A Birds Eye View on Solid Lipid Nanoparticles and Applications in Drug Delivery System

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ABSTRACT

Solid lipid nanoparticles (SLN) might provide fresh opportunities for treating challenging ailments. The SLN were established in the 1990s to replace emulsions and liposomes, in addition to polymeric nanoparticles (NP) as carrier systems. SLN are wet cohesive dispersions with solid biodegradable lipids as their matrices. Drug delivery techniques called SLN use both liquid and solid lipids as their primary matrices. It was demonstrated that SLNs have several benefits over conventional carriers for drug therapy, a longer half-life, tissue-targeted administration, higher permeability, enhanced bioavailability, enhanced solubility, as well as the capacity to enhance storage stability. Because of their exclusive size-dependent characteristics as well as their capability towards incorporating drugs, SLN's currently a possibility towards designing promising pharmacological prototypes for drug transport as well as targeting. The objective of tailored as well as monitored drug delivery is now unsettling researchers' interests across the globe, and can be accomplished through the support of SLNs. The present investigation emphasizes SLNs' numerous characteristics as well as development and evaluation processes, formulation factors, delivery routes, surface changes, toxicity, and biomedical applications.

Keywords: Solid lipid nanoparticles, Cohesive drug carriers, Homogenization, Characterization, Application.

INTRODUCTION

The most difficult field of research in pharmaceutical science right now is the directed dissemination of drug components toward specified organ sites. Micelles, Nanoparticles, and liposomes are additional nanoformulations for medication delivery. When compared to other delivery systems, NP have some advantages Because of their distinguishing qualities, for example, their size, larger surface area, and potential towards changing in surface characteristics. The range of nanoparticle sizes from 10 to 1000 nm is appropriate. Drug incorporation and dissolution are the primary concepts utilized in the development of NP. Recent years have seen significant effort put into promoting nanoformulation for drug delivery. This technique is employed for administering drugs with a limited range of particle sizes.[1]

To replace other conventionally available cohesive systems, including liposomes, and emulsions, in addition to polymeric NP, solid lipid particles were first proposed in 1991. For intravenous drug delivery, solid lipid-containing nanoformulation is a more alluring strategy. Solid lipid nanoparticles (SLN) is also known as submicron cohesive structures with physiological lipids and a small size range of 50 to 100 nm. Examples include glyceryl dibehenate (Compritol 888 ATO, Gattefosse, France), triglycerides with various chain lengths, carnauba wax, as well as beeswax[2] that soften in a water phase that contains surface active agents (surfactants). The most significant qualities of SLN are its tiny diameter, maximum loading efficiency, broad surface area, as well as increased drug assimilation. Using solid lipids improves oral bioavailability and reduces drug-level variations in the blood.[3] Figure 1 depicts the SLN structure.

The disadvantage of employing lipids in a liquid state and oil droplets was avoided in the SLN formulation by expending lipids in the form of solids.[1] The NLC matrices have more flaws than the SLN matrices because it is made up of a blend of spatially dissimilar lipid particles, typically it consisting of a mixture of lipids made from solids and liquids. Even though the NLC structure contains liquid lipids, it is stiff at the body or ambient temperature. Because of the defective crystal lattice, it is anticipated that the capability for adding drugs will be increased, by altering the lipid matrices's composition, it is simple to change in the profile of drug releasing as well as limit drug evacuation throughout retention.[4]

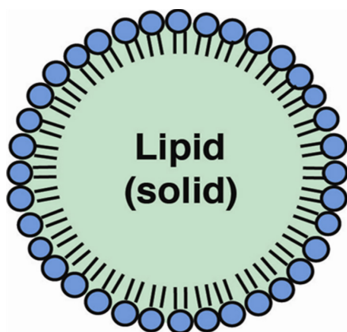*Author for Correspondence: anu.h.pagar@gmail.com*

Figure 1: Structure of SLN

Benefits of SLN

- Increase the bioavailability of the lesser water-soluble chemicals.[1,5]
- SLN contains physiological lipids to reduce toxicity risk.[1]
- Concentrating the drug in a specific location and enhancing dermal absorption.[1]
- Excellent biocompatibility.[3]
- Significant and rising drug content.[3]
- Improved drug stability.[3]
- Regulate the drug release.[3]
- It has been reported that high-pressure homogenization has excellent repeatability and is economical.[6]
- There are numerous ways to administer SLN, including intravenously, topically, orally, and dermally.[6]
- Achieved high functional ingredient concentrations.[1]
- Lyophilization can be accomplished.[1,7]
- The formulation of SLN does not require an organic solvent.[3]
- SLN is fairly stable over the long term.[3]
- Applications resources.[3]
- May be utilized to profit from the sterilizing process.[3]

Disadvantages of SLN

- Minimum loading capability as compared to emulsions, NLCs, and solid lipids.[1,8,9]
- Dispersion's comparatively substantial water content.[1]
- Unknown gelatin inclination.[3]
- There are polymeric transitions.[3]
- Particle propagation.[3]
- Increased likelihood of drug degradation brought on by high pressure, which would result in product defects as well as the removal of integrated bioactive ingredients.[3]

Nanostructured Lipid Carriers

NLCs have been established towards getting over SLN drawbacks including drug ejection with drugs with low uptake. These carriers' non-ideal crystalline structure inhibits lipid crystallization as well as avoids drug ejection by combining solid and liquid lipids.[10] When glycerides and other spatial lipids make up NLCs, there is a greater space between their fatty acid chains and the overall unstructured crystal, which facilitates increased drug accommodation. NLCs come in three main varieties, including Many kinds, amorphous types, and flawed types.[11, 12]

- Inaccurate type NLCs exhibit high drug loading because they are produced by merging liquid lipids with modest amounts of solid lipids.
- Depicted with solid lipids, the proportion of oily lipids is larger in various types of NLCs, which results in higher drug solubility. The reason for this is that lipophilic drugs are less soluble in solid lipids than they are in liquid lipids (oils).
- Other particular lipids, including isopropyl myristate, hydroxyl octacosanol, and hydroxyl stearate, are present in amorphous-type NLCs to prevent the solidification of lipid's subsequent cooling. Therefore, amorphous-type NLCs might stop drug evacuation brought on by solid lipid crystallization.[12]

NLCs offer various advantages, such as the capacity to generate dispersions with increased solid content, greater drug-loading capability compared to SLNs, flexibility in adjusting the release profiling of drugs, reduced drug leakage rates throughout storage compared to SLNs, and the capability to formulate final dosage forms like tablets and capsules.[13,14]

Lipid Drug Conjugates

Poor drug loading in SLNs is the main issue because of partitioning effects. Nevertheless, solid lipid matrices can effectively integrate tiny doses of highly strong hydrophilic drugs. Lipid drug conjugates (LDCs), which improved the drug loading capabilities of SLN by up to 33%, were utilized to get around this problem. LDC is first synthesized by first establishing an insoluble drug-lipid conjugate mass through salt production or covalent bonding. Finally, using a high-pressure homogenization procedure, it is treated through a wet surfactant solution (like Tweens). These matrices have demonstrated promise for hydrophilic drug targeting in unfavorable protozoal infections.

Compositional Profile of SLN's

The foremost constituents utilized to produce SLNs are lipids and surfactants/stabilizers, along with co-surfactants, preservatives, cryoprotectants, as well as charged regulators (Table 1). Surfactants play a part in alleviating the structure of SLNs by reducing the friction amongst the wet surroundings as well as the hydrophobic surface of the lipid core.[11,15]

Manufacturing Techniques of SLP

High shear homogenization

Higher pressure between 100 and 2000 bar is utilized in the HSH process. This process breaks up the particles by forcing a liquid with a very little space of a few microns can transmit a really higher viscosity. The approach has been tested on lipid concentrations ranging from 5 to 40%. Hot (HSH) in addition to cold HSH are the two additional variations of the high-pressure homogenization procedure.[1,16]

Hot high-pressure homogenization

In this, the temperature requirement is above the MP of the lipids. The procedure entails melting the fat and dissolving the drug inside. This drug-loaded lipid is then distributed in the hot

Table 1: Compositional profile of SLN's preparations

Ingredients	Illustrations
Lipid component	The lipid composition includes substances such as beeswax, stearic acid, cholesterol, cetyl palmitate, glyceryl stearates, glyceryl tri laurate, glyceryl tri myristate, compritol, monostearate mononitrate
Surfactant/Emulsifiers	Phosphatidylcholine, soya, egg lecithin, poloxamer, polysorbate 80
Co-surfactant	SDS, tyloxopol, sodium taurocholate, sodium glycocholate
Preservative	Thiomersal
Cryoprotectant	Gelatin, glucose, mannose, maltose, sorbitol, mannitol PVA, and PVP
Charge modifiers	Dipalmitoyl phosphatidylcholine, stearyl amine, dicetylphosphate, and dimyristoyl phosphatidyl glycerol

surfactant solution that has been prepared after being prepared in a hot wet surfactant solution. Pre-emulsion is formed by pre-mixing utilizing a magnetic stirrer. Subsequent to that, a high-pressure homogenizer (HPH) is utilized to pass this pre-emulsion at a temperature over the lipid melting point. A hot O/W nanoemulsion is produced, and after cooling to room temperature, it solidifies, producing SLN.[1,16]

Cold high-pressure homogenization

To prevent issues with hot homogenization procedures, like loss of drug, drug degradation, and crystallization complexity that results in polymeric transition that results in changes, cold homogenization is required. The procedure entails melting the fat and dissolving the drug inside. Liquid nitrogen and dry ice are utilized to quickly cool this drug, which contains lipids. The lipid-containing drug is ground in a ball mill or mortar mill to form microscopic particles (50–100 µm). In a cooled surfactant solution, the powder is then dissolved. The resulting dispersion is run at or below room temperature through an HPH. Although cold homogenization lessens the sample's thermal sensitivity, it doesn't eliminate it since the melting of the lipid or drug occurs first. The procedure of homogenization is given in (Figure 2).
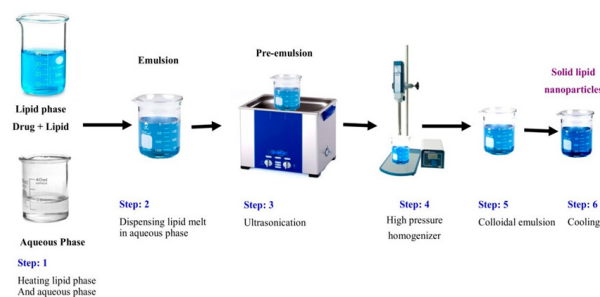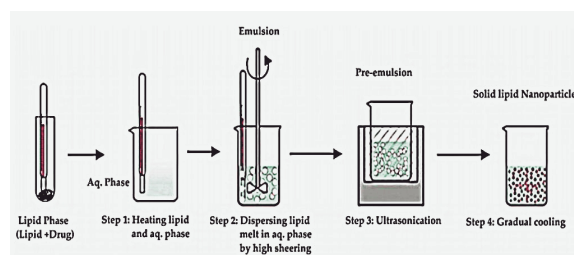
Ultrasonication or HPH

The manufacture of SLN can also be conceded out utilizing sonication or high-speed stirring. Because such basic equipment is readily available, this approach may produce SLN at a lab scale (Figure 3). This approach generates instability-like particle development during storage and produces a wide range of particles (micrometer range). In this procedure, a significant amount of surfactant is required. High metal contamination is a result of ultrasonication.[1,17,18]

Solvent emulsification

The lipid is liquefied in organic solvent (C_6H_{12}), which is insoluble in water, as well as then added to the wet surfactant solution although actuality vigorously agitated towards developing the emulsion. Under low pressure, evaporation is utilized to remove the solvent from the emulsion. Lipid precipitation from evaporation results in NP. Although there is no heat energy utilized in the process, the approach relies on an organic solvent, which has drawbacks.[18,19] Figure 4 depicts the process of solvent evaporation.

Solvent emulsification/diffusion

The lipid matrices must be liquefied in an organic solvent to

Figure 2: Process of homogenization

Figure 3: Ultrasonication or HPH

produce the emulsion since it is insoluble in water. Under low pressure, evaporation is utilized to remove the solvent from the emulsion. Figure 5 illustrates how evaporation results in lipid precipitation, which produces NP. The size of the particle is assessed through the type of surfactant and lipid content utilized in the organic solvent. Particles of the sizes of 30 and 100 nm are produced using this approach.[1,17,20]

Double emulsion

The double emulsion technique is widely utilized for producing NP that encapsulates hydrophilic drugs along with stabilizers or surface-active agents.[21] This process also referred to as the multiple emulsion technique, consists of three elementary phases: 1) the development of the water in oil emulsion (also recognized as the inverse emulsion); (2) the addition of the W1/O emulsion into the wet solution of polymer or surfactant towards forming a W1/O/W2 emulsion through constant rousing (sonication or homogenization); in addition to (3) evaporations By adding hydrophilic polymers, for example, PEG, throughout step ii, the double emulsion approach made bigger sized particles, allowing for surface alteration.[22]

Spray drying

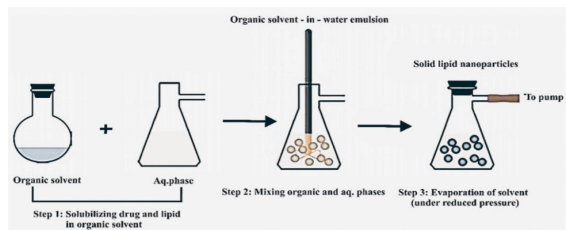This is an additional technique for turning SLN's liquid formulation into a dehydrated drug product. This methodology,

Figure 4: Evaporation

Figure 5: Diffusion

which is more commercial than lyophilization, makes more use of solid lipids with melting points over 70. Because of extensive heat, shear stresses, as well as fractional melting of the NP, this approach causes nanoparticle aggregation.[1,22]

Solvent injection technique

This technique involves liquefying solid lipids in an organic solvent that is miscible through water. Lipid is added to the aquatic stage, during mixing, regardless of the surfactants that make up the organic solvent. The preparation was lastly clarified towards getting rid of excess fat. Up until the solvent diffusion is complete, wet phase emulsion helps create the few drops of extra lipid in addition to equilibrium the solid lipid NP preparation.[22]

Supercritical fluid technique

This approach has the benefit of solvent-free meting out because it manufactures SLNs using constituent parts from gas-saturated solutions. Supercritical carbon dioxide solutions can be quickly expanded to arrange SLN.[23] Gas-saturated solutions. aids in the melting of the lipid material as well as the molten lipid and gas-saturated solutions are then dissolved under pressure in the supercritical fluid (SCF). Spraying the saturated solution *via* the solution is produced the nozzles or actuator to expand, allowing SCF to quickly escape and leave the little, dry lipid particles behind. The lack of organic solvents and the extensive miscibility of lipids in SCF support this technique's advantages.[24]

Microemulsion extrusion technique

Researchers modified the microemulsion methodology to produce the formulations, which were then extruded with a 100 nm polycarbonate membrane with an Avanti mini-extruder (Millipore, Darmstadt, Germany). In a nutshell, melted lipid was mixed vigorously with a solution of PLF68 (surfactant) as well as DOTAP (co-surfactant) that had been pre-heated overhead the melting point of the solid lipid employed. Before extrusion, some samples required sonication to form a homogenous suspension. Unless otherwise stated, the heated emulsion was then put into the donors' syringes and then extrusion fifteen times using the double-syringe extruder, usually concluding at the receiving syringe for prevent infection. Throughout the procedure, the system was kept warm by a heating block that was pre-heated above the melting point of the lipid. After that, the lipid NP was transferred to an ice bath and stored there at 3°C. The frequency of extruded cycles (0, 5, 10, 15, 20, 25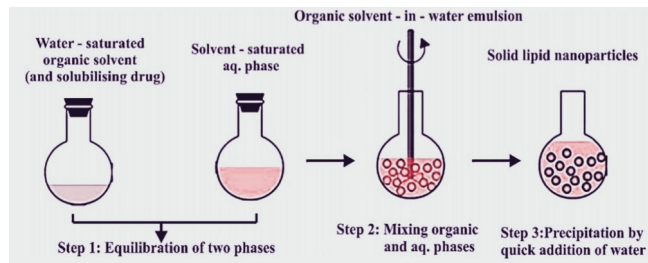, and 30) as well as the temperature utilized in the preparation (5, 10, or 15°C above the solid lipid's melting temperature, which is 56–58°C for GMS and 68.8°C for SA) were tested in a systematic investigation. It should be noted that the maximal lipid concentration employed in our studies was 10 mm to prevent extruder membrane damage. Its concentration may change depending on the lipid mixes employed as well as the formulation formed (liposomes, SLN, or NLC). The lipids, hydrophilic, as well as heating blocks need to be warmed to the appropriate temperature to ensure that the entire system has attained the same temperature.[25]

Drying Technique of SLN

Spray drying

Spray drying can be utilized to produce a re-dispersible powder while adhering to the standard guidelines for intravenous injections. The protection of the cohesive particles is favored by the accumulation of carbohydrates as well as the reduction of lipids throughout spray drying. Because of the low inlet temperatures, ethanol-water mixes (dispersion media) can be utilized in place of clean water be utilized towards decrease lipid melting. For the best results, it was suggested that SLN concentrations of 1% in solutions of 30% trehalose in H_2O or 20% trehalose in combinations of 10% C_2H_6O and 90% H_2O might be utilized.[25]

Lyophilization

The persistence of SLN, both chemically as well as physically is improved through lyophilization for long-term storage. It also maintains the initial particle size and stops degrading reactions. To prevent crystal development, SLN components must have sufficient chemical strength and a restricted size distribution of particles. The SLN formulation shouldn't be impacted by changes in transport temperature. It has been demonstrated that over several months, the particle sizes in wet SLN dispersions have not changed. Lyophilization involves the protective action of surfactants. The lipid fulfilled of SLN dispersion shouldn't surpass 5% in order to avoid an upsurge in particulate matter.[25]

Characterization Techniques of SLN

Size, variation in particle size, ZP, crystallinity category, as well as degree, lipid modification brought along with polymorphism, surface morphology, other than the appearance of many supplementary cohesive frameworks (micelles, super-cooled melts, and drug NP) are some of the parameters that must be assessed in direction towards comprehend the fate of SLNs.[25]

Particle size

Photon correlation spectroscopy (PCS) with a 5-mW helium-neon laser at 633 nm determines particle size, providing PDI and mean diameter (Z average). Glassware, washed with detergent and rinsed twice, maintains cleanliness. Measurements at a 90° angle and 25°C use the "CONTIN" technique. PCS, based on dynamic light scattering, gauges particle movement-induced light fluctuations. Laser diffraction measures larger particles at varying diffraction angles (100 nm–180 µm). Lipid and surfactant quantities dictate SLN/NLC particle size; more surfactant yields smaller sizes. Laser diffraction handles 100 nm to 180 µm, while PCS covers 3 nm to 3µm.[26]

Zeta potential

Zeta potential (ZP) measures the ability to determine the stability of the SLN/NLCs during storage. Because of electrical repulsion, there is less agglomeration of particles when the particles are charged, which is defined as having a high ZP. The stability of the dispersion is likewise decreased if the ZP is lower. Excellent stability requires a ZP of more than -60 mV, while good stability necessitates a ZP of more than -30 mV. Because of the adsorption of steric stabilizers, traveling in the particle's shear plane will result in a drop in ZP, hence formulations incorporating them do not adhere to the same rule. Agglomeration and gelation of SLN/NLCs take place when energies like temperature and light are increased, which ultimately results in a decrease in ZP. When such energies are utilized, crystalline changes take place. The ZP of SLN is decreased by autoclaving. Positively charged NLCs are needed for the passage the BBB. Because the BBB's paracellular location is anionic. To stabilize the system, a negative charge is occasionally needed.[26] The ZP is determined using a zeta meter. The SLN or NLCs dispersion is 50 times diluted before measurement. Disaggregation is indicated by a higher ZP value.[27]

Electron microscopy

Scanning electron microscope (SEM) and transmission electron microscopy (TEM) are two approaches of using an electron microscope (SEM and TEM). This is the most popular technique for viewing NP up close. It is preferable to use SEM for morphological examination. For size detection, TEM has some restrictions. Nanoparticle size and radius analysis are done using SEM and TEM. Although TEM usages electron transmission through the material, SEM usages electron transmission from the NP' surfaces. Sample preparation for SEM is simple and has great resolution. Sample identification by TEM requires freeze drying.[27]

Atomic force microscopy

A topological map's creation in atomic force microscopy depends on the forces that are applied amongst the probe tip in addition to the sample surface. The material is crossed by a probe tip with an atomic scale. Depending on the force utilized, the probe whichever makes interacts with the sample or does not. Atomic force microscopy (AFM) is more beneficial since it can map samples with more resolution in terms of size, cohesive attraction, or in opposition to deformation. AFM measures structural characteristics that are too tiny. AFM is based on the probe tip principle rather than on photons or any other kind of electron. AFM is a more favorable technology since it requires less time to prepare samples and provides higher nanoscale levels of magnification.[27]

Dynamic light scattering

Dynamic light scattering (DLS) is a quasi-elastic light scattering technique in which the time scale utilized for determining the altered concentration of scattered light is the microsecond. A system with an auto-correction function measures changes in the amount of light that each particle in Brownian motion scatters. The benefits of the approach include analysis speeds, the absence of calibration requirements, and equipment sensitivity.[27]

Static light scattering

In static light scattering (SLS), an electromagnetic equation is utilized, in which size is one of the variables. The direction of scattered light is determined, in addition to the equation is then fitted to it. compared to DLS, this approach is quick but demands cleanliness.[27]

Differential scanning calorimetry

Differential scanning calorimetry (DSC) is utilized for calculating the enthalpy of melting as well as the recrystallization of solid lipids from SLN and NLCs. Numerous lipid alterations have a range of melting temperatures in addition to varied heat contents. The degree of crystallite of NLCs is assessed through the proportion of NLC heat concentration towards bulk lipid heat content. The concentration of liquid lipid oil has an inverse relationship with the degree of the crystalline character of NLCs. Hence, a key element in lowering crystallinity is liquid lipids. Liquid oil promotes structural disruption that leads to high drug entrapment.[27]

Nuclear magnetic resonance

The size as well as qualitative characteristics of the SLN/NLCs can be evaluated using nuclear magnetic resonance (NMR). Because of chemical shifts, the physical and chemical makeup of the inner core is examined. Proton NMR spectroscopy is utilized to examine the portability of the inner component of the NLC. The half intensity of the impulses is proportional to the movability of the lipids, both solid and liquid. Small-scale size and broad signals point to the presence of particles through constrained movement as well as robust connections. In NLCs, a reaction between liquid oil and solid lipid occurs when the line width of the NLC is greater than the physical mixing of the materials. In comparison to SLN with a crystalline inner core, the incapacitation of NLC is stronger.[26,27]

Encapsulation efficiency

The effectiveness of medication loading must be assessed because it affects the release mechanism. The primary signal of the drug colloid system is the amount of drug entrapment. According to the SLN amalgamation mechanism, the amount of drug solubility in lipids, liquid melt solubility, the

physicochemical makeup of solid as well as liquid lipids, and lipid crystallization are all factors that impact how well a drug affects the lipid core. The drug's lipophilic by nature molecules are evenly spread in the lipid core or shell. Wet as well as interfacial locations are favorable places aimed at hydrophilic drug loading. The requirement for accomplishing a larger loading size is adequate drug solubility in lipids. Subsequently, it decreases when the lipid melt cools as well as may even decrease in a solid lipid, the solubility must be higher than the demand. The decoupling of the exterior and interior phases is what determines how much drug gets trapped in NLCs. Several techniques, including gel filtration, ultrafiltration, dialysis, and ultracentrifugation, are utilized for the dissociation process. In contrast to SLN, the NLC matrix structure is flawed because of the trapping of liquid lipids into solid lipids, which allows for the most room for drug entrapment. Thus, NLC has a higher loading capacity and entrapment efficiency than SLN.[27,28]

The entrapped drug afterward un-entrapped drug was removed with a centrifugal filter and was calculated to evaluate the entrapment efficiency[29,30]

Drug release

Surfactant concentration and temperature release characteristics can be altered by altering lipid structure. The releasing mechanism might change from hindered release to the phenomena of burst release. Thermostat, surfactant concentration, and lipid structure are the variables that affect the mechanism of release. When SLN is generated *via* the HPH technique, the drug diffuses from the oil toward the wet phase. As the wet phase's temperature or surfactant concentration rises, the drug's concentration in the wet phase similarly rises. Increased surfactant concentration and temperature result in greater solubility in the wet phase.[30] Drug concentration in the wet phase decays as a consequence of the emulsion's cooling, which causes it to move from the wet phase toward the oil phase. At the temperature of lipid recrystallization, the solid lipid's central core is established. Some of the drugs are integrated into the core at that temperature; however, as the temperature of the dispersal phase drops, the drug's solubility in the wet phase declines, and it is disseminated in the oil phase. The interior component confines the new substance within; as a result, the substance saturates the SLN's outside shell. The drug in the inner core then exhibits sustained release whereas the drug on the outside shell exhibits burst release.[28]

The drugs' controlled/sustained release from NLCs may result in a sustained half-life and a postponed enzymatic breakthrough in the bloodstream. The production temperature, emulsifier content, and proportion of oil trapped in the lipid matrices all affect how quickly drugs are released from NLCs. The drug that is concentrated in the NLCs' external shell as well as on the surface is released through a burst mechanism, but the drug that is confined in the interior core is released over time. The Franz cell and the dialysis technique are the approaches for figuring out the *in-vitro* drug release of NP. The particular environment in the *in-vivo* position should be examined when elucidating *in-vitro* drug release.[26]

Figure 6: Applications of SLN

Applications of SLN

By altering the rate of drug dissolution, SLNs increase therapeutic targeting and tissue distribution while also increasing the bioavailability of entrapped drugs. Figure 6 is a representation of potential SLN applications.

Parenteral application

Because they are made with full physiological toleration ingredients in addition to having excellent preservation potential subsequent lyophilization and/or sterilization, SLNs are very suitable for systematic distribution. In the event of deliquescent coating, SLN is sufficiently small when administered intravenously to scatter in the microvascular system as well as inhibit macrophage uptake. SLN has been suggested as a result of viral non-viral gene delivery. Targeted gene treatment for the management of malignancy may benefit from the ability of cationic SLN to precisely attach genes through electrostatic processes. The composition of a particle can change its charge, allowing molecules with opposite charges to bind. The inability of drugs to cross the blood-brain barrier commonly limits the capacity to treat central nervous system (CNS) ailments like brain tumors, acquired immune deficiency syndrome (AIDS), and neurological and mental problems (BBB). After 24 hours of intravenous treatment of doxorubicin, it was discovered that the stealthy nanoparticle remained in the bloodstream at significantly higher amounts than the non-stealth SLN.[31] Drugs with a hydrophilic covering pass through the BBB and are distributed more evenly throughout the body.

Nasal application

Because of rapid absorption, instant action, avoiding gastrointestinal (GI) tract degradation of reactive pharmaceuticals (such peptides and proteins), as well as deficient transportation beyond epithelial cell layers, nasal administration was an auspicious noninvasive drug delivery technique. Perspectives including formulation development and derivatization of prodrugs have been utilized towards improving drug absorption by the nasal mucosa. SLN has been proposed by various research groups as an alternative transmucosal delivery route for macromolecular pharmaceutical components and diagnostics. PEG-coated

polymeric NP demonstrated promising outcomes as vaccine carriers in a recent study. It has been successfully demonstrated that the polyethylene glycol (PEG) coating on polylactic acid NP enhances the transmucosal transport of the contained active component. For solid lipid NP, this technique may be practical.[31] In comparison to traditional (parenteral and oral) dose forms, inhalational drug delivery provides several benefits; including non-invasiveness, minor first-pass effects, and lower systemic toxicity. The lung epithelium might be directly reached by inhaled medications, increasing regional drug concentrations. Because of their greater diffusional mobility, particles smaller than 500 nm may facilitate lung deposition.[31]

Respiratory application

In avoiding first-pass metabolism, the lungs act as a massive surface for drug absorption. Since the extremely thin alveolar wall in the lung, drugs are quickly absorbed by aerosolization (1–3 m). An essential role for lymphatic discharge is played in the respiratory tract's intake of particles. Anti-cancer drugs' bioavailability should be increased, and SLN may be suggested for the management of lung cancer. The analysis of inspired radio-labeled SLN distribution has been described, in addition to the consequences showing that subsequent inhalation, radio-labeled SLN is essential and significantly absorbed into the lymphatic system. In a recent study, several preparations of SLP with sizes ranging from 1.1 to 2.1 m were utilized to atomize preparations for straight pulmonary delivery to guinea pigs. These formulations contained drugs utilized to treat TB, for example, rifampicin, isoniazid, and pyrazinamide. For the effective management of pulmonary TB, the atomization of solid lipid particles containing anti-tubercular medicines was found to be beneficial in increasing drug bioavailability as well as reducing the need for frequent dosage.[32]

Ocular application

The usage of SLN for the ocular route has been comprehensively deliberated. The biocompatibility as well as mucoadhesive possessions of SLN advance their reaction with ocular mucosa and extend the drug's corneal retention time with the goal of ocular drug targeting. The effectiveness of SLN as a delivery system for tobramycin in rabbit eyes is examined. The drug availability in the blood and wet humor can thus be improved by SLN. Moreover, pilocarpine administration using SLN, which is typically utilized to treat glaucoma, has been examined. For the improvement of the drug's ocular bioavailability, they reported similar results.[33]

Rectal application

In the literature, there are very few accounts of the rectal delivery of a particular drug via the SLN. For quick effect, diazepam is encapsulated in SLN and administered via the rectal route. On rabbits, they conducted an animal experiment. They discovered that the lipid matrices is not a good delivery mechanism for diazepam by rectal injection since it is solid at body temperature. In the subsequent trials, they chose to include lipids that melt at body temperature to achieve this. Especially whenever the benefits of the rectal approach are

taken into account, this area look as if to is particularly open to investigation. PEG encapsulation looks like an appealing alternative strategy for increasing bioavailability and rectal administration.[34]

Topical application

Because of their various beneficial effects on the skin in addition to the usual properties of cohesive systems, SLN, as well as NLC, are incredibly pleasurable cohesive carrier arrangements utilized aimed at skin treatments. They can be utilized on skin that is damaged or irritated since they contain lipids that are non-irritating and non-toxic. The topical usage of SLN has been extensively discussed by researchers. For their topical application, SLN and NLC have been examined recently and combined with active substances.[35]

On behalf of topical administration, many drugs including antifungals, anti-cancers, tropolide, imidazole, isotretinoin, and glucocorticoids can be included in SLN or NLC. Utilizing glyceryl behenate, vitamin A containing NP can be synthesized. These techniques help to increase penetrating while maintaining controllable delivery. The isotretinoin-containing lipid nanoparticle was designed aimed at topical administration. The hot homogenization process is utilized for this, and the lipid and surfactant employed are soybean lecithin and Tween 80. The approach works well because it increases isotretinoin absorption through the skin. By integrating flurbiprofen with SLN as a topical gel for distribution, which places the medication right where it is needed, a higher tissue concentration of the drug can be produced. Polyacrylamide, glycerol, and water are the main materials utilized to make this kind of SLN.[17,21]

Cancer chemotherapy

SLN contains a variety of chemotherapeutic drugs, and *in-vitro* and *in-vivo* effectiveness is evaluated. Tamoxifen is encapsulated in SLN for prolonged release after intravenous administration in the management of breast cancer. Tumor-targeting drugs like methotrexate and camptothecin are one way that SLN is utilized in cancer therapy. Mitoxantrone is put into SLN for local injections toward treating breast cancer and lymph node metastases. This increases bio-efficacy and safety while reducing toxicity. According to studies, cationic SLN with paclitaxel loaded on it was made by solvent-emulsifying and sonicating cationic lipids and cholesterol (mPEG-DSPE). The subsequent polyelectrolyte complexation utilized to attach MCL-1-specific minor interfering (si) RNA towards this formulation produced a co-delivery arrangement through improved anti-tumor action *in-vitro* and *in-vivo*.[34]

Prospects for SLN in cancer therapy

Multifunctional nanocarriers have been the subject of extensive research aimed at improving cancer treatment. A highly organized and coherent arrangement aimed at the usage of drugs, diagnostic tools, and genes would be provided by the ideal multifunctional drug nanocarriers. With a better optimal temporal, spatial, as well as delivery form of the anticancer agents, this technique-ology would have separate purposes

working in a synchronized mode. Versatile nanocarriers offer various benefits in drug delivery: (1) PEGylation for prolonged circulation, (2) co-loading multiple drugs, (3) incorporating magnetic particles for responsiveness to an exterior magnetic field as well as serving as a contrasting mediator in magnetic resonance imaging (MRI), (4) pH sensitivity for targeted drug delivery in acidic tumor regions, (5) attaching ligands for active targeting, (6) serving as contrast agents for imaging, and (7) possessing cell-penetrating capability for DNA or RNA complexes. While liposomes are considered, SLN and NLC stand out, because of their advantages, making them optimal for multifunctional pharmaceutical nanocarrier systems integrating therapeutic and diagnostic roles.[35]

Oral SLN in anti-tubercular chemotherapy

Rifampin, isoniazid, and pyrazinamide-loaded SLN structures were capable of lowering the intensity of doses and boost patient adherence. SLNs loaded with anti-tubercular drugs were produced utilizing the solvent diffusion approach. Animal nebulization using the aforementioned medication in SLN has also been described in the direction of increasing the drug's bioavailability.[36]

SLN for agricultural use

When included in SLN, the essential oil from *Artemisia arboreseens* L was capable of slowing down the rate of evaporation when compared to emulsions, and the techniques have been employed in agriculture as an appropriate pesticide importer that is secure for the environment.[37]

SLNs as gene vector importers

SLNs have shown promise in gene delivery, with formulations incorporating gene vectors. Studies have used HIV-1 HAT peptide (TAT 2) to enhance gene transfer in SLN gene vectors. SLNs may contain genetic/peptide components such as DNA and plasmid DNA. The removal of organic solvent from nanophase results in stable lipid-nucleic acid nanoparticles called geospheres (70–100 nm). Specific targeting is achieved by incorporating an antibody-lipopolymer conjugate in the particle.[38]

SLNs as cosmeceuticals

For both types of NP, SLN, topical products have the same formulation. Generally speaking, there are three techniques for formulating products: (1) adding SLN to already-existing items. (2) Making SLN-containing gels by adding agents that increase viscosity towards the wet phase of the dispersions. (3) Through synthesis of the ultimate merchandise with just NP in a single stage utilizing the highly concentrated dispersion manufacturing development.[36] In other words, they function as physical sunscreens on their individual and can be coupled through molecular sunscreens to boost photoprotection.[37] SLN has UV-blocking capacity. The *in-vivo* investigation shows that the addition of 4% SLN to a regular cream will increase skin hydration by 31% subsequently 4 weeks. SLN and NLCs are revolutionary occlusive topicals with controlled release. Compared to standard formulations, glyceryl behenate SLNs have improved vitamin A localization in the higher layers of the skin.[38] There are presently a lot of cosmetic goods on the market that comprise NLCs (for instance, Supervital products from Amore Pacific's "IOPE" label are available in South Korea).[37]

Nanotechnology for oral drug delivery

Research on drug delivery has undergone a revolution thanks to nanotechnology. Many nanotechnologies have been utilized to enhance oral drug delivery. It's interesting to note that there are a limited number of items being tested in clinical trials for oral formulations based on nanotechnology in the pharmaceutical market.[38,39]

SLN for targeted brain drug delivery

They improve a drug's ability to traverse the BBB. Abbas et al. employed nano lipid carters co-loaded with superparamagnetic iron oxide NPs to guide the nanocarrier via an external magnetic field, targeting clonazepam to the brain through intranasal olfactory mucosa. In situ integration of the nano lipid carriers into thermosensitive mucoadhesive gels improves clonazepam delivery, presenting a novel intranasal approach for epilepsy treatment with reduced clonazepam side effects.[40,41]

SLN for antimicrobial drug delivery

For the efficient eradication of infectious microorganisms residing at lymphatic locations, SLNs release antibiotic payloads. NP and surfaces with nanostructures prevent the spread of ailments and germs, which is a successful remedy for problems caused by biofilm and antibiotic resistance. SLNs

Table 2: Recent patents on SLN

S. No.	Application number	Status and date	Drug utilized
1	CN110585171A	Active (12/12/19)	Temozolomide
2	US20200197360A1	Active (25/06/20)	Formononetin
3	WO2020144377A1	Active (16/07/20)	Felodipine, Naproxen, and Ketoconazole
4	WO2020109989A1	Active (04/06/20)	Curcumin
5	KR20200085529A	Active (15/07/20)	Tacrolimus, dexpanterol
6	WO2019206738A1	Active (31/10/19)	Natural Pigments
7	WO2020028916A1	Active (06/02/20)	Amphotericin
8	WO2020053609A1	Active (19/03/20)	Mometasonefuroate, Xylometazoline, and Loratidine
9	CN110585121A	Active (20/12/19)	Temozolomide

are developed to administer antimicrobial drugs, and they work to combat germs by encasing the antimicrobial drugs, disrupting microbial adhesion, and binding to receptors on cellular surfaces.[42]

SLN as adjuvant for vaccines

Adjuvants for immunity are materials added to vaccinations to improve their potency, persistence, or stimulation. In this work, an adjuvant system based on SLNs loaded with squalene was developed for a yeast-based vaccination. Evaluation using static and dynamic light scattering (DLS) techniques revealed the size of the squalene-loaded SLNs to be inside the series of 120 to 170 nm. When tested on a mouse model, the novel vaccine adjuvant exhibited significant effectiveness in contradiction of the virulent bursal virus disease. Squalene-based adjuvants displayed notable biocompatibility and immunostimulatory properties comparable to Freund's adjuvant.[43]

SLN in bio-imaging

In pharmaceutical formulations and food products, the identification and removal of lipopolysaccharides are crucial for effective delivery and to prevent septic distress. Utilizing SLNs as an abiotic system offers a reversible capture, detection, and elimination method for LPS in wet solutions. To assess LPS elimination quickly and easily, the revitalized particles can assist as colorimetric markers in dot blot bioassays. In the realm of nanomedicine, there are various choices for treating rheumatoid arthritis (RA).[44] Albuquerque et al. focused on targeting macrophages in RA by developing a theranostic system using anti-CD64 antibody-anchored SLNs, incorporating SPIONs and methotrexate (co-encapsulated in SLNs). The formulations demonstrate characteristics suitable for intravenous delivery, including diameters below 250 nm and a ZP of -16 mV. TEM images confirmed the encapsulation of SPIONs within SLN matrices, with MTX association efficiency exceeding 98% in efficiency tests. *In-vitro* experiments indicated low cytotoxicity of SLN-based preparations in THP-1 cells up to a concentration of 500 μg/mL. Consequently, these SLN-based formulations present appealing prospects for both pharmaceutical and radiological applications.[45]

Toxicological characteristics of SLN

It is necessary to assess biocompatibility and materials utilized in controlled delivery systems should be biocompatible. Even though an actual determination of a formulation's toxicity requires *in-vivo* investigations, A wide range of *in-vitro* toxicology studies conducted in carefully selected cell lines may offer immensely helpful information. Most people agree that these tests serve as the early toxicity signs.[46]

Cytotoxicity of SLN

The toxicity of SLNs made with Softisan® 154 and soy lecithin by an HPH process was examined in the study utilizing the malignancy cell lines MCF-7 and MDA-MB231. After 24, 48, and 72 hours, the IC_{50} values aimed at MCF-7 cells were determined to be around 0.28, 0.26, and 0.22 mg/mL. Similar results were achieved for MDAMB-231 cells, whose IC_{50} values were discovered to be around 0.29, 0.29, and

0.27 mg/mL after 24, 48, and 72 hours, respectively.[47] The lipid employed towards making NP has a considerable influence on the cytotoxicity of the SLNs that are produced.

Impact of surface charge

The surface charge of the particles affects how cells and cohesive NP interact. The immune system can become sensitive when cationic surfactants are utilized in SLNs and can cause abnormalities in membrane integrity.[48-50]

Genotoxicity

According to several research, SLN does not exhibit whichever DNA damage or gene-related toxicity. When SLN through a negative charge was incubated using A549 cells, Dolatabadi *et al*. and Bhushan *et al*. looked into the effects, and they discovered that there was no toxicity or damage to the genomic DNA as indicated by gel electrophoresis.[51,52] Yet, research revealed that acetyl shikonin-containing SLN may have damaged DNA, leading to an increase in comet generation in A549 cells. The drug that was SLN-encapsulated made the DNA damage worse.[53]

Hemolytic toxicity

When Lakkadwala *et al.* tested SLNs made of polysorbate 80 and glycerol monostearate for their hemotoxicity, the results showed that the SLNs had low hemotoxicity even at high doses (1-mg/mL).[54] No matter whether the formulation had an anionic or cationic surface, SLN coated with hyaluronic acid and containing antineoplastic drug also showed mild hemolytic toxicity.[55] It was discovered that a different cationic SLN containing doxorubicin wasn't hemolytic. When SLNs were coated with galactose, this influence was further elaborated.[56]

Commercially available Solid Lipid Nanoparticle Preparations

Drugs in BCS class II have a higher bioavailability because to lipid-based preparations. Around 4% of products on the market in the US, UK, as well as Japanese markets are oral lipid-based preparations. Oral lipid-based techniques include things like straightforward lipid solutions including self-emulsifying drug delivery systems.[57] Table 2 provides details on current patent filings for solid lipid NP with SLN.

CONCLUSION

SLN combines the merits of liposomes, polymeric NP, and fat emulsions as a cohesive drug carrier. SLNs are developed using a variety of cutting-edge processes, including hot and cold homogenization. The use of SLNs allows for more effective site-specific and prolonged drug release. SLNs combine the advantages of polymer-based carriers with liposomes, making it possible to encapsulate together lipid-soluble in addition to water-soluble drugs. Scaling up SLN production is possible and affordable. They exhibit remarkable stability throughout their shelf life, and a variety of lipids can be utilized to adjust the release kinetics. Because of their several important features, SLNs have established towards being effective drug delivery systems, and they will continue to play a vital part in lipid-based delivery of drugs in the future. Scientists have already

applied for a large number of SLN-related patents, and more SLN-based delivery systems are likely to follow soon.

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