nanoparticle carriers, lipid drug assessments, etc[125]. SLNs have proven their utility as effective compositions to enhance treatment options in beauty products and related industries.

To capitalize upon the many potential uses of lipid-based nanoparticulate compositions, the pharmaceutical sector must focus on creating novel ways to approaches drugs and formulating new products in order to advance and broaden their SLNS. To maximize effectiveness and minimize negative effects upon non-target cells, SLNs offer a patient-friendly and reasonably priced way to administer drugs using several channels. After greater than 20 years of research, the occasional use of SLN seems to get better developed[126]. Several medicines having shorter half-lives, low chemical resistance, and low absorption within environment have additional options in injectable preparations. Additionally, SLN is probably going for additional uses as tailored drug delivery methods that lower systemic toxicities while carrying medications of particular relevance to tissues. As a result, researchers may offer remedies with APIs which didn't pass in tests due to insufficient cell specificity[127].

OPPORTUNITIES AND CHALLENGES:

Within many investigations, compositions that utilize SLN and NLC were created and assessed over nose-to-brain transportation since they boost drug absorption and permeation, decrease mucociliary clearance, boost respiratory retention, decrease medication enzymatic degradation, and strengthen Naso mucosal biological compatibility[128]. Building evidence suggests SLNs and NLCs are efficient medication administration mechanisms capable of directly delivering medications into the brain. Certain obstacles must be addressed, though, because experimental compositions that are effective with SLN and NLC might not do effectively after clinical testing because a variety of causes. Initially people and rodent models' nasal passages are physically different[129]. Variations in the nostril length, exterior areas, dimensions, histology, and morphology impact medication uptake and distribution and vary by individual. Because rats and mice are inexpensive as well as easily accessible, they were employed in PK and PD tests within almost all for the research that were associated with this overview[130]. These respiratory cavities, still vary greatly between those found in humans and animal species including dogs, sheep, rabbits, and primates. Compared to rabbits, lambs, primates, and dogs, who have much bigger nasal orifices, rats and mice have smaller ones, making intranasal delivery challenging[131]. Although it makes up to 50% from the nose with mice, rats, and dogs, the olfactory area only makes up around 10% about total nostril space in humans, rabbits, sheep, and primates. Additionally, the quantity of IN administered varies by organisms, between around 10 µL with mice to 40–50 µL for rodents, and higher quantities for various bigger species[132].

Additionally, using tools such as syringes, nasal atomizers, sprays, micropipettes, and cannulas may have an impact upon this total digestion of the medication and its medicinal benefits. Furthermore, multiple methods were employed to look into brain targeted efficiency of established formulations, while various investigation organizations employ various testing procedures during PK investigations on nose-to-brain transport by IN injection[133]. As a result, PK investigations involving compositions meant direct nose-to-brain distribution have to employ somewhat uniform procedures. For instance, to facilitate entrance for the olfactory route while decreasing mucociliary clearance, compositions ought of being applied to the olfactory area, which occupies the posterior most portion of the nose[134]. Additional medications may reach the circulatory system because an outcome of frequent nasal sprays that improve medication absorption via the respiration area. Drugs will be delivered into the further, posterior area using certain administration

methods, like syringeless injections and aerosols. Thus, it is important to use suitable carriers when developing compositions that utilize SLN while NLC. Lastly, for better medication administration and the greatest contact to the olfactory area, the skull should be inclined upwards[135]. Certain carriers (such as natural cation carrier 2 and natural anion carrier 3) must be taken into account when developing formulations since they can assist in the passage of drugs through the nose to the brain. The development of SLNs and NLCs targeting nose-to-brain medication administration has increased recently[136]. This effectiveness of SLN and NLC-based compositions to obtain nose-to-brain administration and their possibilities over clinical usage are demonstrated by the data compiled through in vivo PK and PD investigations. The shift between animal preclinical research to clinical research is a difficult one which demands more exacting techniques[137]. Several nostril preparations are now licensed to application in medicine or have begun research trials. Nevertheless, each of these include SLN and NLC-based compositions as far as we're aware. Preclinical research has so far shown the indisputable value of SLN and NLC-based compositions, despite the fact that clinical trials are still being conducted on them. Within a few years, we anticipate these SLN and NLC-based compositions may improve the treatment of many CNS disorders by undergoing clinical studies[138].

LIMITATIONS AND REFLECTIONS:

Overall, there are certain unavoidable limits to this work. There were considerable differences among the SLN compositions plus medications employed in all 38 trials we had analyzed. Furthermore, despite the reality that rodents were employed for both in vivo research subjects between any of the analyses, there was a great deal to heterogeneity because of the wide variations within the rats' development and nutrition circumstances[139]. That hampered the reliability for what we found by rendering it difficult to sustain modest discrepancies while contrasting findings from several investigations. They also updated all PK-related values to prevent mistaken calculations[140]. There were differences between their estimations with the initial ones since in research study, they employed the amount of AUC0-t during recalculating, but in other research, other measure of AUC0-∞ was utilized for all pertinent computations. Yet, we needed to depend on AUC0 ∞ data in cases if no AUC0-t data was given[141]. According to certain research, the most effective method to determine DTE% and DTP% was by contrasting SLNs (IN) against no medication (IV) in order to remove the impact on the SLNs or NLCs itself. They needed to contrast what was accessible using SLNs (IN) with the outcomes for SLNs (IV) because several trials employed a free medication (IV) delivery technique[142].

SLNs have several benefits when it comes to addressing CNS illnesses by IN distribution, yet come with many drawbacks. For example, SLNs can possess a lower drug-loading capability if that lipid centre crystallizes, and they could grow unsustainable over preservation, resulting in gelation with early drug distribution[143]. The durability of SLNs might be impacted due to the formulation's high-water content (70–90%). Such limitations prevent SLNs from being widely used in therapeutic settings. Currently, many studies involving lipid-based nano formulations belong to Phase I or II, mainly concerning liposomes[144].

ABBREVIATIONS:

1. SLN: Solid Lipid Nanoparticles.
2. CNS: Central Nervous System.
3. DDS: Drug Delivery System.
4. FDA: Food and Drug Administration.
5. API: Active Pharmaceutical Ingredients.

6. NNI: National Nanotechnology Initiative.
7. BBB: Blood Brain Barrier
8. RES: Reticulo Endothelial System.
9. NLC: nanostructured lipid carriers.
10. PEG: Polyethylene Glycol.
11. NALT: Nasal-Associated Lymphoid Tissue.
12. ISF: Interstitial fluid.
13. OAT: Organic Anion Transporters.
14. IV: Intravenous.
15. MS: Multiple Sclerosis.
16. HD: Huntington's Disease.
17. PD: Parkinson's Disease.
18. AZ: Alzheimer's disease.
19. N2B: Nose-to-Brain.
20. GRAS: Generally Regarded as Safe.
21. COMT: Catechol-O-Methyltransferase.
22. PDI: Polydispersity Index.
23. MAO-B: Monoamine Oxidase-B.
24. NFTs: Neurofibrillary Tangles.
25. APP: Amyloid precursors proteins.
26. PXRD: Powdered X-ray Diffractometry.
27. DSC: Differential Scanning Calorimetry.
28. PCS: Photon Correlation Spectroscopy.
29. TEM: Transmission Electron Microscopy.
30. NMR: Nuclear Magnetic Resonance.
31. AFM: Atomic Force Microscopy.
32. PRCA: Purified Red Cells Aplasia.
33. CMC: Critical Micelle Concentrations.
34. CFT: Critical Flocculation Temperature.
35. HPH: High-Pressure Homogenization.
36. PK: Pharmacokinetic.
37. PD: Pharmacodynamic.
38. NCC: Neurocysticercosis.
39. HIV: Human Immunodeficiency Virus.
40. AIDS: Acquired Immuno Deficiency Syndrome.

CONCLUSION:

In conclusion, Solid Lipid Nanoparticles represent a transformative innovation in CNS drug delivery, particularly via the intranasal route. Their unique ability to successfully traverse the blood-brain barrier, coupled with efficient drug encapsulation and controlled release profiles, underscores their promise in addressing critical therapeutic challenges in neurological diseases. As research continues to refine formulation strategies and overcome issues related to scalability and long-term safety, SLNs are poised to redefine non-invasive brain therapeutics. Future investigations should prioritize clinical validations and streamline regulatory frameworks to fully unlock the clinical potential of these lipid-based nanocarriers, ultimately paving the way for more effective treatments with minimal systemic side effects.

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