SOLID LIPID NANOPARTICLES: A SYSTEMATIC AND CRITICAL OVERVIEW

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Abstract
In the golden age of pharmaceutical nanocarriers, witnessing a maturation stage of the original concepts and ideas. SLNs are at the bleeding edge of the quickly creating field of nanotechnology with few potential applications in drug delivery, clinical medication and investigate, as well as in other varied sciences. Solid lipid nanoparticles were created in early 1990s as an elective to other conventional colloidal carriers like liposomes, polymeric nanoparticles and emulsions as they have preferences like controlled medicated discharge and focused drug delivery with expanded stability. We could review fully different types of SLN, their diverse routes of administration. The various technique of production of SLN as homogenization and their evaluation, their application in medicine. SLN have promising attributes for getting the goal of controlled and site-specific drug delivery and hence attracted developer's wide attention. This review expands on the future potential of SLNs, as they can be easily fabricated with a variety of functionalities, offering significant promise for targeting and diagnosing a wide range of diseases. To discuss their benefits and limitations with a view in their future perspective of this review could help us to find out the unexplored areas of the SLN with their current scenario.
Keywords: Homogenization, Nanoparticle, Solid lipid nanoparticle, Nanotecnology, Liposomes, Emulsions.

Introduction:

Solid lipid nanoparticles (SLN) introduced in 1991 represent an opportunity service gaget to way of life colloidal carriers such as - emulsions, liposomes and polymeric micro – and nanoparticles. [1] Lipid nanoparticles has drug transport systems were considered from the start of the nineteen century by professor R. H. Müller from Germany and Professor M. Gascon from Italy.[2, 3] Three types of SLNs are sub-micron colloidal carriers, ranging from 50 to 1000 nm in size, composed of physiological lipids and dispersed in water or aqueous surfactant solutions. SLN provide unique characteristics such as small size, large surface area, high drug loading and the interaction of phases at the interface and are appealing for their capacity to improve ability of drugs. [4,5,6] SLNs are used for the manage and focus delivery of drugs which are entrapped in the solid lipid matrix. SLNs are stabilized through a layer consisting of a single surfactant or via combination of surfactants which result in smaller particle size and improved storage stability.[7,8]

The solid matrix of SLN can preserve encapsulated drugs against chemical instability and offer controlled drug release patterns. SLNs can provide strong nano-suspensions for extended periods compared to liposomal delivery systems. The compositions of SLNs are bodily well-tolerated and generally identified as safe (GRAS), which significantly minimizes cytotoxicity, one of the development polymeric nanoparticles lack. Their minimal cytotoxicity leads to SLN's broad usage range such as dermal, oral, pulmonary and parenteral administration[9,10,11] Several potent formulations do not display fulfilment in remedy leading to an increase inside the rejection rate of API from the FDA.[6,7] Factors contributing to treatment failure include poor absorption, rapid metabolism, and uneven drug distribution, which result in inadequate drug concentrations (e.g., peptides and proteins). Additionally, drugs classified under BCS Class II and IV (excluding intravenous aqueous injectables) and unpredictable bioavailability also play a role.To improves the therapy achievement, instead of developing or focusing on a new molecule, it price powerful to suitable modification in drug molecule with an present colloidal carrier like SLNs. Solid Lipid Nanoparticles (SLNs) also incorporate specific surfactants and co-surfactants to improve stability within the concentration range of 0.5% to 5%. Thanks to the combination of solid lipid and submicron-sized nanoparticles, SLNs demonstrate reduced toxicity and enable efficient sustained release. Additionally, SLNs facilitate controlled and targeted drug release, as the surface of the solid lipid can be easily modified with appropriate ligands and polymers. .[12,13,14]

SLNs additionally contain distinct surfactants and co-surfactants to enhance the stability in the concentration range of 0.5% to 5%. Due to the presence of solid lipid and submicron-sized nanoparticles, SLNs show less toxicity and without difficulty attain sustained release.[15,16] SLNs also provide controlled and targeted release because the surface of solid lipid can be effortlessly tailored with suitable ligands and polymers. [17]Incorporation of active compounds into the solid matrix of SLNs gives balance against chemical degradation and environmental element.[18] Each hydrophilic and lipophilic drugs can be easily integrated into the matrix of solid lipid.[19,20]

2. Components of solid lipid nanoparticle

SLNs are primarily composed of lipids as the core matrix material, along with emulsifiers, co-emulsifiers, and water as additional components in their formulation.

2.1 Lipid matrix

Lipids are the primary ingredients of the method and play an important role in determining the stability, release, and encapsulation of an API. An important problem with SLNs is their confined capacity to accommodate hydrophilic drugs, basically because of partitioning effects that occur during the production technique. Most effective tablet with high potency and low dosages which might be hydrophilic can be appropriately integrated into the solid lipid matrix. In lipid medication, at the same time has a surfactant interfacial region stabilizes the lipid drug core, the conjugates have a spherical morphology. Core lipids embody fatty acids, acylglycerols, waxes, and combinations thereof. The surface stabilizers encompass bile salts, cholesterol, phospholipids, and sphingomyelins. [21]

The lipids utilized in the formula of solid lipid nano particles include the following beeswax, behenic acid, caprylic/capric triglyceride (Miglyol 812), cetyl palmitate, cholesterol, glyceryl trilaurate (Dynasan 112), glyceryl trimyristate (Dynasan 114). [21] Witespol W35 (a mixture of triglycerides 65–80%, diglycerides 10–35%, and monoglycerides 1–5%).

2.2.Surfactants

Surfactants are employed to beautify the colloidal stability of particles during the manufacturing process of traditional SLNs. SLNs also have different physical and chemical properties depending on the surfactant's composition and awarness. Surfactants have two important capacity: they disperse the lipid soften in the aqueous phase and stabilize the lipid nanoparticles in dispersions after cooling. The main factors to consider when using surfactants in solid lipid nanoparticle systems are their safety and compatibility with other ingredients. Surfactants can decorate the permeability of epithelial cells and triumph any constraints in the absorption of drugs. [22]

It is essential to bear in mind the toxicity of the surfactant. It isn't not feasible to appoint all surfactants for every type of SLN. The method of SLN generally include the utilization of anionic and nonionic surfactants, with occasional employment of cationic surfactants. It is vital to do not forget concerning the surfactants hired in drug formulations intended for oral, parenteral, and ocular administration. [28]

Cationic lipid nanoparticle preparations have utilized quaternary ammonium surfactants, whereas in maximum studies, soy or egg lecithin have been desired amphoteric stabilizing agents. Moreover, polyvinyl alcohol (PVA) is commonly chosen as a substitute stabilizing agent. [29]

Co-surfactant Sodium dodecyl sulfate, Sodium oleate, Butanol, Taurocholate sodium salt, sodium glycocholate.

2.3 Emulsifiers

The selection of an emulsifier significantly affect the quality of solid lipid nanoparticles. Improving the emulsifier concentration facilitates the reduction of surface tension and particle partitioning during homogenization. Decreasing the scale of particles results in an augmentation of the uncovered surface area.

They enhance the circulate of SLNs via inhibiting the Reticuloendothelial System and enhancing the delivery of drugs to the brain. [23]

The emulsifiers encompass phosphatidylcholine 95% (Epikuron 200), soy lecithin (Lipoid S 75, Lipoid S 100), egg lecithin (Lipoid E 80), poloxamer 188 (Pluronic F 68), poloxamer 407, poloxamine 908, polysorbate 80, Cremophor EL, and Solutol HS. Phosphatidylcholine (Epikuron 170, Epikuron 200 (Amphoteric).

2.4 Co-emulsifers

Vesicle-certain phospholipid molecules showed confined mobility. Therefore, they lack the ability to promptly envelop the recently formed interfaces, at the same time while solid lipids undergo recrystallization. . To save this, co-emulsifiers, such as glycocholate (an ionic substance) and tyloxapol (a nonionic polymer), are used. Those encompass tyloxapol, taurocholate sodium salt, taurodeoxycholic acid sodium salt, sodium dodecyl sulfate, sodium glycocholate, sodium oleate, cholesteryl hemisuccinate, and butanol. [24]

2.5 Cryoprotectants

Cryoprotectants are generally required inside the manner of lyophilization to lessen or eliminate the aggregation of solutes or suspended substances. Examples of these substances: trehalose, glucose, mannose, maltose, lactose, sorbitol, mannitol, glycine, Polyvinylpyrrolidone (PVP), Polyvinyl Alcohol (PVA), and gelatin. [25]

2.6 Charge modifiers

Surface modifiers, along with hydrophilic polymers, may be used to lower the uptake of lipid nanoparticles by means of reticuloendothelial system. These include substances such as dicetyl phosphate, dimyristoylphosphatidylglycerol (DMPG), polyethylene glycol, and poloxamer. . [26]

2.7 Active molecules embedded in SLN

Lipid structure have been utilized to incorporate multiple active molecules, either independently or as factor of a codelivery approach. Several drugs are capable candidates for nanoparticle integration on account hydrophobic characteristics and poor water solubility. Those drugs respectively categorized as anesthetics, antipyretics, antibiotics. [27,]Example are Tripalmitin, cetyl alcohol, cetyl palmitate, glyceryl monostearate, trimyristin, tristearin, stearic acid, etc.

3. Models of Drug Incorporation into SLN

The structural configuration of drugs incorporation into SLN depends on the chemical composition formula and the methodology employed in the preparation process. and the temperature at which the manufacturing runs is carried out. [28]

SLN Type 1: Homogenous matrix model

SLN type 1, a version of solid solutions, is categorized as a homogeneous matrix model because of the molecular dispersion of the active element within the lipid center or its existence as amorphous groups. The version, has noted in advance, is derived through the usage of high-pressure homogenization (HPH) or cold homogenization methodologies conducted at temperatures surpassing the melting point of lipids. [29]

SLN Type 2: Drug-enriched shell model

The SLN type 2 is synthesized through a homogenization process that involves warmth induction. This model asserts that the attainment of the lipid's recrystallization temperature results in forming a solid lipid center. Upon the reduction of the dispersion temperature, the o/w nano emulsion review lipid precipitation, ensuing in an elevation of drug concentration within the liquid lipid. The drug tends to concentrate within the outer shell of the solid lipid nanoparticle that remains in a liquid state. As a result, solidifying the outer shell will result in wide spread amount of the drug being contained within it. [30] It become commonly obtained under low lipid concentrations in liquids, rendering them inadequate for sustained drug release. [31]

SLN Type 3: Drug-enriched core model

In SLN type 3, drug precipitation takes vicinity previous to the re-solidification of lipids. This phenomenon befell whilst the drug concentration inside the lipids approaching. The factor of solubility saturation, then an excessive drug concentration incorporated into the lipid. Upon cooling, the liquid lipid in the nano emulsion reaches a state of super saturation regarding the drug. The subsequent drop in temperature reasons the lipid to recrystallize close to the core, which has been enriched with drug molecules and now resembles a membrane structure. [32]

4. Methods of Preparation of Solid Lipid Nanoparticles:

Lipid nanoparticles could be prepared with the aid of special method such as hot and cold high pressure homogenization.[34 ,35]

4.1 High pressure homogenization technique

4.1.1. Hot high pressure homogenization

In this method, lipid section is heated up to 90 °C, then the hot lipid phase is dispersed in aqueous phase containing surfactants with identical temperature. The pre-emulsion is homogenized at 90 °C below 3 cycles of high strain homogenizer at 5 × 107 Pa. Eventually, the received oil in water emulsion is cooled down to room temperature to solidify SLNs or NLCs. [37]

4.1.2. Cold high pressure homogenization

In this method, the melted lipid phase is cooled to solidify and forms the lipid micro particles. Obtained lipid micro particles that are dispersed in cool aqueous phase involving the surfactants to form pre suspension. Then the pre-suspension is homogenized within 5 cycles of high pressure homogenizer at room temperature and pressure of 1.5 × 108 Pa. [38]

4.2 Double emulsion-based method

Warm w/o/w double micro-emulsions may be organized in two steps. First of, w/o micro emulsion is ready by means of adding an aqueous solution containing a drug to a mixture of melted lipid, surfactant, and cosurfactant at a temperature slightly above the melting point of lipid to achieve a transparent system. In the second step, w/o prepared microemulsion is delivered to aggregate of water, surfactant, and cosurfactant to get a transparent w/o/w system. SLNs can be produced by dispersing warm micro double emulsions into a cold medium, followed by washing with the dispersion medium using an ultra-filtration system. Multiple emulsions have inherent instabilities because of coalescence of the internal aqueous droplets within the oil phase, the coalescence of the oil droplets, and the layer's rupture on surface of the inner droplets. [39]

4.3 Ultra-sonication

SLN can be acquired by way of high-speed stirring using ultra-sonication. This approach is used to produce an oil-in-water emulsion in which high-speed stirring is applied to the melted lipid phase and the new aqueous dispersion of surfactant. After cooling the resulting emulsion, solid particles of lipid are received. The main drawback of this method is the use of a high quantity of surfactant, which is essential to produce nanometer-size particles. The bodily instability and a micro-sized range of particles are some of the alternative hazards of this approach. [40]

4.4. Micro-emulsion technique

Warm micro-emulsion is ready containing molten lipid, surfactant, and co-surfactant brought with stirring. This method is then dispersed in chill water at the time stirring. Excess water may be eliminated by freeze-drying. This technique has sure advantages, along with no need for specialized equipment, energy for production is not required, and scale-up manufacturing of lipid nanoparticles is possible. SLNs generally comprise lipids as the primary matrix material, supplemented by emulsifiers, co-emulsifiers, and water in their formulation. Also, high concentrations of surfactants and co-surfactants in the formulation raise regulatory concerns. [42]

4.5. Coacervation method

This is the solvent-free method for the production of SLNs with the aid of acidification of salt of micelles. When the pH is low, fatty acids begin to precipitate due to proton transfer between the acidic solution and the soap. This process is commonly utilized in the formulation of polymeric nanoparticles.. Nanoparticles inside the range of 250-500 nm length size with round shape are obtained with this method.[43 , 44]

4.6. Spray drying method

It is a much less luxuries and opportunities system of lyophilization. This method leads to the aggregation of molecules as a result of high temperature, shear forces, and partial melting of the particles. The impact of spray drying on the W/O/W double emulsion containing methyl testosterone-loaded stearic acid matrix was discussed by Mlalila et al.[40] The lipid usage with a melting point >700°C for spray drying changed into encouraged was recommended by Freitas and Muller. SLNs supplies the best results with 1% solution of trehalose in water or 20% in ethanol-water mixtures (10/90 v/v). [45]

4.7 Water/oil/water double emulsion

The present technique involves the preparation of SLN that caries hydrophilic pharmaceutical agents and various biomolecules such as peptides and insulin. The manufacturing of SLN was carried out by using the solvent-in-water emulsion diffusion method from a w/o/w double emulsion. The final result of this phenomenon is the dispersion of natural solvents into the aqueous medium and the subsequent formation of SLN through precipitation. The efficacy of this approach is contingent upon the characteristics of the solvent and the interplay between the hydrophilic drug each the solvent and excipients. [47]

4.8 Membrane contractor

The membrane contactor method is also likewise to put tighter SLNs. The procedure incudes pressing the lipid through the membrane pores at a temperature exceeding the lipid's melting point. Water is then circulated past the pores, within the formation of droplets of melted lipid that are cooled at room temperature. [48]

This method offers various advantages, such as simplicity, the ability to control the size of the SLNs by adjusting the procedure parameters, and scalability. In addition with the membrane contractor technique is used to prepare polymeric nanoparticles by utilization of interfacial polymerization method or the nanoprecipitation method, which include the dispersion of preformed polymers. [49]

4.9 Cryogenic micronization method

Cryogenic spray processes are beneficil methods in reduction of the size of particles, which can greatly improve the rate at which drugs that are not easily soluble dissolve. They mostly produce nanostructured, amorphous drug particles with a more level of porosity at extremely minimum temperatures.

This method involve cryogenic processes, as a range of drying technique, such as spray freeze drying, atmospheric freeze drying, vacuum freeze drying, and lyophilization, can be generate to dry powders. Different cryogenic spray techniques can be used including the spray freezing onto cryogenic fluids, Spray Freezing into cryogenic Liquids, spray freezing into vapor over liquid, and ultra-rapid freezing for the manufacturing of smaller drug particles with enhanced wettability. The broken droplets subsequently descend into the refrigerant and promptly solidify into contact with the cryogen. The solidified substance is aggregate into subjected to lyophilization in order to eliminate the solvent. The utilization of chlorofuorocarbon as a cryogenic medium in this process is mostly restricted due to their detrimental impact on the ozone layer. Even certain substituents for chlorofuorocarbons, like hydrofuoroalkanes, have the potency to dissolve the API and reduce the capability of the powdered formulation. [50]

5. **CHARACTERISATION**

Adequate and correct development of the SLNs is essential for its allure control. However, evolution of SLN is a dangerous challenge on account of colloidal breadth of the particles and the complicatedness and complex character of the delivery system. The essential parameters judged for the SLNs surrounds atom size, size distribution kinetics (zeta

potential), degree of crystallintity and lipid qualification, coexistence of additional colloidal structures (micelles, liposome, super cooled melts, drug nanoparticles), time scale of distribution procedure, drug content, in-vitro drug release and surface anatomy.

5.1. Particle Size and Polydispersity Index

The length of the atoms is a key parameter in the process control and quality assurance during the production of SLNs. The atom magnitude impacts the whole surface extent of the nanodispersion device and its physical stability. Particle size can be determined using dynamic light scattering (DLS), also referred to as photon correlation spectroscopy, and laser diffraction. [51] DLS measures the atom length, located at the fluctuation of the sporadic light depth due to the particles motion. Its breadth ranges from any nanometers to 3 µm. [52] Laser dissemination is based totally on the diffraction perspective that relates to the particle radius within the nanodispersion. It could measure larger particle sizes than DLS .[53,54] As a result, DLS is commonly employed to measure the particle size of SLNs. Light-weight microscopy is an alternative preference for samples that comprise many size ranges. [55]The polydispersity index (PI) display the size distribution of a nanodispersion. A decrease PI value shows an extra monodispersed nanodispersion .normally, a nanodispersion with a PI value and API value less than 0.5 indicates monodisperse and homogeneous sample.Indicates then on-homogeneity and polydispersity of a nanodispersion . [56]
[57] However, most studies endorse a PI value < 0.3 as an indicator of a good size distribution .[58,59] PI may be measured using DLS. [60]

5.2 Percent Entrapment Efficiency

The entrapment efficiency (EE) is the ratio of the drug encapsulated in nanoparticles to the total amount of drug used during the manufacturing process.[61 ,62]

$$\%EE = \frac{\text{Amount of entrapped drug}}{\text{Amount of total drug}} \times 100 \quad (1)$$

At the same point of preparation of SLNs, special parameters of the technique and formulation are usually varied to increase EE as high as possible. [63] The quantity of the entrapped drug may be decided after separating the unentrapped drug from the SLN dispersions. Several technique are currently used, which include the gel filtration chromatography [64]dialysis [65]ultracentrifugation , and filter membrane (MWCO 10–20 kDa) .The entrapment efficiency (EE) is the ratio of the drug encapsulated in nanoparticles to the total amount of drug used during the manufacturing process . The unentrapped drug can, additionally be quantified, and the quantity of the entrapped drug is, then, indirectly determined. [66]

5.3 Zeta potential

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the maximum effective strategy for determination of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light, which is due to particle motion. The particle size determination with the aid of photon correlation spectroscopy (PCS) detects size range of 3nm to 3µm and by using laser diffraction in size variety range of 100 nm to 180 µm. Despite the fact, That PCS is a super tool to characterize nano-particles, however is capable for the detection of larger microparticles . [67] The LD tecnique is based totally at the dependence of the diffraction angle on the particle size . Smaller particles cause greater exescive scattering at high angles in comparsion to the larger ones. Zeta potential measurement can be completed using zeta potential analyzer or zeta meter. Earlier than measurement, SLN dispersions are diluted 50-fold with authenthic dispersion preparation medium for size determination and zeta potential measurement . [68]

5.4 Atomic force microscopy (AFM)

In this method, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces that play on the end and the surface. The probe can be dragged through out the sample , or allowed to hover just above, with the exact nature of the particular force employed serving to distinguish among the sub stargery. That ultra-high resolution is offered with this technique, At the side with the ability to map a sample according to properties in addition to size, e.g., colloidal enchantment or resistance to deformation, makes AFM a valuable tool. [69]

5.5 Static light scattering (SLS)/Fraunhofer diffraction

This method research the sample of light scattered from a solution of particles is acumlated and fit to fundamental electromagnetic equations where in size is the primary variable. Its far fast and rugged technique, However it requires more cleanliness than DLS, and advance knowledge of the particles' optical qualities.

5.6 Scanning microscopy

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) offer manner to directly observe nanoparticles. SEM is however good for morphological examination. TEM has a small size lenght limit of detection.[70ff]

5.7 Acoustic spectroscopy

Another ensemble method, acoustic spectroscopy, measures the attenuation of sound waves has a way of determining size via the fitting of physically relevant equations. Further, the oscillating electric field generated by using the movement of charged particles under the impact of acoustic energy can be detected to provide records on surface charge.

5.8 Crystallinity

5.8.1 X-ray diffraction

The procedure hired right here is to quantify the volume of crystallinity, which is ascertained by analyzing the scattering of radiation from the crystal plane inside a solid material. The X-ray diffraction method can also be used to decide the level of crystallinity that a nanoparticle revel. This method is precious for comapring the mass material. [72] There are two primary categories: polymer/polymer and polymer/salt systems. pH, biomolecule concentration, polymer concentration, and the characteristics of the biomolecule's surface all have an affects on the segment separation. They represent delicate circumstances that do not harm susceptible biomolecules. [73]

5.9.Molecular weight

5.9.1 Gel permeation chromatography

Size-exclusive chromatography, also known as gel filtration chromatography, allows for the separation of analytes based totally on their size . [74]

5.9.2 In-*vitro* release

The membrane diffusion method is exetensevly employed for the investigation of in vitro drug dissolution. Diverse techniques, Reverse dialysis sac method, reverse dialysis sac technique, and side-by-side dialysis method, are employed in numerous gaget. Separation method are employed to isolate the dispersed nanoparticles from the continuous phase. The amount of the drug is also assessed. Due to the small dimensions of nanoparticulate systems, it is extremely hard to spilt them from the surrounding medium. [75]

5.10 Dialysis tubing

Drug launch in a laboratory setting (in vitro) can be carried out by employing dialysis tubing. The solid lipid nanoparticle dispersion is enclosed within pre-rinsed dialysis tubing, which may be tightly sealed. Utlimately, the dialysis sac is subjected to dialysis towards the precise dissolution medium at ambient temperature. At suitable duration, samples are extracted from the dissolution medium, subjected to centrifugation, and analyzed for drug content the use of a suitable analytical technique. [76]

5.11 Reverse dialysis

This method involves the location of more than one small dialysis sacs, each containing 1 ml of dissolution medium, into an SLN dispersion. Eventually, the SLNs are transferred into the encircleing solution.11

5.12 Franz diffusion cell

For motive of figuring out the extent to which drugs are able to penetrate an artificial surrounding, Franz cells are exceedingly reliable method. One of the benefits of those tests is they require simplest a small quanity of drug for analysis, limited tissue manipulation, and no ongoing sample collection. Additionally, there is no requirement for continuous sample collection. One of the components of the FDC system is a receiver compartment that holds five milliliters of PBS. Following the passage of the compound through the skin surrogate, it is then lauch into this compartment. It is far viable to conduct a comprehensive evaltion of the penetration kinetics over the years by applying the infinite-dose experimental situation immediately onto this surrogate while it is located inside the donor compartment. A magnetic stirrer and a water tube that is controlled with the aid of thermostat can be found in the Franz difusioncell system. This water bath is able of maintaining a temperature of precisely 32 °C. [76]

6. Route of SLN:

The in vivo desiny of the solid lipid nanoparticles will rely specifically on the administration route and distribution method (adsorption of biological cloth on the particle surface and desorption of SLN components into the organic surrounding). SLN are composed of physiological or physiologically ssocaited lipids or waxes. Probably the maximum important enzymes of SLN degradation are lipases, that are present in diverse organs and tissues. Lipases separate the ester linkage and form partial glycerides or glycerol and free fatty acids. Maximum lipases require activation by an oil/ water interface, which opens the catalytic center. [77]

6.1 Topical route of administration

Skin related illeness are very common around the world. The major barriers for remides of these diseases are low drug efficacy due to poor skin penetration or skin permeation of medicine from the most conventional formulations. Stratum corneum of epidermis is the fundamental skin barrier and it should be by passed through changing the penetration pathway from transcellular to paracellular or follicles. Lipid nanoparticles together with SLNs and NLCs have been evolved to increase skin penetration or permeation. Those particulate formulations are prepared by combining SLNs or NLCs with traditional formulations. They can be immediately prepared in a one-step process which produce drug-loaded SLNs or NLCs. Lipid nanoparticles have so many advantages for topical drug delivery consisting of biocompatibility

and biodegradability, controlled and prolonged drug release profile, near contact and strong skin adhesion, skin hydration and film formation in order to elevate skin and dermal penetration.[78,79,80,81,82]

6.2. Oral route

Oral drug administration is the maximum common place of drug delivery system due to the highest person compliance. Low oral bioavailability because of limited drug solubility and excessive hepatic first pass impact are the most crucial limitations in oral drug delivery which we need to overcome. Lipid nanoparticles which include SLNs and NLCs have the benefit of sustained drug release capability to keep a constant plasma levels. Further, nanoparticles with better unique surface vicinity and higher saturation solubility have more fast dissolution rate that could boost up the onset of drugs action. The lipid structure of SLNs makes them ideal for oral administration, enhancing bioavailability by protecting the drug from chemical and enzymatic degradation, thus prolonging its in vivo metabolism. [55] Aqueous dispersion or traditional dosage forms, such as pellets, capsules, or tablets, are the oral dosage varieties of SLNs. The situation of gastric parts lead to particle aggregation due to the high attention of acid and ionic energy present in the stomach. However, the actual impact of stomach and pancreatic lipase on the degradation of SLNs remains uncertain .[83,84,85,86,87]

6.3. Ocular route

Eyes are a very complicated and complex organ and have diverse barriers that should be triump over to reach specific ocular tissue. The eyes are most sensitive organs of our body, as a result the drug delivery to eye tissues is especially hazardous. Ocular drug delivery has many obstacles and stays challenging due to particular physiological and anatomical capabilities of the eyes. Novel drug delivery systems such as lipid nanoparticles had been considered to triumph over those limitation and improve ocular tissue bioavailability. The discharge of the can be assisted or regulated into the ocular mucosa, which in assessment to traditional ophthalmic arrangements expanded the pre-corneal protection time of the drug. SLNs went for visual conveyance should want to satisfy specific criteria, much like visual safety, sterility, isotonicity, and pH of suspension (like lachrymal liquid). This direction of administration has many and is the benefits to choose for superficial ocular diseases. Crucial barriers in this pathway are corneal epithelium, blood ocular barrier, and tear drainage.[88,89,90,91,92]

6.4 Parental route

Nanomedicine and nanotechnology play an essential role in enhancing the parenteral drug delivery. The most crucial function of lipid nanoparticles for this purpose are ease of scale up production, biocompatible and biodegradable nature of the method constituents, managed and modified drug release pattern, stopping drug degradation and maintaining extra constant serum levels of drugs. Drug-loaded solid lipid nanoparticles may be injected intravenously, subcutaneously, intramuscularly, and directly to target organs. Drug release from lipid nanoparticles may additionally occur through erosion (such as enzymatic degradation) or diffusion that could support a sustained drug release.

Current researches have confirmed the capability of lipid nanoparticles in peptide and protein incorporation. On this context, SLNs are not appropriate carrier due to restrained drug loading capacity but NLCs are appropriate opportunity. By this method peptides and proteins can be protected from harsh environmental conditions .[93,94,6,95]

Table 1 – Different loaded drug nanoparticles routes of administration route of administration drug loaded

Route of Administration	Drug
Topical	RhEGF Olanzepine Arthemeter Adapalene Methotrexate Vitamin A
Oral	Cycloserine Oxyresvertrol Silymarin Trans – ferulic acid Lumefantrine Vinpocentine Hydrochlorthiaz Miconazole Penolic Compound
Ocular	Diclofenac sodium Ibupfropen Ciprofloxacin

	Coumarin Cylcosporin A
Parenteral	Peptides and Protiens Polyphenols Itraconazole Silybin Docetaxel Celexocib

6. Advantages of SLN [1 ,4, 96, 97]

- Control and enhance drug release.
- Fine biocompatibility.
- Enhance stability of pharmaceuticals preparations.
- Excessive and enhanced drug content.
- Convenient to scale up and sterilize.
- Superior control over release kinetics of encapsulated compounds.
- More advantageous bioavailability of entrapped bioactive compounds.
- Chemical protection of labile integrated compounds.
- Less complication to manufacture than biopolymeric nanoparticles.
- No special solvent needed.
- Standard emulsion manufacturing methods applicable.
- Flexibility.
- Raw materials as vital as in emulsions.
- Very high durable stability.
- May be subjected to commercial sterilization process.

7. Disadvantages of SLN [4, 98, 99]

- Particle increase.
- Uncertain gelation tendency.
- Unexpected dynamics of polymeric transformation.
- Excessive pressure-induced drug degradation.
- Drug expulsion after polymeric transition throughout storage.
- Lack of excessive amount of Drug
- Lack of sturdy Control drug release
- Restrained Transdermal Drug delivery
- In vitro dissolution research show changes in drug release study.
- Lipid/aqueous partitioning is a production challenge to face in loading of hydrophilic drugs in SLNs. Water soluble drug loading in SLNs with less capacity and the excessive water content of SLN dispersions (70–99.9%) is a limitation of SLNs
- SLNs have negative drug loading capacity, which is a drawback.

8. Recent application in SLN

8.1 Food Delivery

SLNs are utilized in a variety of food products and as delivery systems for tablets or active compounds. Another key application of SLNs in the food sector is their ability to act as effective carriers for sensitive ingredients, thereby improving food quality and nutritional value. [100] SLNs have also been implemented for the fortification with nutrients which are without problems Environmental factors or certain nutrients may impart undesirable flavors or aftertastes, which can be mitigated by encapsulating or "blanketing" them in Solid Lipid Nanoparticles (SLNs). This technique helps mask the unpleasant taste and improves the overall sensory experience. [101] In addition to carrying nutrients, SLNs have also been widely utilized as a drug delivery agent or as a service for other active compounds which might be useful to substances that promote health, including pharmaceutical compounds and antioxidants . [102 ,103]

SLNs are a great opportunity in terms of capability and biocompatibility. Because they can directly target the site of infection, enhance drug bioavailability, and minimize toxicity or side effects. [104] . SLNs are lipid-based drug delivery systems with exceptional characteristics, including a large surface area, high drug-loading capacity, and the ability to shield the drug or active ingredients from environmental factors. [105 ,106] In addition, SLNs can increase the absorption potency or bioavailability of drug transport systems. SLNs may have two advantages in drug delivery systems,

specifically in the effective protection of medication and active compounds during the production process due to increased encapsulation performance the effect of this system is desired because of the improved release of drugs and active compounds SLNs are lipid-based drug delivery systems with exceptional characteristics, including a large surface area, high drug-loading capacity, and the ability to shield the drug or active ingredients from environmental factors.[107]

8.2 Transdermal Delivery

SLNs are efficient in transdermal delivery of both hydrophilic and hydrophobic drugs. SLNs are physiologically secure and capable to moisten the skin. [108 ,109] Some studies reported in vitro, ex vivo, or in vivo assessment of SLNs or SLN gels. For instance, tacrolimus-loaded SLNs exhibited 25–40% skin permeation, while SLN gel decrease skin permeation .However, SLN gels enhanced drug retention in the skin, making them suitable for treating atopic dermatitis.[11] Previous studies have demonstrated that quercetin and resveratrol were co-loaded into SLN gels to enhance drug delivery to the epidermal layers.[111] The permeation of those drugs from the SLN gel tested turned into better than that from the conventional gel, with an enhancer index of 1.95 and 1.50, appropriately. The SLN gel additionally confirmed higher maximal drug concentration in the skin as well as the area below the curve for both quercetin as well as resveratrol in the epidermal and dermal layers , suggesting the capability of SLN gel in treating skin cancer. In another study, SLNs loaded with isotretinoin and α-tocopherol acetate demonstrated prolonged drug release over 24 hours and exhibited strong anti-acne effects without causing skin irritation.[112] In reference to tacrolimus-loaded thermo sensitive SLN gel showed the penetration of SLNs into a deeper layer of skin, balance with a reference product in both ex vivo and in vivo studies. [113]

8.3 Breast Cancer

Breast cancer is one of the maximum often going on cancers deaths in women and the second leading cause of cancer deaths in women. Some of the good sized demanding situations in effective breast cancer chemotherapies are inadequate drug concentrations reaching the tumor, their speedy removal, systemic toxicity, unfavorable outcomes. SLN has the capacity to triumph over cutting edge chemotherapeutic limitations in breast cancer treatment and to solve the troubles associated with conventional chemotherapy and multidrug resistance. [114 ,115] SLNs in breast cancer and lymph node metastases: Mitoxantrone-loaded SLN local injections has been formulated to lessen the toxicit and improve the safety and bioavailability of drug. [66]Efficacy of doxorubicin (Dox) has been reported to be greater via incorporation in SLNs. [116] In this method, Doxorubicin is complexed with a soybean oil-based anionic polymer and then dispersed with a lipid in water to form Dox-loaded solid lipid nanoparticles. The gadget is more suitable its efficacy and decreased breast cancer cells.

8.4 SLN in beauty and dermatological preparations

An area of big potential for SLN and with a brief time-to market are topical products based totally on the SLN era, meaning pharmaceutical however also cosmetic formulations. SLN are considered as being the next era of transport system after liposomes. [117]Due to the lower risk of systemic aspect outcomes topical remedy of skin disease appears favorable, but the stratum corneum counteracts the penetration of xenobiotic into possible skin. Particulate carrier systems may additionally mean an option to improve dermal penetration. Considering the epidermal lipids are observed in excessive amounts in the penetration barrier, lipid companies attaching themselves to the pores and skin surface and also allowing lipid trade between the outermost layers of the stratum corneum and the provider appear promising. Besides liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) were studied intensively. [6] Following the evaporation of water from the lipid nano-dispersion carried out to the skin surface, lipid particles shape an adhesive layer occluding the skin surface. Then hydration of the stratum corneum may additionally boom via which reducing corneocyte packing and widening of the inter-coenocytes gaps can facilitate drug penetration into deeper skin strata. Occlusive effects appear strongly associated to particle size. Nanoparticles have grew to become out 15-fold more occlusive than micro particles, and particles smaller than 400 nm in a dispersion containing at least 35% lipid of excessive crystallinity has been most potent.

8.5 Solid lipid nanoparticles for ultrasonic drug and gene delivery

Drug delivery studies using micelles and nanoparticles has wide application in ultrasonic drug and gene delivery in recent years. Of precise interest is the use of those nano-vehicles that deliver high concentrations of cytotoxic medicine to diseased tissues selectively, for this reason lowering the agent's side effects on the rest of the body. Ultrasound, traditionally utilized in diagnostic remedy, is finding an area in drug transport in connection with these nanoparticles. Further to their non-invasive nature and the fact that they may be focused on targeted tissues, acoustic waves have been credited with releasing pharmacological dealer from nanocarriers, In addition to rendering cell membrane extra permeable. Ultrasonic drug delivery from micelles. Generally employs polyether block copolymers and has been found effective in vivo for treating tumors. Ultrasound releases drug from micelles, maximum probably via shear stress and shock waves from the disintegrate collapse of cavitation bubbles. Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genes in vitro and in vivo. The small packaging allows nanoparticles to extravasate into tumor

tissues. Ultrasonic drug and gene shipping from nanocarriers has outstanding capacity because of the huge range of drugs and genes that could be delivered to targeted tissues by pretty non-invasive means. [118]

8.6 Solid lipid nanoparticles for parasitic illness.

Parasitic diseases (like malaria, tryanosomiasis) are one of the important problems around the world. Antiparasitic chemotherapy is the only preference of remedy for these parasitic infections, the purpose for this is that these infections do not longer elicit said immune response consequently powerful vaccination may not be viable. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) constitute a second generation of colloidal delivery systems and have emerged as an effective opportunity to liposomes particularly because of their better stability profile, ease of scalability and commercialization and relative fee efficacy. Moreover, SLN and NLC due to their particulate nature and inherent shape exhibit proper capacity within the treatment of parasitic infections. Latest review consisting of our research have conformed their utility at the least to a point. However, the need of hour is to adopt huge investigations on SLN and NLC matrices so one can increase versatility with respect to encapsulation capability and target ability and to arrive at a versatile, effective and economical approach for the delivery of anti-parasitic drugs. [119 ,120]

8.7 Solid lipid nanoparticles for neurodegenerative disorders

Recent studies on SLNs as a carrier system have aimed to target the brain, turning in drugs throughout the BBB. SLNs, with its superior capabilities , is a new smart drug delivery system for the treatment of neurological issue, with perfect characteristic functions the short of nano diameter variety, site-specific targeted delivery (via receptor-mediated transcytosis across brain capillary endothelial cells), physical stability, ability to escape the reticulo-endothelial system, extended blood circulation time, sustained launch, and free, biodegradable, as well as biocompatible characteristics. From an economic perspective, SLN production is scalable and value-effective. [122]Donepezil (an anti-Alzheimer's drug), Whilst tailored to ApoE-targeted and SLN-based formulations, the Pharmaceutics in vitro observe findings showed that it has increased drug delivery with a positive release profile in CMEC/D3brainendothelial cells and humanSH-SY5Yneuronalcells. [123] Some of the conventional and recently developed drug transport strategies, a nano-technological SLN based method has shown possible improvements in overcoming the existing barrier in the remedy of epilepsy. Further, muscimol SLNs and amiloride loaded SLNs have been evidenced to have anticonvulsant outcomes, suppressing focal seizures in in vivo rat models with a better and more sustained release in assiment to the management of free drugs only. Details of SLNs loaded with carbamazepine, diazepam, clonazepam, and raloxifene. [124]

Another study found that lipoyl-memantine (LA-MEM codrug)-loaded SLNs are an progressive approach, which might be stable in simulated gastric and intestinal fluids, enhancing stability, solubility and absorption through the gastrointestinal tract. This indicates that they can pass the BBB at most concentrations. Moreover, LA and MEM were released as the end product of hydrolysis, exhibiting therapeutic potency in a safe and risk free manner. [125]

9 .Conclusion and Future Prospective

SLN systems are designed to address various pharmaceutical aspects, such as enhancing bioavailability, controlling drug release, and optimizing Stability. The properties of active and supplementary Ingredients play an important role in the formulation process determining the type of SLN. Despite their limitations, Using SLN remains a viable option in nanotechnology to modify hydrophobic and hydrophilic drugs since SLN can be manufactured through a straightforward and purposeful process using materials that are known to be safe. Thus, those advantages indicate that SLN is a promising method for drug delivery

The future prospects and potential advancements in drug delivery lie in the characterization and design of SLNs. various potential future developments can be anticipated in this rapidly progressing fled. Solid lipid nanocarriers have a Lot of potential for drug delivery. This is because research is still going on, which should lead to new improvements in their functionality, specificity, and therapeutic uses. The ongoing advancement in these carriers requires the cooperation of researchers, physicians, and industry partners to bridge the gap between scientific breakthroughs and practical Healthcare applications.

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