Solid lipid nanoparticles the emerging approach in pharmaceuticals: An overview

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Abstract:

In recent years, great attention has been attentive to lipid-based drug delivery systems to concur with limitations associated with conventional formulations. Among these are solid lipid nanoparticles (SLNs) which are considered a promising delivery system because of the ease of manufacturing processes and scale-up proficiency, biocompatibility, the biodegradability of ingredients involved in the formulation, and numerous additional advantages related to various routes of administration.

The present review provides insight into how SLNs are finding a role as promising nanocarriers and forms a comprehensive basis for overcoming problems related to traditional drug delivery systems. It also demonstrates variables affecting formulation, methods of preparation and evaluation, as well as routes of administration.

Keywords: Biocompatibility**,** drug loading, innovative lipid nanoparticles, nanostructured drug delivery, stability

الجسيمات النانوية الدهنية الصلبة النهج الناشئ في مجال التحضيرات الصيدلانية: نظرة عامة

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الخلاصة

حظيت انظمة الايصال العلاجي المعتمدة على الدهون في السنوات الاخيرة على الكثير من الاهتمام لتلافي العوائق المرتبطة بالأنظمة التقليدية. وتعد الجسيمات النانوية الصلبة من ضمن انظمة التوصيل الواعدة بسبب سهولة عملية التصنيع على نطاق واسع، التوافق الحيوي وقابلية التحلل الحيوي للمواد الداخلة في تصنيع التركيبة والعديد من المزايا الاضافية المتعلقة بطرق الاعطاء المختلفة. توفر مراجعة المقال نظرة ثاقبة عن دور الجسيمات النانوية الصلبة كنظام نانوي حامل للعقار والتي تشكل اساسا شاملا للتغلب على العوائق المتعلقة بأنظمة توصيل الادوية التقليدية كما يوضح المتغيرات التي تؤثر على عملية التصييغ , طرق التحضير والتقييم اضافة الى طرق الاعطاء.

الكلمات المفتاحية: التوافق الحيوي، تحميل الدواء، الجسيمات النانوية الدهنية المبتكرة، ايصال الدواء ذا البنية النانوية، الاستقرارية.

Introduction

Employing large molecules in drug delivery systems imports many challenges, for instance *in vivo* instability, deprived bioavailability, low aqueous solubility, poor absorption, and issues with site-specific drug targeting. Consequently, developing novel drug delivery systems could be an option to overcome these critical concerns [1].In recent decades, great attention has been paid to colloidal lipid-based carriers to defeat some drawbacks of conventional formulations. Among these carrier systems are solid lipid nanoparticles (SLNs) [2].

SLNs were invented in 1991, and since that time they have taken the main share in drug delivery modules. They have been developed as substitutes for traditional colloidal carrier systems such as emulsions, liposomes, and polymeric nanoparticles to overcome their weaknesses (for instance polymer and phospholipid degradation, cytotoxic effect, instability issues, difficulties in scale-up production, drug fusion and leakage, costly production, and sterilization problems) [3].

By comparing SLNs for instance (which developed upon liposome technology) with liposomes, their solid lipid bilayers will result in a rigid strecture, an easier scale up manufacturing once accessibility of equipment is assured with a more stable final product. Additionally, because of shortage and safety concerns and the high production cost of polymeric nanoparticles , SLNs are considered an ideal alternative for drug delivery systems.[4].

SLNs are spherical colloidal carrier entities in the range of a submicron size (50–1000 nm) and made up of biodegradable and biocompatible ingredients having the potential of incorporating water-soluble and lipid-soluble active ingredients. The drug release from SLNs depends mainly on the type of matrix as well as the drug location in the vesicle [5].

Structurally they comprise of dense hydrophobic core possessing a distinct layer of phospholipids coating in which the active ingredient is either dissolved or dispersed in the solid high-melting lipid matrix as shown in **Figure 1**. The phospholipid's hydrophobic chains are entrenched in the lipid matrix [6].

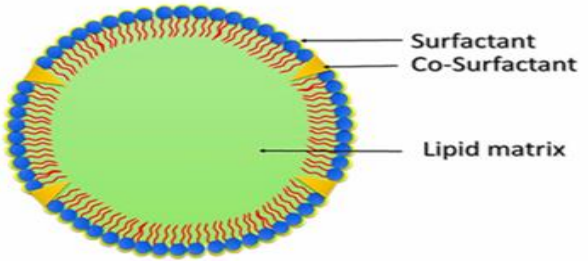

Figure 1:Structural composition of SLN [7]

SLNs provide numerous advantages in comparison to traditional colloidal carriers such as reduced toxicity, improved stability as a result of the rigidity of core lipid matrix, enhanced drug protection, targeted controlled drug release, higher cellular uptake, enhanced drug bioavailability and solubility as well as ease of scale up and sterilization [8, 9]. The main drawbacks associated with SLNs are deprived long-term drug retention as a result of the polymorphic transition of lipid matrix during storage, limited capacity of drug loading due to low space available for drug encapsulation, and high water content [10]. This mini-review covered the influence of formulation variables on the characteristics of SLNs, numerous methods

of preparation employed, characterization, and the route of administration.

Variables affecting SLN formulation

SLNs consist mainly of lipids which are in a solid state at room temperature, emulsifying agents, active ingredients, and a proper solvent system (water). Additional ingredients may also be used to provide the necessities of targeting characteristics and stability such as stealthing agents that prolong circulation time and targeting ability and charge modifiers. These pharmaceutical ingredients play a crucial role in determining product criteria and efficiency [11].

Lipid

Lipid has a great influence on the features of prepared SLNs. Lipids with less organized crystalline lattice like glyceryl monostearate provide higher drug inclusion in comparison to highly organized crystalline lattice lipids like bee wax when the hot homogenization method was employed [12]. Though the employment of different solid lipid mixtures disturbs crystal order, no enhancement of drug inclusion capability has been noticed [13].

Alternatively, significant enhancement of drug loading capacity as a result of disruption in crystal packing can be achieved by mixing solid long-chain glycerides and liquid medium-chain glyceride lipids to develop innovative SLNs designated as a nanostructured lipid carrier (NLCs). NLCs are characterized by high drug inclusion capacity compared to traditional SLNs. In opposition, NLCs demonstrate a reduction in controlled release behavior provided by SLNs which is related to the reduction in matrix diffusion length as a result of the packing of oil droplets between the NLC lipid pallets [14, 15].

For the development of a drug delivery system, crucial points should be taken into consideration; the proposed use and drug loading capacity. For instance, hard fats (fats that endure meltting at 37 C^{O}) are not appropriate for formulas requiring controlled release. As lipid complexity increases, less faultless crystals with defects form. These defects in turn give space for drug loading. Alternatively, lipids with a perfect crystal lattice that develope extremely crystalline particles are responsible for drug expulsion [12, 15].

The average particle size in SLN dispersion is affected mainly by the melting point of the lipid. A significant increase in average particle size was observed for SLNs formed by high-pressure homogenization when lipids with higher melting points were used.Larger particles and a wide-ranging distribution of particle size result when the SLN formulation lipid content is higher than 5 to 10 percent [16].

The stability of SLN is affected by the purity of the lipid used due to zeta potential alteration[14, 17].Partial glycerides, triglycerides, ,waxes, free fatty acids, and steroids are among the most widly employed lipids [18].

Surface active agents (Surfactant)

Surfactants are defined as amphiphilic molecules distinguished by possessing a hydrophilic (anionic, cationic, or nonionic) head group in addition to a hydrophobic tail. They can adsorb to solid /liquid boundaries by allocating the hydrophilic head group in the aqueous phase and the hydrophobic tail in the second phase permitting them to be employed as emulsifiers, dispersion, and wetting agents, etc [19].

The main purpose behind using surfactants in SLN formulas is the reduction of interfacial energy between the lipid as well as aqueous phases throughout particle formulation. Surfactants provide the required dispersion phase stability during storage due to their ability to aggregate at the boundary (charged surfactants) and provide particle coating resulting in the disaggregation of particles [20]. The SLN formulation usually involves

the implementation of both anionic and nonionic emulsifiers, additionally infrequent utilization of cationic ones. Proper selection of emulsifiers is considered a vital point due to their potential toxicity. Selection modulation should be utilized based on the route of administration of formulated SLN whether it is oral, parenteral, or ocular. Nonionic emulsifiers for instance poloxamer 188 are highly recommended for the above-mentioned routes [21].

An *in vivo* fate is an additional point to be considered concerning the emulsifier selection. The higher the molecular weight emulsifier the longer the redistribution interval. For example, poloxamers are used to formulate SLNs mainly due to their ability to prevent the reticuloendothelial system from uptake the particles and hence prolong their circulation extent in the body [15, 22].

Additionally, the concentration of the emulsifier used greatly influences the SLN's particle size. Generally, a reduction in particle sizes was obtained when a higher emulsifier/lipid ratio was selected to a certain limit. The lower the emulsifier concentration the bigger the particle size throughout storage since it reduces the surface tension between the boundary of the particles resulting in the distribution of the particles and thus increasing the surface area [23].

The main drawbacks associated with utilizing surfactant in SLN formulation are their toxic effect mainly for rapidly circulating surfactants [24] ,aggrigiation as a result of formation of polydisperse system mainly when 100 to 1000 fold excess of surfactants utilized [25].Additionally instability during storage may developed when a high amount of surfactant employed to prepare SLNs by ultrasonication for instance due to the production of wide particle size distribution [26].

Co surfactant

Co-surfactants impart a significant role in the development of SLNs because of their capability to improve stability and crystallization behaviour of these colloidal nancarriers.They act mainly through the interfacial properties modification together with surfactant essentially by polymorphic transision which accordingly influnce both partical size variation and drug release behavior [27] .

The hydrophobic nature of phospholipids employed in SLNs development resulted in their insolubility in the external phase mainly due to failure of dynamic micelles formation.During homogenization process the additional molcules of phospholipid primarly develop small , mainly unilamilar vesscles to which phospholipid molcules providing inadequit mobilitySubsequently, the incapability to cover the newly developed boundaries during the recrystallization of solid lipids, which results in the particles aggregation and an increase in the average SLN size. Water-soluble co-surfactants are usually utilized in the formulation to avoid this by providing micellization and decreasing the average SLN size in dispersion [28].

Drug lipid solubility.

Lipid-soluble drugs are probable candidates for nanoparticle incorporation due to their poor aqueous solubility as well as hydrophobic characteristics. For instance anesthetics, antibiotics, analgesics, antihypertensive and anticancer agents. Furthermore, there have been studies concerning integrating peptides and nucleic acids into lipids [20, 29].

Among the most widely oil solvents used for lipid-based formulations are different chain-length glycerides (mono, di, and triglycerides), carboxylic fatty acids, fatty alcohols, and fatty esters. Glycerides with medium-chain lengths with lower melting points have optimum drug solubilization characteristics in addition to microemulsion

formation, while the ones with long chain lengths and higher melting points are crucial for the formulation of SLNs. It was recognized that a superior solubility of the drug in the lipid preparation in comparison to the calculated (theoretical) value of the drug solubility in lipids alone specifies the existence of the drug not only in the oil phase but also in lipid assembly interphase regions [15, 30].

Additionally, the solubility of the drug in the molten lipid is superior to that in the solidified lipid which affects both the drug loading capacity and entrapment efficiency (EE) [31].

Methods of Preparation of Solid Lipid Nanoparticles:

Different methods are designated in various literature and are employed to formulate SLNs.Among these methods are high-pressure homogenization, emulsification, lipid nano pellets, and lipospheres, an aqueous needle process, *in situ* gelation, and membrane contractor technique [7, 32].

1. High-pressure homogenization (HPH) method

High-pressure homogenization is considered the most widely used technique in which a high pressure is employed (100 to 2000 bar) to drive the liquid or dispersion via a micronized gap to form submicron-sized particles. Reduction in the size of the particle is related to both higher shear stress as well as cavitational forces that result in particle breakdown [33]. HPH can be operated at either low or high temperatures [34]. The main advantages of this method are production simplecity , minimal manufacturing time, avoidance of organic solvent, flexibility and versality ,low energy conception as well as viability of scale up [35, 36]. Main drawbacks for this method are high energy load , lipid degradation and loss due to high energy employed,inconsistent nanoparticle size due to high particles kinetic energy,physical instability,coastly equipment as well as potential contamination with metal [36, 37]

1.1. Hot homogenization method

This method includes heating the lipids above their melting point so convert them into liquid material with lower viscosity due to the high temperature The drug at that time dispersed or dissolved in the lipid, consequently dispersing the drug-loaded lipid in a hot aqueous mixture of surfactant with mixing resulting in coarse pre-emulsion The emulsion at that point exposed to high-pressure homogenization at a temperature more than the melting point of the lipid forming hot (O/W) nanoemulsion, then after cooling down the hot (O/W) nanoemulsion to room temperature, the solid lipid nanoparticles obtained from recrystallization of lipid [38, 39].

The hot homogenization method is appropriate for active ingredients with low-temperature sensitivity since there is short exposure to high temperatures [40]. The disadvantages of this method result from a temperature rise leading to an elevated rate of decomposition of the loaded drug, and unreliable lipid conversions, due to the high kinetic energy involved in the preparative steps [38]. **Figure 2** illustrates hot homogenization method.

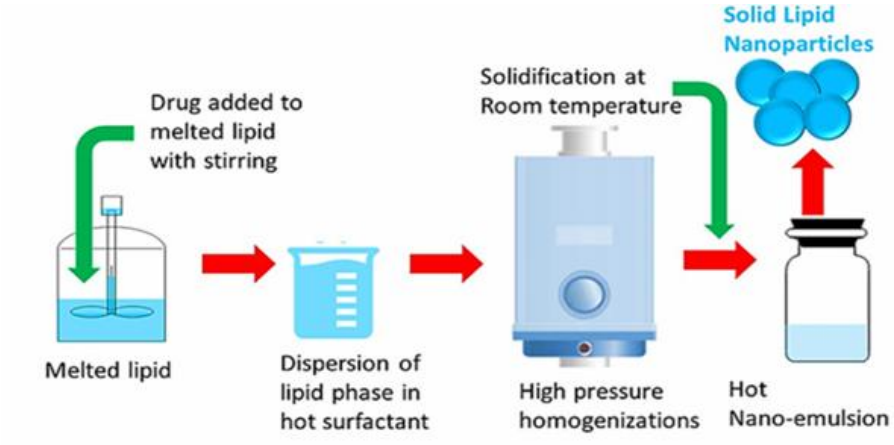

Figure 2: Hot homogenization method [7].

1.2 Cold homogenization method

The lipid melt-loaded drug is cooled, and the solid lipid is ground to lipid microparticles (approximately 50±100 mm) which are dispersed in a cold solution of surfactant yielding a pre-suspension that homogenized at a temperature below that of room, the lipid microparticles are broken directly to solid lipid nanoparticles by cavitation forces. (9) The advantage of this method is minimizing, the melting of the lipid due to decreasing thermal exposure and therefore decreasing the loss of hydrophilic drugs to the aqueous phase. The disadvantages of this method are larger particle size production and wide size distribution [30].**Figure 3** illustrates cold homogenization method.

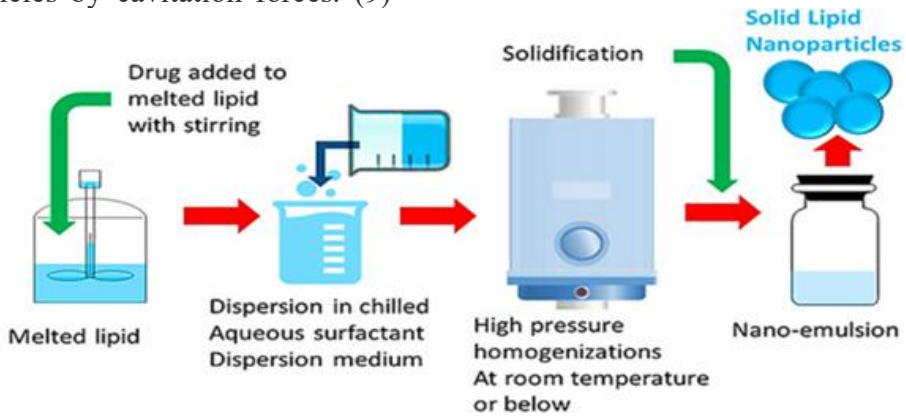

Figure 3: Cold homogenization method [7].

2. Emulsification method

2.1 Solvent emulsification/ evaporation method

In this method the lipid is dissolved in an organic solvent like chloroform followed by emulsification of this solution in an aqueous phase, the solvent is evaporated, and the lipid precipitates leaving nanoparticles. The procedure was implemented at room temperature and was thermolabile. The need to use organic solvents is the disadvantage of this method [37]. This method is a continuous and easily scalable process. The main drawbacks of this method are an expensive method, the occurrence of poly distribution, and toxicological issues mainly related to solvent residues [27].

2.2 Microemulsion method

In this method, the microemulsion is prepared from solid lipid at room temperature (25 ºC) and requires to be prepared at a temperature more than the melting point of the glycerides and/or fatty acids. When the lipids are melted, an aqueous blend of surfactant and co-surfactant(s) is heated to the same temperature as the melted lipid. An aqueous mixture is then added under mild stirring to the melted lipid. This microemulsion is then added to aqueous medium at (2-3°C) under mild mechanical mixing, small particles in size are formed due to the precipitation. The main advantage of this method is low energy input to achieve the submicron size [41].The main drawback associated with this techniques are high surfactant implementation, large volume of water utilization as well as labour exhaustive [35, 42].

2.3 Emulsification-sonification method

Active ingredients were added to the melted lipid (s) at 5–10°C and then added to a hot solution of liquid surfactant resulting in emulsion formation that sonicated to decrease the size of particles. Lastly, the gained SLNs were cooled at room temperature. The disadvantage of this method is metal contamination since the metal probe is used in the ultra-sonication method as well as the wide distribution of particle size [43]. **Figure 4** demonstrates the emulsification-sonification method.

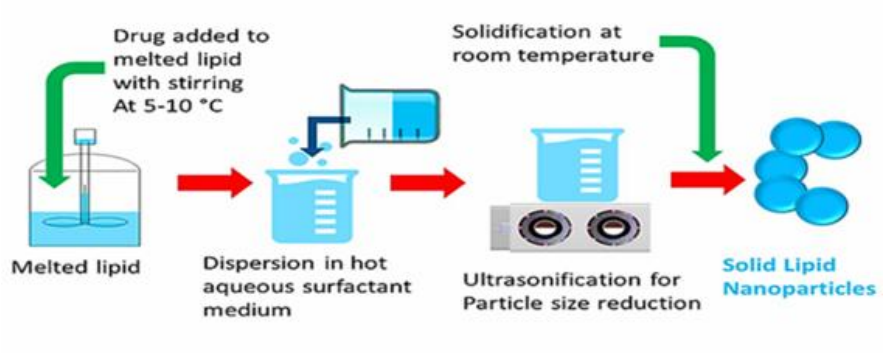

Figure 4: Emulsification-sonification method [7].

3. Spray drying method (SD)

This method is recommended when a lipid has a melting point higher than 70 ºC. In this method, numerous techniques are used to formulate drug-loaded SLN. The first technique involves the conversion of the drug-loaded SLN nanosuspension to a powder while in the second technique, a SLN/ polymer composite is prepared by loading a drug suspension loaded SLN in a polymer solution which is then dissolved to form free SLN; the third technique by forming a solution of drug, lipid, and polymer which can be changed by SD step to SLN-loaded polymer particles, and the SLN finally obtained by dissolving the later in an aqueous medium. It is a cost-effective method since the obtained SLN is completely dried and utilized when the bottom-up self-assembly of nanoscale substances is required [44]. Among the main limitations of this technique are utilizing expensive equipments, high energy conception, dust generation potential lipid melting during drying process , can not be effectively employwed for high viscous sticky substances as wel as product loss mainly for heat sensitive substances [45].

4. Coacervation method

This method which is a solvent-free process initially involves the formation of an aqueous polymer stabilizing stock solution in which

the sodium salt of the fatty acid is dispersed. The resulting mixture is then heated to a point above the Krafft point of the fatty acid of sodium salt with continuous stirring till a clear solution is obtained (Krafft point is the lowest temperature required for micelles formed by surfactants) [46]. At this point, an ethanolic solution of the drug is added with continuous stirring til a single-phase system is achieved. Eventually, drop by drop coacervating solution addition (acidifying the solution) to form nanosuspension which is then cooled by a water bath, with continuous agitation, forms drug-loaded nanoparticles [47, 48]. This method is an easy scale-up, solvent-free, and provides a monomeric drug encapsulation with high efficacy since it provide immobilization of drug molecule insid solid lipid shielding them from chemical and oxidative degradation hence reducing its lekage [21, 49].

4. Supercritical fluids method

In this technique, the lipophilic active ingredient is dissolved in supercritical carbon dioxide (CO_2) and then combined by ultrasonication to prepare SLNs.This method process provides no heat degradation, uses nontoxic solvents, provides optimum control of particle size distribution, and directly produces a stable water suspension as shown in **Figure 5** [50].

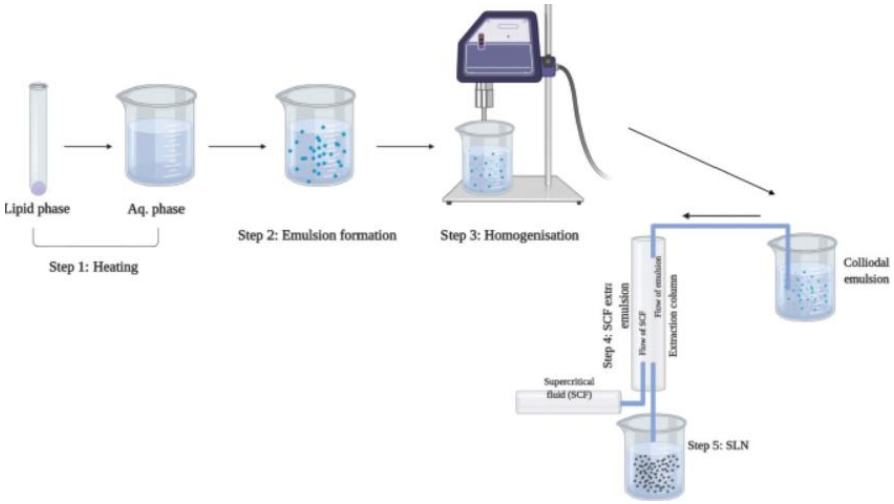

Figure 5:Supercritical fluids method [51].

5. Membrane contractor method

This technique is performed by using a membrane contractor for scale up production. The lipid phase is forced via the membrane pores at a temperature more than the lipid melting point, leading to the development of tiny droplets. The aqueous phase passes through the membrane module and sweeps away the droplets that form at the pore outlets. Then cooling of the product to room temperature leads to the formation of SLN [52].**Figure 6** illustrates membrane contractor technique.This method provides the capability of use, size control of the prepared particles by the proper selection of production parameters, additionally its scaling-up capacity. The key limitations of this process are possible metal impurities and physical instability due to particle progression on storage [53].

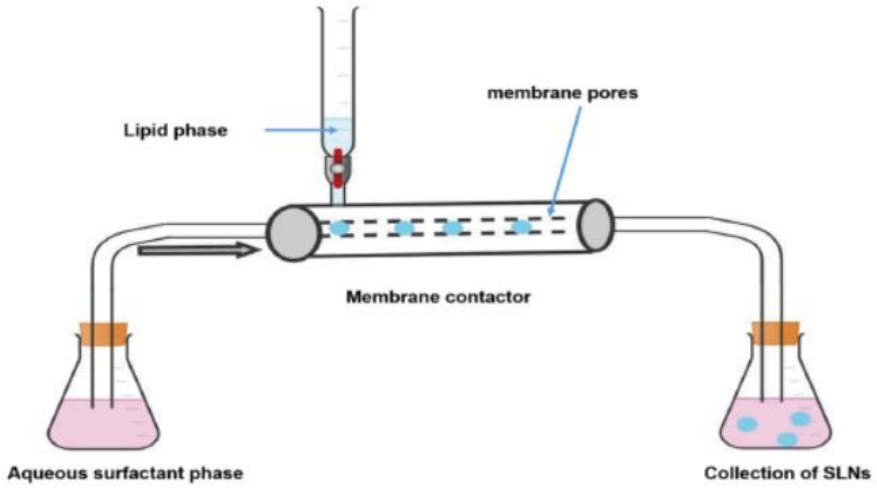

Figure 6:Membrane contractor technique [54].

6. Aqueous needle method

In this process, a water-miscible organic solvent (e.g. acetone, and methanol) is employed to dissolve lipids. The obtained solution is then introduced to an aqueous solution of surfactant by a needle with continuous stirring. Finally formulated nanosuspension is filtered to eliminate the excess lipid. This method is a cost-effective process that has a faster production rate [55].

7. In situ gelation method

In this method SLN are prepared by mixing the drug and lipids in a solvent, then the solvent (miscible solvent to dissolve both lipid and drug for instance water and methanol) is removed (by for instance evaporation under pressure and solvent evaporation), leaving a gel holding the SLN. When SLNs are required to be targeted to specific tissues in situ gelation process can be used [26, 56] . Targeting is mainly related to abilty of thes nanoparticals to be guided by the surface ligand of the target cell hence bind to receptors [57].The main disadvantages associated with this method are the limitation of drug loading,weak mechanechal strength,stability issues as well as high level of fluid requirement [58]

8. Film-ultrasound dispersion method

In this process, the drug in addition to lipids is dissolved by appropriate organic solutions. At that point, the surfactant solution (aqueous phase) is presented to the lipid phase with constant stirring and the used organic solvent evaporates forming a lipid film. The SLN is finally made by continuous stirring by the ultrasound [59].

Characterization of SLN

Convenient characterization of SLN is important not only for inspecting the formation of SLN but also for adjusting their quality to encounter the demands of numerous applications However, owing to the colloidal size of the particles in addition dynamic nature complexity of the delivery system. characterization of SLN is a serious task[60, 61].The parameters needed to evaluate SLNs include the following:

1. Particle size and size-distribution

Particle size is a crucial parameter for nanoparticle drug delivery claims. The average particle size of SLN is usually in the range of (50–1000 nm) in addition, the polydispersity index (PDI) indicates particle size distribution extent. Generally, a PDI of less than 0.1 reflects a narrow particle size distribution while a PDI value of more than 0.2 reflects a polydispersed system [62]. The particle size could be studied by photon correlation spectroscopy (PCS) [63].

2. Zeta potential (ZP)

ZP is the surface charge of particles which detected by a zeta potential analyzer. It could be implemented to assess the stability of colloidal dispersions by means of measuring the degree of repulsion force. High repulsion force inhibits particle aggregation. Generally, when the ZP value is more than 30 mV or less than 30 mV it is judged strong enough to provide particle repletion and remain stable electrostatically. It should be well-known that SLN formulations holding nonionic surfactants for instance polyhydroxy surfactants be liable to have ZP of lower values, while an increase in oil content increases the ZP value of SLN [22]. The techniques employed for the evaluation of the ZP are electrophoretic light scattering (ELS) as well as electroacoustic determination [64].

3. Degree of crystallinity

Differential scanning calorimetric analysis (DSC) can be used to analyze the lipid crystallinity or polymorphic modifications. The role of the glass and melting point temperature accompanying the enthalpies are used to measure the crystallinity within nanoparticles. The degree of crystallinity provides a significant effect on the occlusion degree by the formulation. A direct relationship is observed between crystallinity and the occlusion factor, which explains why liquid nanoemulsions do not show an occlusive impact in comparison to SLN and the reason behind the reduction in the extent of occlusion by nanostructured lipid carriers compared to SLN [65].

4. Drug release

Drug release from the SLN is generally governed by two manners biodegradation in addition to diffusion. To estimate the *in vivo* behaviors of drug-loaded SLN *in vitro* studies are very valuable. To simulate the *in vivo* release of the drug, different buffer systems could be implemented to study *in vitro* drug release via side-by-side diffusion cells with artificial or biological membrane-like dialysis bags, reverse dialysis sacs, ultracentrifugation, ultrafiltration, and centrifugal ultrafiltration. Then HPLC or UV spectrophotometer is used to analyze the release profile of the drug. In vitro release profiles of SLN are influenced by many factors such as drug location, drug loading, size distribution, particle size, types of release medium, degree of crystallinity, lipids contents, surfactants applied, morphologies, and preparation methods [66, 67].

5. Entrapment efficiency (% EE)

Drug EE is an essential parameter for assessing the drug encapsulation preparation technique. The main method employed for EE evaluation is centrifugation wethod where the prepared SLN dispersion is initialy centrifuged. Subsequently the obtained supernatant liquid is poised to quantify the concentration of free drug spectrophotometericaly [68]. The EE% is then calculated by means of the following equasion:

% EE = (Encapsulated drug amount / Total drug amount) ×100%

EE is necessary for understanding the percentage of the drug that is successfully entrapped in carriers. For drug delivery applications a higher EE is required. Many factors impact EE including crystallinity, composition, and types of the lipid materials, and solubility of the drug in the aqueous phase and organic phase [60, 69].

6. Surface morphology

Surface morphology could be better examined by employing transmission electron microscopy (TEM) as well as scanning electron microscopy (SEM). The main diffrence between the two technique is how to resolve images where TEM results in 2D images with advanced resolution, illuminating internal composition details while SEM delivers 3D images of the surface morphology providing a valuable perception

for surface characteristics and shape of nanoparticles consequently the later is more efficient to be utilized [70].

Though, cryo-microscopic analysis comprises fast freezing, consequently the specimen is kept in its hydrated condition. Cryoelectron microscopy (cryo-EM) such as cryo-FESEM and cryo-TEM delivers 3D images of stable particles that frozen-hydrated. Atomic force microscopy (AFM) is more innovative compared to SEM and TEM allowing the atomic-level resolution to be retrieved together with size, resistance to deformation, and colloidal attraction, making AFM a significant tool [71].

Drug loading capacity

Numerous drugs have been encapsulated via SLN. Loading capacity is considered a crucial point in the determination of the drug carrier system suitability. In general, the loading capacity demonstrated in percent is related to the lipid phase (lipid + drug) [72] and could be obtained employing the following formula [73]

Loading capacity % = [(Total amount of drug – Free amount of drug) /Nanoparticle weight] × 100

Drug loading capacity in lipid carriers could be influenced by many factors including the solubility of the drug in the melted lipid phase, chemical and physical structural characteristics of solid lipid matrix, the presence of supercooled melts, polymorphic lipid material, and gelatin phenomena. Implementing a lipid matrix consisting of alike molecules will result in a perfect crystal with few deficiencies. Since the incorporated drug is positioned between the chains of fatty acid as well as among the lipid layers and in crystal imperfections, an extremely ordered crystal lattice cannot lodge bulky quantities of the drug. Consequently, a higher drug loading could be obtained when more complex lipids are used [22, 53]

Storage condition for SLNs

Appropriate storage conditions are crucial for the stability of SLNs.SLN dispersion system should be stored in a plastic amber container at 4ºC. It has been proven that the acceleration of particle growth and gelation is directly related to the light radiation intensity of SLNs since generally the inception of energy by temperature or light consequences in gelation as a result of particle growth.This could be characterized by reduction in zeta potential [35, 74]. Consequently, SLN dispersion should be stored in amber color container since it can reduce the intensity of short waves of light (300–600 nm) falling on the SLN system and reduce destabilization [72].

The effect of temperature, unlike the effect of exposure to light, relates to energy input to the SLN system and could result in changing the lipid crystalline structure, microviscosity reduction (less rigid emulsifier film), and high temperatures generally result in destabilization of the SLN system because of a decrease in zeta potential as well as rapid particle growth [75, 76].

The effect of the materials employed for packing on SLN physical stability was minor when compared to the temperature effect. However, aggregation as well as gelling could be supported employing the inner surface. Stability enhancement was detected when plastic containers were used as an alternative to glass containers for SLN systems with a gelling affinity [72].

Route of administration of SLNs

1. Oral route

Despite the advantages of the oral route for drug administration, many drawbacks exist for instance first-pass hepatic metabolism, poor aqueous solubility, and bioavailability [60]. SLNs provide an encouraging potential for oral drug delivery mainly due to drug solubility enhancement, the protection effect of encapsulated drugs from different physiological conditions as well as the potentiation of drug transmucosal

permeability consequently improving bioavailability [7].
The improved oral bioavailability is related to their improved uptake by the lymphatic system and avoidance of hepatic metabolism. Drug absorption enhancement could be because of the prolonged gastric retention time due to small particle size and adherence to the GIT wall [77, 78]. SLN could be administered orally as aqueous dispersion or otherwise after formulating to a conventional dosage form for instance tablets, capsules, powders , or pellets [79].Venie *et al* developed linagliptin SLNs employing central composite design module to overcome to the poor drug bioavailability [80].Shavita *et al* prepared and optimized pioglitazone loaded SLN's and the obtained results demonstrates that it could be a latent drug delivery with improved bioavailability [81]. An additional attempt was made by Mura *et al* to formulate an effective and aqueous stable formula of hydrochlorothiazide [82]. A suitable acyclovir SLN's delivery system was established to enhance the pharmacokinetic restrictions and reduction in the dose and /or frequency of drug administration by Hassan *et al* [83].

2. Pulmonary route

The lung's large surface area and the thin lining of the alveoli provide rapid drug absorption and permeation. Pulmonary drug delivery considered as is a non-invasive route for both local and systemic drug delivery. It allows rapid onset of action, and dose reduction due to direct drug delivery hence reduction in adverse effects [84].

SLN powders cannot be administered to the lung directly due to micronized particle size accordingly they will breathe out. Therefore aerosolization of SLN dispersion is crucial to overcoming this limitation [85]. The nebulization of SLN is considered an innovation in respiratory drug delivery systems that offers many advantages over traditionally designed systems among them: sustained drug release, low toxicity, biocompatibility, and biodegradability. Additionally, both higher availability for systemic effects as well as reduction in systemic side effects due to the local availability of drugs in high-concentration are among the advantages [86]. Liang wang *et al* prepared an aerosolizable small interfering RNA encapsulated SLNs for a possible inhaled delivery system with enhanced stability [87]. An attempt was made to enhance the anti-lung cancer therapeutic effect of paclitaxel SLNs along with curcumin [88]. An additional attempt was made by Da Rocha *et al* to investigate the antineoplastic activity of docetaxel SLNs in the management of metastatic breast cancer [89]. A study was done by Carvalho et al to assess the influence of carvacrol SLNs on lung injury by smoke inhalation [90].

3.Topical route

The major problem associated with the treatment of skin diseases is low drug efficacy because of low drug permeation through the skin from the most traditional formulations. The main skin barrier that must be overcome is the stratum corneum (SC) of the epidermis [91]. Due to the availability of a high amount of epidermal lipids in the penetration barrier, the SLN carriers system will attach themselves to the skin surface and consequently permitting lipid swap between the outermost layers of the SC and the drug carrier system seems to be promising [92].SLN is considered a very tempting colloidal drug carrier system for dermal applications due to its numerous required effects on the skin as well as its colloidal characteristics that enhance both drug penetration and permeation [93].
For topical application, these systems could be manufactured by incorporating SLN dispersion traditional formulation (ointment or gel). Additionally, direct preparation could be implemented by the one-step process to produce drug-loaded SLNs [22]. Tacrolimus SLNs loaded gel was developed to improve topical applications by Khan et al and

overcome the limitations associated with traditional formulations [94]. Farahat *et al* optimize fluoxetine SLNs loaded topical gel to enhance wound healing in diabetic patients [95]. Etodolac SLNs topical formulation was prepared and evaluated by Patel *et al* to enhance its transdermal permeation[96]. An additional attempt was made by Panmand *et al* to enhance the topical delivery of acitretin by optimization of SLNs loaded gel [97].

4. Parenteral route

Since the effective development of a micronized lipid emulsion parenteral formulation in the 1960s, continued efforts have been made to achieve a novel parenteral colloidal nanocarrier system. This is related to many advantages associated with these systems, for instance, the ease of scale-up production, modified and controlled drug release models, avoiding drug degradation as well as first hepatic metabolism, and preserving more persistent blood drug levels [98].

Drug-encapsulated lipid nanocarriers could be administered either intramuscularly, intravenously, subcutaneously, or straight to the target organ. Drug release from lipid nanoparticles may take place via erosion for instance enzymatic degradation or by diffusion which could provide a sustained drug release. Current research has established the ability to utilize lipid nanoparticles for peptides as well as proteins to overcome the effect of harsh GIT environments [99].SLNs could be implemented as carriers for parenteral use mainly due to their sustained circulation time as well as low toxicological issues [98].

Rudhrabatla *et al* developed melphalan-loaded SLNs for parenteral administration [100]. A long-acting intramuscular and subcutaneous drug delivery platform for bedaquiline and celecoxib as SLNs was developed by Elibrink *et al* [101].

5. Ocular route

Drug delivery via the eye route is principally problematic due to the complexity of this organ and the presence of several barriers like tear drainage blood ocular barrier, corneal epithelium, and conjunctival blood flow that should be overawed to reach the target ocular tissue. Innovative drug delivery systems like SLNs were considered to increase ocular tissue bioavailability by overcoming these barriers [102, 103]. Ophthalmic preparation containing drugs loaded in SLN processes biocompatibility and mucoadhesive characteristics of SLN which enhance their interaction with ocular mucosal tissue and extend the drug corneal residence time providing ocular drug targeting [104].

Clarithromycin-loaded SLNs were formulated by Nair *et al* to develop their therapeutic activity in topical ocular therapy and to enhance their ocular permeation [105]. Alhakamy et al investigated the loading of ofloxacin into SLNs to enhance residence time and solubility [106]. Lutein-loaded SLNs were optimized as an ocular delivery platform by Shah *et al* to accomplish nanosized particles with sustained drug release and enhanced corneal permeation [107]. An ocular *in situ* gel inclosing bimatoprost SLNs was developed by Wadetwar *et al* as a platform for a drug delivery system [108].

6. Rectal route

A rectal route is usually employed when a rapid therapeutic effect is required by avoiding hepatic metabolism. Additionally, it could be implemented for patients with impaired swallowing ability, drugs irritating the stomach, and drugs that are unstable in the GIT environment [109]. The incorporation of drug-loaded SLN into rectal formulation has been studied in a few research and the obtained results showed rapid therapeutic activity of the drug. These researchers also found that lipid matrix has a great influence on drug delivery where the ones that are solid at body temperature are not

a proper system for the drug rectal delivery consequently the lipids with a melting point around body temperature were implemented. Coating with polyethylene glycol seems to be an encouraging approach for rectal drug delivery and consequently, bioavailability enhancement [110].

Smart SLNs were optimized by Smith *et al* to boost the efficiency of 5-fluorouracil in the management of colorectal cancer [111]. Xing *et al* formulated thermosensitive *in situ* gel-enclosed topotecan-loaded SLNs as an antineoplastic delivery platform against colorectal cancer [112]. Optimization of a celecoxib-loaded SLN colon drug delivery system was implemented by Alajami *et al* for the improvement of the anticancer effect [113].

Challenges in scale-up and commercialization for SLNs

Specific requirements must be achieved by pharmaceutical products to be marketed for instance processing inexpensive large-scale production procedures with concomitant compliance along with regulatory standards. SLNs scale-up processes necessitate a proficient line to perform effectively [114]. Various production techniques demonstrated scale-up perspectives such as HPH and microemulsion-based methods, supercritical methods, and membrane contractor methods [36, 115].

Among the main challenges related to SLNs scale-up are the raw material composition and quality, conserving reliable particle size, equipment adaptation to handle large batch sizes deprived of affecting final product quality, sterilization, assuring Good Manufacturing Practices requirements for regulatory authorization as well as meeting regulatory standards (for instance US FDA) established to implementation of strict quality control requirement. Additionally, a careful evaluation of the utilized excipient should be implemented assuring their GRAS (Generally Recognized as safe) status or are authorized by other regulatory authourties [36, 57].

Moreover, SLNs stability for the long term ought to be labeled to provide the regulatory needs for both efficacy and safety.Generally, SLNs dispersions are physically stable over more than three years despite gelation being perceived with certain formulas due to environmental variables such as temperature alteration, light disclosure, and lipid recrystallization. Such destabilizing circumstances led to an alteration in both particle size and structure mainly due to lipid matrix recrystallization [17]. To overcome this problem optimization of formulation variables such as pH , concentration of surfactant as well as the employed technique is crucial to preserve the SLNs integrity for a prolonged time [116].

Recent advances in SLNs applications

SLNs have emerged as an encouraging method for both mRNA drug delivery as well as personalized medicine. Concerning mRNA drug delivery SLNs provide many advantages mainly the protection of mRNA from nuclease degradation through encapsulation, displaying lower toxic effects compared to other types of lipid nanoparticles, and providing specific drug targeting [117].

The implementation of SLNs for personalized medicine provides many advantages as well among them is the ability to offer the individual prerequisites of patients via modifying SLNs with precise targeting entities (for instance antibodies) consequently minimizing the adverse effect [118, 119]. For instance, SLNs provide a promising means to deliver chemotherapeutic agents directly to tumor cells consequently reducing side effects [119]. Accordingly, further development of SLNs is needed to fully exploit these advantages through pharmaceutical aspects.

SLNs-based marketed products

Various research is continuing in the development of SLNs for numerous treatment lines. Though only a few SLN-based preparations reached the market as shown in Table **1**.

Table 1: SLNs-based marketed products [118]

Brand name	Active ingredient	Manufacturer	Administration
Mucosolvan retard	Ambroxol	Boehringer	Oraly
Cipro	Ciprofloxacin	Bayer	Oraly
Nanobase	-	Yamanouchi	Topically

Conclusion

SLNs are considered striking drug carrier systems as well as an alternate technique for other colloidal dispersion systems due to the successful incorporation of active ingredients. The SLNs are also considered an effective and safe carrier for the drug because of the biocompatible nature of the used lipid. Additionally, SLN offers an economical patient-friendly drug delivery system employing various routes of administration.

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