Review Article

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Solid lipid nanoparticles for targeted natural and synthetic drugs delivery in high-incidence cancers, and other diseases: Roles of preparation methods, lipid composition, transitional stability, and release profiles in nanocarriers' development

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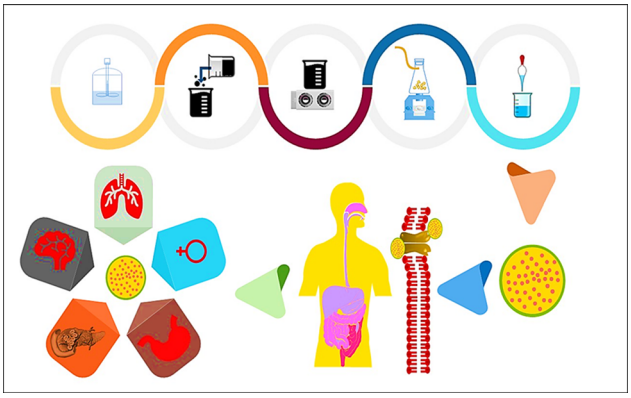
Abstract: Solid lipid nanoparticles (SLNs), the spheroidal-shaped, colloids state lipophilic-natured, innovative nanoscale particulate materials, are being concurrently prepared by the quality-by-design approach for cellular and sub-cellular delivery of drugs and other payloads with facilitated physicochemical characteristics for targeted delivery. The delivery of drugs, other pharmaceuticals and biopharmaceutical materials, and genes to the diseased body organs, tissues, and cellular mass have been developed as promising nanocarriers for different high-incidence cancers and other disease therapies, including the Alzheimer's, Parkinson's, and tuberculosis. SLNs have evolved as favorable lipid-based formulation, and have served as oral and intravenous carriers that targeted the drug with stable and sterile transport, sustained delivery, controlled drug/payload deloading, and requisite biodistributions. SLNs advantages, shortcomings, and bottlenecks have been discussed with plausible remediation strategies. The laboratory-scale and bulk preparations, use of different lipids in various preparation, surface coatings, physicochemical properties of the final product, and characterization protocols are also encompassed, as are



Graphical abstract

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the routes of administrations, specific-sites-targeting, and on-site outreach with biocompatibility, bioavailability, and the absorption, distribution, metabolism, and excretion and pharmacokinetics, and pharmacodynamics inputs with relevance to the therapy. Plausible applications in complex and genetic disorders, and as personalized medicine, also of traditional and alternative medicine prospects, are also discussed.

Keywords: solid lipid nanoparticles, lipids, triglycerides, lipidic encapsulation, stability, release model, drug incorporation, drug delivery, anti-cancer, Alzheimer's disease

1 Introduction

1.1 Solid lipid nanoparticles (SLNs) developmental perspective and concurrent applications

SLNs came into being in 1991, and ever since have captured the major share in drug and other payload delivery modules. SLNs were developed in place of the conventional existing colloidal systems, *i.e.*, emulsions, liposomes, and polymeric nanoparticles (NPs) [1–9]. SLNs are also spherical in shape with average size range variations from 10 to 1,000 nm. These NPs were primarily made from the natural and synthetic lipids as the major constituent (Figure 1). SLNs have been established as preferred carriers, especially, for the lipophilic drugs for the high-yielding, efficient, and optimized drug delivery of the encapsulated/entered drugs with enhanced bioavailability.

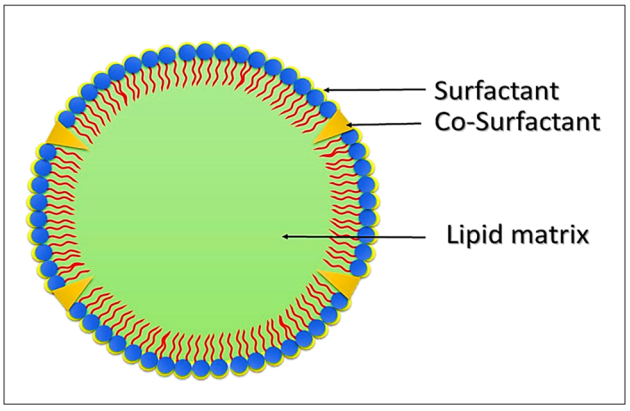

Figure 1: Compositional lay-out of the structure of a typical SLN showing the lipid core and the peripheral surfactant/co-surfactant, the drug may or may not, based on QbD approach, concentrate on the peripheries, or at the core.

SLNs also provided toxicity reduction at the site of action of the drug, as well as least interfered and toxicity during transport latency of the drug-loaded NPs to the site. SLNs have also emerged as a parallel substitute for liposomal deliveries owing to their better penetration through anatomical restrictions, sustained, and to some extent chrono-control deliveries. SLNs also provided, the much sought after, stability of the carrier from its biochemical and physicochemical damage and degradation while under transport in the biosystems [10,11]. Hence, SLNs are considered a novel approach for controlled and directed drug delivery systems in contrast to the direct oral and parenteral administrations of a drug. The troubles associated with the conventional drug delivery systems such as stability, toxication, and degradability were, to a major extent, overcome by SLNs. The scarcity of safe synthetic and natural polymers with regulatory approvals, and high preparative/production costs limited the other polymeric NPs modules used for drug delivery. The advancing clinical applications catapult the opening up of the possibilities for SLNs as the preferred delivery format for a number of difficult to deliver, especially, lipophilic drugs [12].

SLNs, conceptually, are a hybrid of the lipid suspensions and polymeric nanoparticles, and have successfully embedded both polarity types of drugs, the lipophilic and hydrophilic drugs. Thus, the drug-embedded SLNs have, comparatively, provided better stability in bio-environments during transfer/transport, and mobility of SLNs. The controlled and targeted drug delivery with precise specificity concerning the nature of the site has thus been achieved. SLNs' size-dependent physicochemical characteristics, delivery preferences, transport feasibility, and the site-specific outreach have opened up a plethora of possibilities in types and classes of drug's loading, drug's loading capacity, encapsulation efficiency, choices with physicochemical and polarity-based drug types, together with other tunable properties of SLNs, and have assisted the drugs and other pharmaceuticals, including nutraceuticals to reach the intended site in adequate dose and enough/necessitated bioavailability. The differentiated SLNs prototypes, developed over time with specifications in coating and conjugation approaches for site-directedness, have efficiently targeted the intended drugs to effectively outreach to the site with chronological-control and dose-manipulated deliveries. In this context, different make-up of SLN carriers have also been tested for intravenous and other deliveries, including the oral route deliveries. The advantages, shortcomings, demerits, and bottlenecks of SLNs are here-upon detailed out with plausible remediation strategies, and forms the subject matter of this write-up [13,14].

SLNs laboratory scale and bulk preparations, their applications, and the use of different lipids in preparation, the physicochemical properties of SLNs product, characterization protocols, and involved instrumental techniques are also highlighted, as are the preferred and employed routes of administrations, site-outreach, specific site targeting, biodistribution, and the bioavailability of the drug along with the mechanistic of the delivery and targeting, the pharmacokinetics, the pharmacodynamics, and the drugs absorption, distribution, metabolism, and excretion (ADME) inputs are encompassed. SLNs *in vitro* and *in vivo* applications, clinical and pre-clinical applications toward the development of the therapy of diseases, and their plausible applications in complex and genetic disorders, with a feasibility assessment of SLN-based drugs' bioactivity applications, wherein other delivery modes and carriers are unreachable or restricted, have been encompassed [15]. SLNs preparations are an important and desirable dimension to the lipid-based NPs nanotechnology pitch, where prospective scenarios in drug supplies, clinico-medical treatment, and the path forward to additional research areas are critical to the development of the field of drug delivery and lipid-based nanotechnology applications [16–19]. Among the major aims of this review was also to illustrate different preparative parameters of SLNs, with their preparative techniques, the benefits and disadvantages, and the role of the preparative procedures in it. Also, various characterization techniques for establishing SLNs preparation, identity, drug-loading, and delivery confirmations have been detailed out. Additionally, the bulk manufacturing of SLNs and their operational feasibility has been hinted out. SLNs spherical shapes, lipid matrices nature, which are solid at physiological temperature, the surfactants and the occasionally used co-surfactants, co-surfactants that are used to solidify and stabilize the lipid matrices, have been identified. SLNs made from solid lipids, such as, long-chain fatty acids, and certain other natural and synthetic waxes that are solid and compacted between 25 and 37°C, provided desired characteristics to the lipidic-carrier for specified, targeted delivery through quality by design (QbD) preparative and drug loading approaches, which have provided intended release profile of the encapsulated drugs. The lipid-based solid core also assisted in better characterizations of the lipid excipients, and loading of the drug(s). SLNs that have been further treated by stabilizers and stabilizers that are biological membrane-based lipids helped SLNs to be biologically non-toxic, devoid of adverse reactions owing to the lipid carrier, and stable enough for further clinical applications (Figure 2) [20,21]. For example, SLNs prepared for targeted delivery of piribedil for treatment of neurodegenerative brain disorder were observed to be comparatively faster in drug deloading in an acidic medium, and that was ascertained to be dependent upon the desirable range of the NPs' sizes that were able to cross the blood–brain barrier (BBB), and the pH value which assisted in the drug release through opening of SLNs at the site. The factors of the size and pH considerably affected the release rate and duration/sustainability of the drug release. The *in vitro* and *in vivo* analyses proved that these SLNs had controlled drug release rates, with improved piribedil bioavailability and tissue/cellular uptake of the drug [22,23].

SLNs have still been considered as highly biocompatible, and *in vitro* studies have confirmed this aspect of SLNs characteristics [24]. Studies have also demonstrated that absorption mechanism of SLNs against the polymeric NPs, as well as the oil (lipid), and water-based suspensions tend to be providing stable adsorption patterns for the SLNs. The interaction between the plasma and the polymer NPs, and oil and water-based suspensions seemed to be the deciding factor in drug loading and delivery patterns [25]. SLNs have been demonstrated to load higher quantities of the drug (drug volumes) than the polymeric NPs and nanoemulsions that are not primarily lipid based. Also, from the manufacturing and commercial stand-point, the low manufacturing costs without using any organic solvents, with enhanced feasibility of maintenance of the sterility of SLNs formulations [26] have added to the SLNs' advantages. On the contrary, the longer storage time and long duration sitting time of the drug in SLNs formulations have the tendency to lead to several disadvantages [27], including changes in drug release patterns and particles' size growth, and occurrence of polymorphic transition are too high, together with gelation occurrences that are quite often encountered and are of high incidence for SLNs.

In the backdrop of these contrasting situations, as against the non-lipid nanocarriers, SLN modules of drug delivery provided several advantages, and also negated the shortcomings of other colloidal preparations, although the bottlenecks are, again, the expulsion of the drug after the process of SLNs preparation and comparatively longer storage time, together with poor drug-loading, again, along with comparatively high water contents in SLNs, if seeped through the process of preparation owing to SLNs preparative constituents behavior, although this water content is comparatively very low as against other non-lipid nanocarriers' water content in the formulation, but, nonetheless, this water content is of higher ratio when compared to different SLN types. This behavior has questioned the controls of the preparative process and the nature of the lipid used to prepare SLNs, and this has

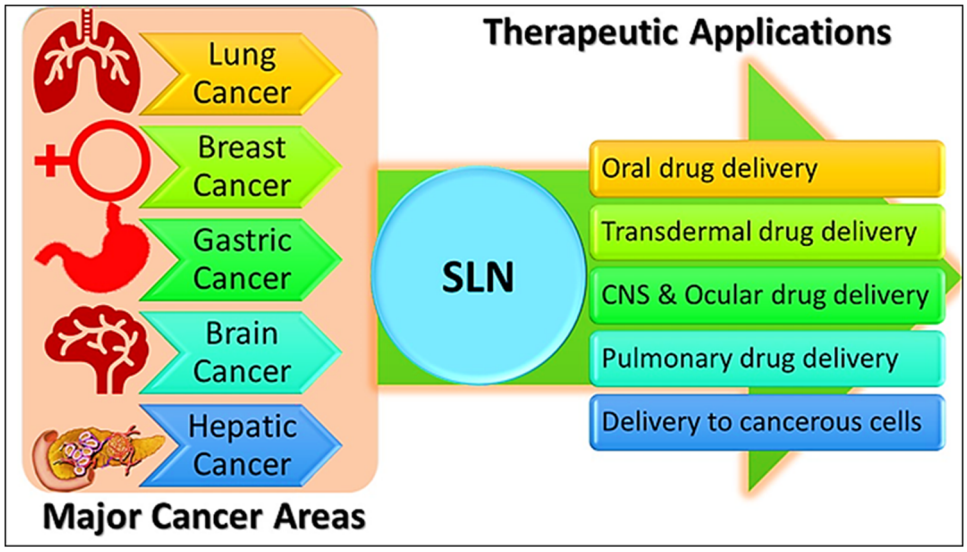

Figure 2: Major therapeutic applications of SLNs in high-incidence cancers, and their delivery through different alternatives.

paved ways for different preparative processes development, and use of various lipid types. Notwithstanding, the normal drug loading, in SLNs, is dependent upon the solubility of the drug in the lipid medium which is facilitated or restricted by the physicochemical properties of the lipid, the properties that arise out of the lipids' chemical structure, physicochemical properties, and the state of the lipid matrices employed in the preparation. The tristearin and tripalmitin, being in the familiar (polymeric) state, provided better SLN-based products with little or no imperfections in the produced SLNs [28,29].

The loaded drug molecules reside in the molecular spaces of the fats' polymeric chains, in between the layers of the lipid chain and the lipid matrices, and also the crystal lattices of the drug substance during the heating and thaw process of the preparation/manufacturing of SLNs. The procedure provided diminished drug loading in the crystal lattice, and structurally imperfect crystal orders were achieved. The crystalline drug material, for this reason, has not been the preferred physical state to prepare SLNs. Henceforth, the use of physico-chemically compatible, structurally complex but accommodating materials (i.e., lipids, etc.) with sufficient molecular spaces and structural orientations lead to provide cavities for drug loadings, and non-crystalline/amorphous natured lipids have also been preferred for the purpose [13,30].

Nonetheless, SLNs provided controlled and targeted drug delivery to the required site(s) *via* a compatible and competitive release profile, improved the stability of the drug and SLNs formulation from chemical, biochemical, and physiological degradations, with utmost negation to the sun and other light sources, and photocatalysis [31–33]. The inhibition of auto-redox processes during transport and delivery at the site, SLNs' inability to sneak through the reticuloendothelial system (RES) owing to their sizes, the bypassing of the spleen and liver filtrations, reduced levels of drug leaks from the nanocarrier, the comparatively higher drug contents loading of both the lipophilic and hydrophilic-natured drugs, the biocompatibility to the biological system on account of the biodegradability of the lipids, feasible sterilization, the devouring of the organic solvents with the chances of removing solvent-borne toxicity, and the overall lessened toxicity of SLNs and the unexposed drug favored SLNs delivery module. SLNs that were simple to prepare, and cost-effective, with better validations of the final product and the process, eventually assisted in obtaining regulatory approvals. Moreover, some of the shortcomings were overcome by the size limitation and the use of certain types of lipids during the preparation of SLNs [34–36]. The deloading up of the loaded drug from the prepared SLNs was prohibited by employing a cold homogenization procedure, restrictions to the crystallization/recrystallization of the drug and the lipid, and controlling the polymeric transitions, that were achieved by changing the lipidic contents, mixing the lipids, and changing of the proportions of the lipidic contents during the preparation of SLNs. The lipids, *e.g.*, hydroxyl stearate, isopropyl myristate, and hydroxyl octacosanol inhibited the crystallization processes, and preparations containing ketoconazole [37], imidazoles [38],

and clotrimazole were reported [39,40]. The increased drug loading was achieved by the use of structurally and spatially different lipids that provided more inter- and intra-molecular spaces for the drug molecules to be loaded. The glycerides worked better, however, the size of the drug molecule, the average molecular weight drugs, that were quantitatively more loaded than the high molecular weight drugs, were easily achieved, and this observation also pointed out the role of molecular interactions and spacing in SLNs to be developing matrices. However, a solution to further increase the drug loading capacity of SLNs was achieved by amalgamating the solid lipids with small proportions of the liquid-state lipids, *i.e.*, oils were used during SLNs preparations. Another major bottleneck, observed was the loadings of the hydrophilic drugs. The lipidic content partitioning effects on hydrophilic drugs limited the majority of hydrophilic drugs from being prepared as SLNs, but only highly potent drugs with low dose incorporation were prepared as SLNs [41]. The drugs with 33% higher loading capacity were formulated using the salt formulation technique, in which the insoluble drug-lipid conjugate was first prepared using salt, or by chemical conjugation of the covalent type, and then processed with surfactants (tweens) to produce the nanoformulations after the high-pressure homogenization (HPH) technique, one of the methods for preparing SLNs, and brain-targeting hydrophilic drugs were prepared using this method [42].

2 SLNs delivery to organs, tissues, and cellular uptake: delivery mechanisms

SLNs formulations have drawn more attention in recent years as potential drug delivery modules. They have also been massively sought for transporting biomolecules since SLNs are known to penetrate through the cell membrane [43]. Furthermore, as a drug delivery system, SLNs have shielded encapsulated drugs from biochemical and physicochemical degradation [31,44]. It has also overcome the lower aqueous solubility of certain drugs, provided extended-time release of the drugs, and delivered the encapsulated drugs or other payloads to the specifically targeted organ/cells [45]. SLNs, in particular, have exhibited several advantages as a drug delivery vehicle. The biocompatibility of SLNs' constituent lipid's composition, their higher drug loading capacity, the absence of organic solvents in SLNs' preparations, and the feasibility of SLNs' formulations for bulk production in parallel with their sterility maintenance are some of the advantages of abovementioned SLNs. Their perceived and demonstrated efficacy and lowered toxicity are also a cut above other nanoformulation modules used in drug delivery [45].

SLNs carrier's size, surface characteristics, encapsulated drug(s)' physiochemical characteristics, and the composition of SLNs' vesicle-carrier are among the most important factors affecting SLN-based drug(s)' entry pathway to reach the target site. Several studies have been conducted to investigate the targeting mechanism of SLNs formulations toward various tissues and cells (Figure 3). For example, the mechanism by which efavirenz SLNs formulation, as an antiretroviral drug delivery system, targets the lymphatic system has been recently reported. According to the findings of the study on the lymphatic transport, and tissue distributions, a sizeable portion of the efavirenz evaded the portal system, and was retrieved in the lymph through a chylomicron uptake mechanism [46]. In addition, comparatively, a high quantity of the drug has been detected in the major lymphatic organ, the spleen, and it was found that the SLNs enhanced the bioavailability of the efavirenz, and reduced the drug's quantity reaching the liver, which clearly indicated that majority of the drug bypassed the liver [46]. Furthermore, SLNs have been found to increase the cumulative percentage of the drug, lopinavir, at a ratio, 5-folds higher than the conventional drug (as solution) in the lymphatic tissues [47].

Podophyllotoxin-based SLNs with epidermal targeting mechanisms have also been reported, the results indicated that SLN preparations of podophyllotoxin facilitated drug penetration through the stratum corneum, and hair follicle routes [48]. The fluorescence microscopy imaging also revealed that SLNs had a strong localization of podophyllotoxin within the epidermis. The penetration of podophyllotoxin-SLNs was stabilized by 0.5% poloxamer 188 and 1.5% soybean lecithin used in the formulation, and that might be an epidermal-targeting formulation due to their small particle size, and there upon these SLNs passing into the stratum corneum along the skin surface furrow [48]. Similar results and mechanisms for isotretinoin-SLNs penetrations have been reported [49].

Furthermore, SLNs are among the most advanced drug delivery systems for cancer therapy, especially, for the high-incidence cancers of the breast, lungs, gastro intestinal tract, and prostate [50]. The stealth-SLNs (sSLN) have been suggested to be of particular interest for anticancer actions [51]. When combined with a ligand (known as sSLNs), the SLNs possessed affinity for and selectivity toward a particular receptor, thereby making it possible to deliver medication to the breast cancer cells that overexpressed

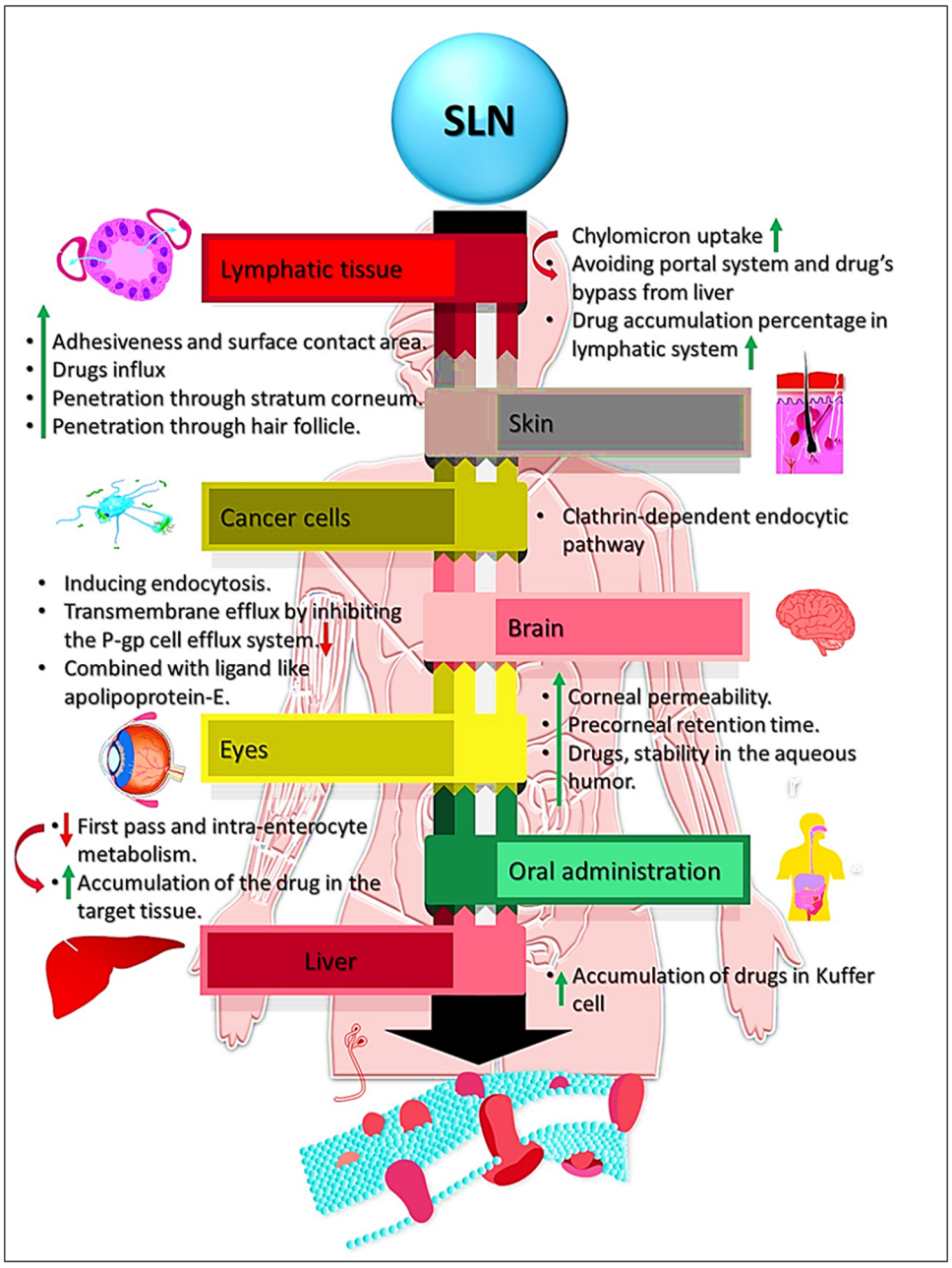

Figure 3: SLN mechanisms involved in various administrative routes'-based drugs delivery to different organs and tissue sites with their cellular level workings to exhibit the bioactivity.

the receptors. Several studies have reported that this approach of sSLNs had stronger anti-breast cancer activity than the straightforward SLNs (non-conjugated to ligand, or no receptor targeting) [51].

Cancer cells' cellular internalization mechanisms of SLNs' formulations in human glioma cell lines (A172, U251, U373, and U87), and in human macrophage cell line (THP1) have been reported. The internalization of SLNs coated with polysorbate 60 and 80 and loaded with rhodamine-123 into the cancer cells has been evaluated by fluorescence microscopy and flow cytometry techniques. The results of Martins *et al.* [52] had indicated that the rhodamine-123-loaded SLN cells internalization is dependent on the size and surface charges of the formulated SLNs. They found that SLNs with a mean size < 200 nm and a slight negative surface charge (around −20 mV) have the ability to be internalized by glioma's cells in higher quantities than by the macrophages. They also described the mechanism

of internalization as being mainly achieved through a clathrin-dependent endocytic pathway.

The mechanisms behind SLNs' uptake by human epithelial cells, *i.e.*, lung A549 and cervical HeLa cells, have also been investigated [43]. In this study, SLNs were loaded with rhodamine 123, and the cellular uptake was assessed by the flow-assisted cell sorting technique, which revealed that endocytosis of SLNs was also mainly dependent on the clathrin-mediated mechanisms [43].

SLN-based drug delivery system for targeting the brain cells has been well studied, and the enhancements of the drug delivery and accumulations of the drug in brain cells have been proven [53–55]. By now, it is well understood that a drug molecule needs, among other characteristics, high lipid solubility, a molecular mass of less than 400 amu, and should not function as a substrate for active efflux transporters in order to cross the BBB [45].

The therapeutic cargo of the NPs is delivered across the endothelial cell layers by transcytosis and/or endocytosis and facilitated through inhibition of transmembrane efflux and openings of the tight junctions between the endothelial cells, allowing the drug carrier to cross the BBB. The surfactant incorporated with SLNs enhanced the drugs' transport through endothelial cells' membrane by their lipids' fluidization [56]. However, the most current method of brain targeting for NPs rely on surface engineering through functionalization, and/or coating with certain ligands. These steps made it easier for the endothelial cells to endocytose SLNs, which continued to be the major pathway to improve the medications' delivery to the central nervous system (CNS) [45]. For example, the functionalization of SLNs with ligands to achieve site-specific targeting made them attractive to overcome the limited BBB permeability of the drug. In the study by Dal Magro *et al.*, SLNs were prepared for brain targeting by exploiting the adaptability of the warm microemulsion process for the covalent surface modification with an apolipoprotein-E derived peptide (SLNs-mApoE). It was found that SLNs-apolipoprotein-E was able to cross intact through the BBB in an *in vitro* model [57].

SLNs were helpful in the brain uptake process in a variety of levels; they stabilized the drugs against chemical degradation in the biological fluids, increased the residence time/biological half-life of the drug carrier in the bloodstream, and indirectly favored their translocation to the brain, as well as triggered the endothelial cells by inducing endocytosis. The internalization activity may also be receptor-mediated through an active targeting mechanism [45]. In general, SLNs as brain drug delivery systems have gained several positive points related to their ability to increase the quantities of the encapsulated drug, circumvent the BBB route to reach the brain, compromise the BBB layer to permeate through to the brain tissue, increase drug retention time in the brain, inactivate the p-glycoprotein (P-gp) cell efflux mechanism, and offer the possibility of site-specific brain targeting by SLNs apolipoprotein-E intermediacy [57,58]. The topical applications of SLNs also showed several advantages related to the lipid composition(s) of the formulation, which enabled SLNs to interact with the *stratum corneum*, thereby managing its lipid rearrangements, which eased the drug molecules' penetration through the skin [59]. Although drugs' physiochemical properties play an important role in skin penetration, SLN's small size enhanced their adhesiveness and surface contact area, promoting drug influx through the skin [59]. The ocular application of SLNs delivery system has also been reported to enhance the drug's corneal permeability and pre-corneal retention time, in addition to lowering the toxicity and enhancing the drug's bioavailability, and stability in the aqueous humor of the eye [58].

SLNs as an oral drug delivery module is reported to reduce the first pass metabolic and intra-enterocyte metabolisms, which led to drug accumulation at the targeted site. SLNs also enhanced the evading of P-gp efflux pumps [58]. Also, SLNs as parenteral drug delivery system, exhibited several advantages related to its long physical stability, controlled drug release, increased drug accumulation levels in the targeted tissues/cells, increased drug bioactivity, increased circulation time in the blood-stream, and improved the drug bioavailability, and increased the drug delivery and drug retention in the cancer cells [58]. SLNs formulation also directed the parenteral liver-oriented drugs to be specifically accumulated in the Kupffer cells, which enhanced the drug's efficacy in the treatment of several liver diseases, including hepatic carcinoma [60].

3 Preparatory processes for SLNs: roles of constituents and conditions

The lipids, emulsifiers, surfactants, or a stabilizer, co-surfactant, preservatives, cryo-protectant, and the charge modifiers are among the key ingredients to formulate SLNs. SLNs use solid lipids, and other components, preferably in the presence of water through certain organic solvents that can be employed for the purpose. Nonetheless, the use of organic solvent is utmost avoided [61]. The major lipid types used are triglycerides, fats/fatty acids, waxes, and steroids with sufficient lipophilic characteristics. Partial glycerides, *e.g.*, imwitor, have also been used. The emulsifiers and their combinations stabilized the lipidic dispersion of the

formulation during the preparation stages, and tend to avoid the NPs agglomeration [11]. The emulsifiers were chosen based on the delivery required characteristics of SLNs, and feasibilities for their routes of administration. Some of the lipidic constituents, namely, compritrol (10%), cetyl palmitate (10%), ethyl oleate (30%), glycerol (4%), isopropyl myristate (3–4%), lecithin (9%), lipids of trimyristin and tripalmitin identities, and mixtures of mono, di, as well as triglycerides (3.3%), PEG 400 (5%), PEG 2000 (0.25%), PEG 4500 (0.5%), phospholipids (0.5–1.5%), pluronic F68 (40%), poloxamer 188 (1–5%), sodium alginate (70%), soy phosphatidylcholine (95%), tego-care 450 (1.2%), tristearin glyceride (95%), tweens 80 and 85 (50 and 0.5%), and a number of lipids in weight/volume (w/v) concentrations and weight/weight (w/w) formulations were used [62–67]. The preservative, thiomersal, and gelatin, glucose, mannose, maltose, lactose, sorbitol, mannitol, glycine, polyvinyl alcohol (PVA), and polyvinyl pyrrolidone (PVP) are among the common cryoprotectants used, while dipalmitoyl phosphatidylcholine, stearoyl amine, dicetylphosphate, and dimyristoyl phosphatidylglycerol were among the charge modifiers that have been used during SLNs preparations, and stabilization procedures [22].

A number of techniques are involved in SLNs manufacturing, wherein the HPH and microemulsion-based processes are popular for preparing large quantities of industrial productions of SLNs [68]. The influence of the microemulsion modules on resultant SLNs' size and shape dimensions, and the tough incorporations of the crystalline structure of the drugs in SLNs have been attempted as against the preparation of the non-lipidic classical NPs obtained through hydrophilic conditions used in the preparation [69]. The subsequent segments describe different existing approaches for SLNs formulations, wherein the HPH was found highly feasible and consistent, for SLNs production. It helped in producing SLNs of spherical shapes and sizes with regular good stability and settlement features [70]. For example, when tetrandrine-loaded SLNs (TET-SLNs) were prepared by two different methods, namely, the HPH method and ultra-sonication, the HPH was found to be a better method to prepare the TET-SLNs, which were smaller in size, steadier, and highly incorporated into SLNs. Their analyses of shapes, sizes, and stability were performed based on Transmission electron microscopy (TEM), particles characterization system, and Zeta potential analyzer [71].

HPH method applies both the pressure gradient and mechanical forces as the stress to achieve reliable and stable SLNs. The high-quality homogenizers have the options of regulating various parameters, *e.g.*, turbulence, shear, cavitation, impact, and process intensity to get optimized, and yield the customized SLNs as per the drug loading and delivery necessities. The HPHs also helped in attaining SLNs with smaller particle size with increased surface area, enhanced drug loading, and eventual high bioavailability. The HPH process is extensively used in bulk pharmaceutical preparations. The HPH was achieved through two methods [72], and the process was held responsible for decreasing the molecular weights of the used polymeric materials [73]. This procedure also caused high shear stress, and later developed free radicals too.

3.1 Hot HPH method

In this process, the lipids were heated above their melting points, and converted into liquid state materials (Figure 4), and the high temperature resulted in dropping down the viscosity of the preparation-stage's present liquid state

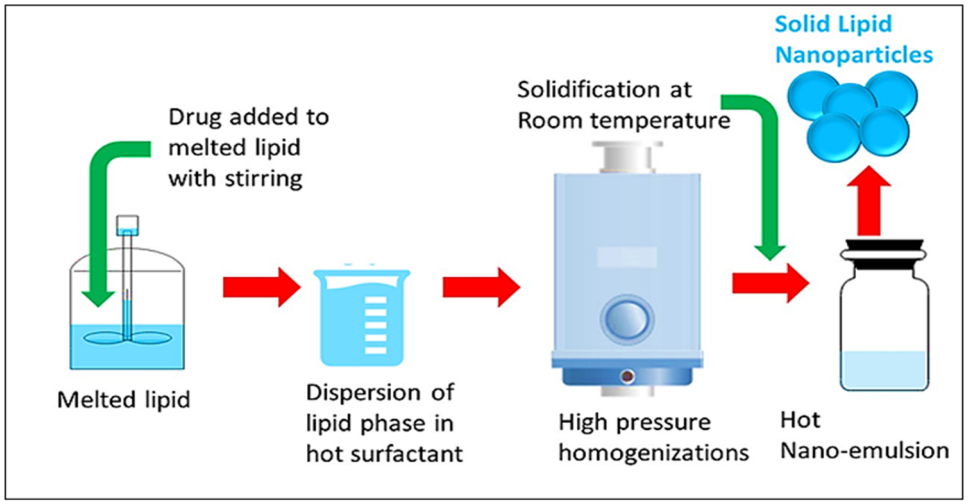

Figure 4: Schematic diagram of the hot HPH technique for preparation of SLNs.

materials, which caused shrinkage in the resultant particle sizes. The process was accompanied by many disadvantages. An increase in temperature was considered to cause high rate of decomposition of the embedded drug, and unpredictable lipid changeovers were also observed. Drug losses from the aqueous phase were also noticed owing to the high kinetic energy of the preparative steps.

3.2 Cold HPH method

To avoid limitations observed in the hot HPH method, cold HPH was tried (Figure 5). The hydrophilic and thermo-labile drug was encapsulated in SLNs matrix. Solid lipid was employed to produce large-sized particles, which were diffused in a chilled solution of surfactant. The blend formed uniformed preparation, both at and under room temperature (RT) conditions that were further broken down by gravitational pull [74].

3.3 Emulsification-sonification method

Drugs were supplemented to the liquefied lipid(s) at 5–10°C of temperature, and supplemented with hot liquid surfactant solution. The emulsion thus obtained was sonicated to reduce the particles size. Finally, SLNs obtained were cooled at RT (Figure 6). However, the process led to metal contamination due to the use of the metal probe for ultra-sonication purpose [75].

3.4 Solvent emulsification method

The lipid was emulsified with the process of HPH in a liquid state by dissolving in organic solvents, *i.e.*, cyclohexane and chloroform. These solvents are water-immiscible and evaporated easily leaving precipitated NPs. The process was carried out at 25°C, and was thermolabile in nature [76,77].

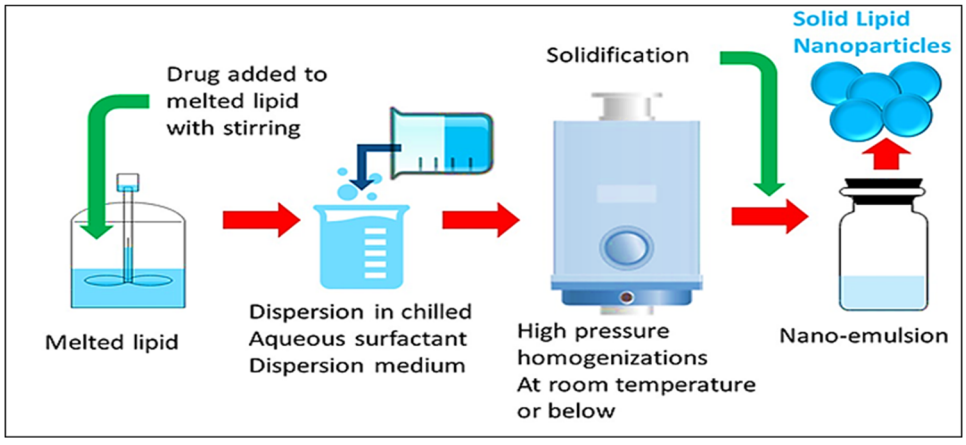

Figure 5: Schematic diagram of the cold HPH technique for the preparation of SLNs.

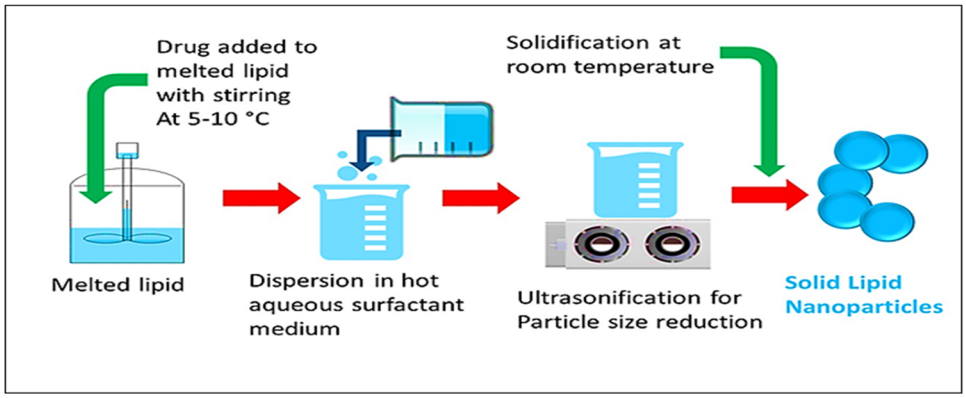

Figure 6: Schematic diagram of an emulsification-sonification processing based technique for the preparation of SLNs.

3.5 Solvent emulsion-scattered method

The organic solvents that were partially water miscible, were used in solvent diffusion method of SLNs preparation. These diluents, when water-saturated, became heat and temperature stable. In this case, the organic liquids satiated all at once to attain thermodynamic equilibrium. The transient obtained was moved to water under constant stirring to solidify the dispersed phase, and SLNs were formed. An overview of the preparation method is depicted in Figure 7 [78–80].

3.6 Aqueous needle process

This process also used the organic solvents that were water-miscible and easy to use with faster production rate, together with being cost-effective. The process is nearly same as that of the solvent diffusion method. The lipids in organic solvents were rapidly immersed under pressure through a needle in a liquid solution of surfactants [81].

3.7 Double emulsion method: water-in-oil-in-water emulsions

The process resulted in the formation of lipospheres as the particles sizes were a little larger than SLNs. The hydrophilic drug was embedded inside the liquid lipid state, and stabilizing material was used to prevent the drug's escape from the liquid part to external layer of the double emulsion [82]. Table 1 summarizes SLNs preparation methods, lipid types used, the drugs encapsulated, and their major therapeutic applications.

4 Drug(s) incorporation models

Generally, there are three models proposed for drugs incorporation to embed an active ingredient in SLNs (Figure 8) which produces different release quantities and patterns (Figure 9).

4.1 Homogenous matrix model

The active pharmaceutical ingredients (APIs) are distributed uniformly within the solid lipid core (Figure 8), and the drug release takes place through the diffusion process from 1 day to a few weeks. Such model types are generated by the HPH process, *e.g.*, prednisolone [83,84].

4.2 Drug enriched peripheral shells model

The drug resides at the periphery of SLNs is shown in (Figure 8). The model is prepared by the HPH preparation

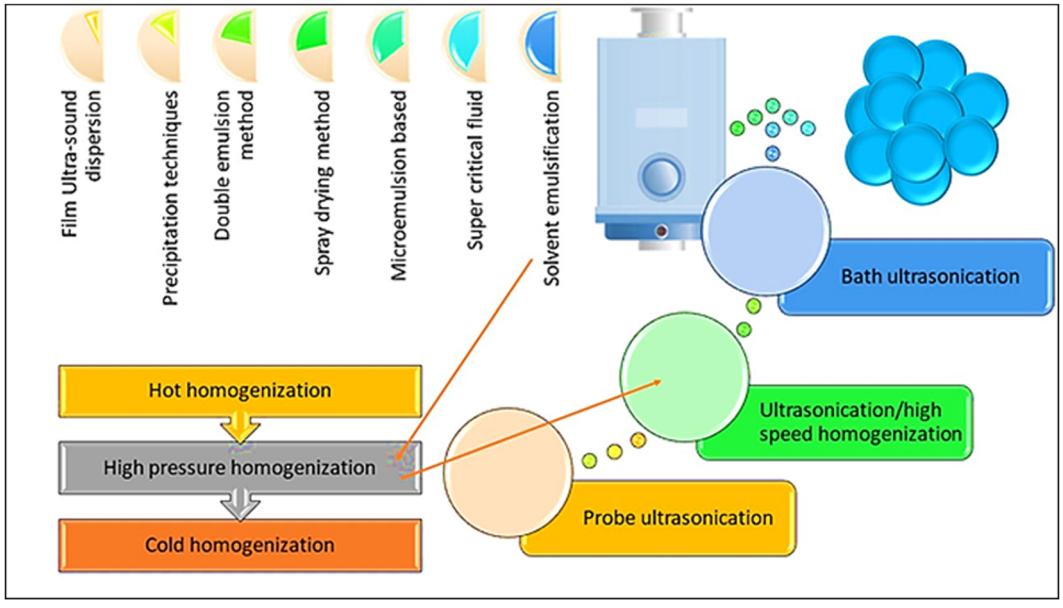

Figure 7: Various methods of SLN preparations.

Table 1: SLNs preparation methods, used lipids, encapsulated drugs, and major therapeutic applications

S. No.	Lipids	Preparation method	Drug	Application(s)	Ref.
A.	**Triglycerides based**				
1.	Tricaprin	Hot-pressure homogenization	Oxytetracycline	Extended-release after single-use	[1]
		Hot-pressure homogenization	Bromocriptine	Parkinson's disease	[86]
		Emulsion/solvent evaporation	Docetaxel	Lung cancer	[87]
		Emulsion/solvent evaporation	Docetaxel	Lung cancer	[87]
2.	Trilaurin	High-shear homogenization	Atovaquone	Pneumonia, malaria, toxoplasmosis	[88]
		Hot-melt HPH	Paclitaxel	Ovarian cancer	[89]
3.	Tristearin	Hot-pressure homogenization	Bromocriptine	Parkinson's disease	[86]
		Hot-pressure homogenization	Oxytetracycline	Extended release after single-use	[85]
		Emulsion/solvent evaporation	Docetaxel	Lung cancer	[87]
		Ultrasonication-based hot homogenization	Nitrendipine	Improved oral bioavailability	[90]
4.	Trimyristin	Emulsion/solvent evaporation	Docetaxel	Lung cancer	[87]
		Water/oil/water (W/O/W) emulsion	Calcitonin	Improved oral absorption	[91]
		Ultrasonication-based hot homogenization	Nitrendipine	Improved oral bioavailability	[90]
5.	Tripalmitin	Emulsion/solvent evaporation	Docetaxel	Lung cancer	[87]
		High-shear homogenization	Atovaquone	Pneumonia, malaria, toxoplasmosis	[88]
		Ultrasonication-based hot homogenization	Nitrendipine	Improved oral bioavailability	[90]
		Hot-homogenization	Ergocalciferol	Rickets, vitamin-D deficiency	[92]
6.	Softisan 100	Quasi-emulsion solvent diffusion	Caffeine	Topical administration	[93]
7.	Stearic acid	Hot melt oil-in-water (O/W) emulsion technique	Ferulic acid and aspirin	Pancreatic cancer cell lines, chemoprevention	[94]
B.	**Hard-fat based**				
1.	Witepsol W35	High-shear homogenization and ultrasound	Diazepam	Pulmonary delivery	[95]
	Witepsol S58	High-shear homogenization and ultrasound	Diazepam	Pulmonary delivery	[95]
2.	Witepsol H35	Hot-melt ultrasonication	Rosmarinic acid	Oral delivery	[96]
3.	Witepsol H15	Hot-melt ultrasonication	Rosmarinic acid	Food applications	[97]
4.	Witepsol E85	Hot HPH	Ibuprofen	Osteoarthritis, musculoskeletal disorders	[98]
		Hot HPH	Buparvaquone	Treatment of leishmaniases	[99]
5.	Glyceryl monostearate	Hot homogenization	5-Fluorouracil	Lung cancer	[100]
		Hot homogenization and ultrasonication	Ramipril	Hypertension	[101]
6.	Cetyl Palmitate	Hot homogenization	5-Fluorouracil	Lung cancer	[100]
		Reverse micelle-double emulsion	Insulin	Diabetes	[102]
7.	Cetyl Palmitate	Microemulsion method	Vincristine	Brain delivery	[103]
8.	Glyceryl caprate	Solvent emulsification-diffusion	Doxorubicin (DOX)	Various cancers	[104]

(*Continued*)

Table 1: *Continued*

S. No.	Lipids	Preparation method	Drug	Application(s)	Ref.
9.	Stearic Acid	Ultrasonication	Tetrandrine	Topical applications	[105]
		Emulsification-evaporation-solidifying	Lipoyl–memantine	Anti-Alzheimer	[106]
		Emulsification	Silibinin	Parenteral administration	[107]
			Astaxanthin	Simulated gastric and intestinal juices	[108]
		Reverse micelle-double emulsion	Insulin	Diabetics	[102]
		High-shear homogenization, ultrasound; HPH	Safranal	Topical delivery	[109]
		Micro-emulsification solidification	Methotrexate	Carcinomas	[110]
10.	Glyceryl behenate	Hot HPH	Budesonide	Nasal formulation	[111]
11.	Compritol 888 ATO, glyceryl dibehenate	Hot homogenization method	Vorinostat	Cancer	[112]
12.	Compritol	Microemulsion technique	Quercetin	Improve permeation across the BBB into the CNS	[113]
C.	**Co-emulsifiers based**				
1.	Soybean lecithin	Micro-emulsification solidification	Methotrexate	Carcinomas	[110]
		Emulsification and low-temperature solidification	Naringenin	Pulmonary administration	[114]
			Curcumin	Enhance brain delivery	[115]
2.	Egg lecithin	Emulsification and low-temperature solidification	Naringenin	Pulmonary administration	[114]
		Microemulsion	Ketoprofen	Arthritic inflammation, pain	[116]
	Phosphatidylcholine	Reverse micelle-double emulsion	Insulin	Diabetes	[102]
3.	Gelucire® 50/13	Melt-emulsification method	Glutathione (GSH)	Deliver the antioxidant GSH to the primary cultures of head-kidney (HK) leucocytes of *Sparus aurata* L.	[117]
D.	**Polyaxomers based**				
1.	Polyaxomer-188	O/W emulsion/solvent evaporation	Docetaxel	Breast cancer	[118]
		Hot homogenization, ultrasonication	Ramipril	Hypertension	[101]
2.	Polyaxomer-407	Hot homogenization	Metoclopramide	Nausea, vomiting	[119]

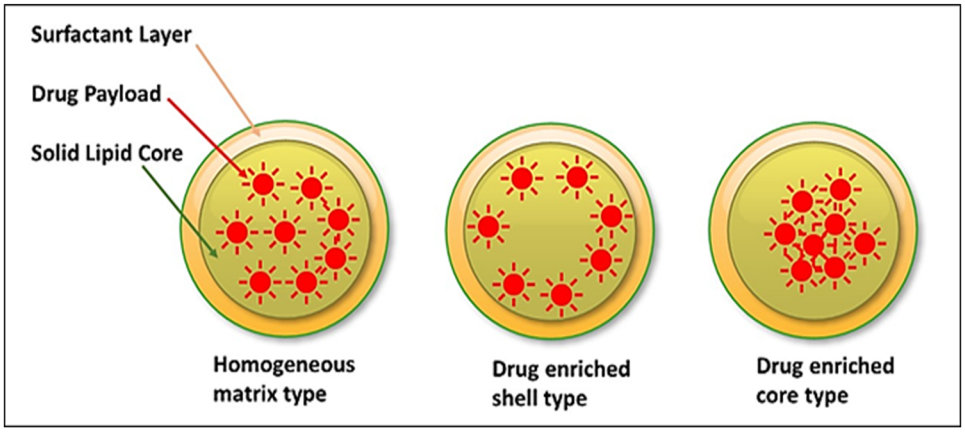

Figure 8: SLNs drug loading models showing homogenous matrix, drug-enriched peripheral-shell, and drug-enriched core shell models.

process, when lipids in the nanoemulsion stage cools faster at core areas than the peripheries, and there are either a minimum quantity of drug molecules, or the area is drug-free. At the periphery, the lipids and the drug precipitate at the same time at the eutectic point. The drug gets accumulated at the periphery, because initially at the beginning of the HPH process, the drug's dispensability in the surfactant solution is increased in a uniform manner with the increase in the temperature. Therefore, the drug may leave the solidifying lipid matrix, and spread in the liquid state; but when the cooling of the nanoemulsion occurs, the drug dispensability decreases and phases separation occurs between the solid lipid matrix and the liquid state. The cooling leads to solidification of the core [120]. In this case, a burst release of drugs takes place. However, the release profile can be controlled by controlling the physical parameters and ingredients, *i.e.*, temperature, and surfactant concentrations [121].

4.3 Drug enriched core-shell model

When the API precipitates faster than the lipid during the cooling of the nanoemulsion stage of SLNs preparation, a drug-enriched model of drug loading is obtained in reversal to the reverse of the peripheral shell model of drug loading (Figure 8). In this model, the peripheries of the prepared SLNs are either drug-free, or contain minimal quantities of the drug which is caused by the drug escaping the phase. The model is shaped when the drug runs through the lipid

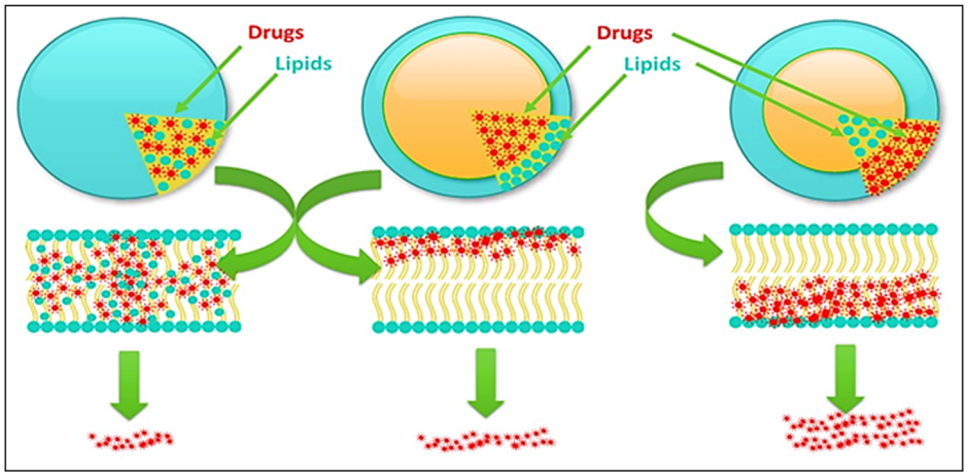

Figure 9: SLNs drug loading models' typical release effects showing homogeneous model's drugs release at minimum, drugs enriched-shell type model's comparatively increased drug release than the homogeneous matrix model, and drugs enriched-core type model's highest drug release phenomena.

matrix, until it is overloaded at the production temperature. The drugs which are cooled at a rapid rate than the lipids, and get concentrated in the core region, produce this model of loading. Herein, sustained drug release is observed, which is membrane controlled, and is based on Fick's Law of Diffusion [121].

5 Drug release profiles

The drug release profiles depend on certain parameters that included the chemical nature of the lipid matrix, the type of the produced SLNs model, the production temperature, and the type and concentration of the surfactant. Generally, the release profiles were often biphasic, *i.e.*, first burst release and then sustained release patterns were followed (Figure 10). The hot HPH process, and high surfactant concentrations, generally led to spurt release of the encapsulated drugs. Since, the high temperature lets the drug to dissolve in water, and upon the nanoemulsion cooling, the lipid starts solidifying but the drug remains in the aqueous phase. A supersaturated solution, that was obtained after further cooling, the drug got partitioned back leaving the central core solidified, and the peripheral areas of the SLNs comparatively in liquid state, which indicated that the drug's burst effect was dependent on the solubility of the drug in the water phase [122,123].

6 SLNs storage stability

Storage stability of a formulation, especially the nanoformulation, is a very important aspect of the formulation's further applications as a therapeutic agent, and SLNs stability is also crucial in producing the therapeutic effects. SLNs when stored for a longer period may yield a gel, which results in increased particle size, and thus SLNs' physical properties get deviated. Therefore, it is necessary to continuously observe their physical properties with the passing of time. This deviation is obtained by variations in the electrokinetic potential (a key feature of SLNs stability), the average size of SLNs particles, drug's chemical condition with regards to its stability and degradation, presence of degradants, drug's leaching, as well as at times the viscosity of the drug formulation's colloid, if stored in a media. The storage temperature and presence of light is also important parameter when long-term stability is concerned. Therefore, the 4°C temperature is considered the most optimal and advantageous temperature for long-term storage. However, at 20°C storage conditions, the drug's loss does not occur, but agglomeration producing fast-growing particles size is observed at 50°C storage condition [124,125].

7 Characterization of SLNs

Toward establishing the characteristics of SLN, the particle size of SLNs material plays a critical role. In order to properly characterize SLNs, one of the most important steps is to get an exact determination of the particle size. The method known as dynamic light scattering, or DLS, is an important approach, that is often used in the process of characterizing a broad variety of nanomedicines. On the other hand, due to the very fine nature of SLNs, methods that are both highly sensitive and reliable need to be used. Electron microscopy technologies, *e.g.*, scanning electron microscopy, TEM, and atomic force microscopy are widely applied for the accurate determination of the particle size of SLNs. These technologies also accurately determine the morphology and internal composition of the SLNs [126–129]. Further, the X-ray photoelectron spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, Rutherford backscattering, and analytical

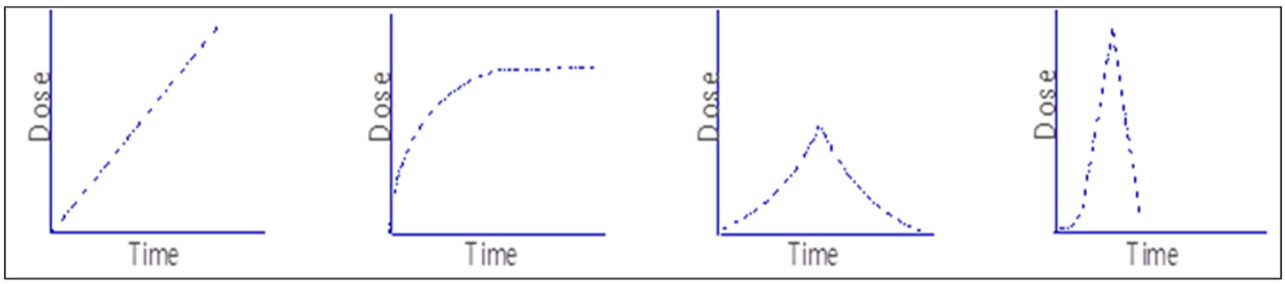

Figure 10: Typical profile of drugs payload release from SLNs: time *vs* drug release dose relationships.

ultracentrifugation are some of the other approaches that may be used to examine the surface chemistry of SLNs [130,131]. In the meanwhile, the optical characteristics of SLNs are often examined by means of UV-VIS and photoluminescence spectroscopies in order to identify their excitation and emission spectra, in addition to their yield and brightness [126]. Fluorescent NPs can be easily detected *in vitro* and *in vivo* conditions [132,133]. SLNs can also be loaded with materials which prove to have excellent optical properties, and these SLNs can be easily tracked intracellularly by fluorescence-based microscopic technologies, such as, fluorescence microscopy and confocal laser scanning microscopy. Furthermore, the biodistribution of fluorescent SLNs in experimental animals can be visualized by various *in vivo* imaging systems [134]. Thus, SLNs' identification has been performed through sensitive and nanoscale resolution techniques. The characterization of the formulation is important to ensure the product quality, stability, and drug release profile. Some important characterization techniques are as follows.

7.1 Particle sizes

The correct estimations of the constituent SLNs average spheroidal part are vital owing to its key role in effective drug delivery. The size of SLNs is also responsible for the drug release profile, the cellular response when absorbed by cells, and its biodistribution. The most widely used and powerful techniques for calculating the constituent particles' size from a few nanometers to 3 microns are photon correlation spectroscopy (PCS), and for the particle size greater than 3 microns, the laser diffraction technique has been used [135,136]. These techniques measure the scattered light intensity due to the particles' movements. The scanning and transmission electron microscopies are also regularly used for shape and particle size determinations. The size stability during prolonged storage is also an area of concern, and has been continuously monitored by the PCS method. It calculates the overall charge acquired by the NPs in a specific medium. Generally, a high charge on SLNs indicate the presence of more repulsive forces, and hence no/less accumulation of NPs resulted in their electrical stability [137–139].

7.2 Measurement of crystallinity and polymorphisms

The X-Rays Diffraction of the molecular crystal lattice is feasibly assessed for the per-unit crystallization. The X-ray is diffracted at certain angles as per the observed planes and atoms arrangements in the crystalline material. The diffraction obtained due to X-rays bent is a unique signature of each type of atomic arrangement, and this technique has been used to gauge the molecular arrangements in the lipids and drugs, SLNs chemical composition, chemical structures, and phase behavior [140,141], whereas to know the melting points, and crystallization behavior of all the ingredients of SLNs, Differential scanning calorimetry (DSC) method was used. It is important to know the crystalline nature of the lipid constituents of SLNs, as it is interrelated with the embedded drug and its release profile [142,143]. The polymorphism of lipid matrices and drug is caused by the long storage time, which eventually affects the drug release pattern [144]. However, the polymorphism can also be slowed down, if the particles size is decreased, and the desired quantities of surfactant are utilized during the preparation stages of the SLNs, including the use of the chemical stabilizers during storage.

7.3 Evaluation of supplementary structures

Drugs' formulations produced several kinds of nanoscale delivery modules, *e.g.*, polymeric NPs, liposomes, and micellar structures under super-cooling and thaw cycles produce supplementary structures that are obtained from the storage conditions-led mutual interactions, chemicals and conditions affecting degradations, and chemical transformations of the drugs and other chemicals, including solvating media present in the formulation. These supplementary structures might be present in the stored, and sometimes, some of these supplementary structures can be present in the relatively-fresh SLN formulations. The characterization of such multimodal entities have been performed by the NMR [145], and electron spin resonance spectroscopies [146]. These techniques are extremely subtle, and are accurate enough to identify the different kinds of supplementary structures, thereby also indicating the colloidal status and stability of the formulation, if stored in the liquid media as well as lyophilized solid formulation that may also contain the cryo-protectant as part of the formulation. The ^{1}H-NMR spectroscopy was also used to evaluate the super-cooled and thawing steps effect with the help of low line widths of the lipid protons in the ^{1}H-NMR (PMR, Hydrogen/Proton NMR) spectrum of the formulation [147].

7.4 Evaluation of SLNs embedded drug (packing and entrapment efficiency)

SLNs provide extensive therapeutic applications in drug delivery, and distributions, and it is significant to know the packing and entrapment efficiency of SLNs entrapped drugs as it sets the discharge pattern for the drug release profiles. Toward estimating the total quantity of SLNs embedded drugs as per unit weight, the free drug is separated out. The process of drug separation is realized by using several techniques, *e.g.*, centrifugation, filtration, and gel permeation chromatography which separate the enclosed drugs from SLNs, and per unit weight of the incorporated drug is evaluated. Analytical methods involving UV and UV-Vis spectrophotometry, fluorophotometric spectral determinations, high-performance liquid chromatography, and liquid scintillation counting for radio-tracer labeled materials are some of the techniques involved [148,149].

8 Evaluations of drug release patterns

Assessments leading to quantification of drugs' release are crucial for calculating the dose availability, maintenance of the drug's supply at the site of action, release pattern's estimation, drug's stability, safety, and overall therapeutic efficiency, including the drug release efficacy and the *in vitro* and *ex vivo* studies on the formulated SLNs are performed. Rarely, but at more advanced clinical implications stages of the drug development and ADME studies including pharmacokinetics/dynamics studies stages, *in vivo* experimentations are performed. Other methods, such as membrane dialysis method, flow rate along with the analytical voltammetric turbidimetry were also used to measure the drug release profiles [150].

9 Routes of drug administration and biodistributions

9.1 Drug administration through oral route

SLNs entrapped drugs offer promising potential for oral delivery. SLNs works as the protecting shield for the entrapped drug against the harsh gastro intestinal tract (GIT) environment [151] and improve the transmucosal transport of the drug [152]. SLNs, under size limits, are easily absorbed by the M-cells of the Peyer's patches of the intestine [91], and gut enterocytes [153]. SLNs entrapped insulin is first burst released and later a constant release is maintained [154]. The all-*trans* retinoic acid, which is poorly water soluble upon SLNs formulation, has shown considerably improved oral bioavailability. The preparation procedure and the quantity of surfactants used in the formulation exhibited significant impact on the oral absorption of SLNs formulation [155].

9.2 Parenteral administration route

Parenteral administration of drugs has evolved as an alternative to the oral route, and the parenteral route effectively avoids the enzymatic degradation in GIT. SLNs, also site-specific in nature, have provided controlled delivery, and improved delivery of the embedded drugs through this method [156].

9.3 Rectal administration route

Rectal administration, for *in vivo* and clinical applications, is an option together with the parenteral drug route for fast therapeutic response. The route is preferable for pediatric, consciousness-altered, and nauseating patients. The extensive rectal vasculature and lymphatic vessels provide the basis for this route's drug absorption, wherein high plasma level is achieved in short time. SLNs formulation entrapping metoclopramide was prepared by the HPH method using surfactants, *i.e.*, polysorbate 80, pluronic® F-68, F-127, and Cremophor. SLNs provided constant and sustained drug release [119,157].

9.4 Intranasal drug delivery route

SLNs' intranasal administration route for brain delivery of drugs has provided faster drug outreach as compared with the intravenous administration. The drug's formulation delivery through nasal cavity has provided enhanced bioavailability, and escape from first-pass liver metabolism of the drug [158].

9.5 Pulmonary delivery route

The non-invasive drug delivery route with large surface area, and high drug absorption rate, has also provided first-pass elimination escape for the drugs. It is also

considered as a substitute for the parenteral route of drug administration. The respiratory delivery of SLNs was carried out by nebulizing the drugs for treatment of asthma, cancer, and allergy. The delivery did not cause the inflammation of the alveolar epithelial lining, and was found safe. The insulin trapped SLNs delivery provided stability and sustained release of the drug with desirable therapeutic effects [159]. PEGylated SLNs were effective in constant and sustained dose release of the drugs with enhanced bioavailability in the lungs. The ligands-coupled, positively charged SLNs were prepared and tested in alveolar macrophages [160]. The RGD-modified paclitaxel-loaded and redox-sensitive SLNs for lung cancer drug delivery have also been prepared [161].

9.6 Ocular administration route

SLNs are considered as successful carrier for ocular administration. Many drugs, *e.g.*, tobramycin® [162], and cyclosporin-A [163], were effectively administrated to the eyes. These drugs were found stable and non-irritant to the subjects. The lipoplex (liposome–poly cation–DNA complex), was also used to deliver drugs and genes to ocular sites. A liposome protamine–DNA lipoplex, an electrostatically assembled payload delivery entity, incorporated a cationic liposome and an anionic protamine–DNA complex as part of the highly condensed DNA forming its core material was surrounded by lipid layers. The carrier was found suitable for delivery to the cornea, targeting the retina in age-related macular degeneration, retinitis pigmentosa, and diabetic retinopathy. Delivery of functional genes, micro RNA, and other genetic materials to treat ocular conditions have also been reported [164].

9.7 Transdermal and topical application route

SLNs entrapped drugs were successfully delivered through transdermal routes also. SLNs entrapping the diclofenac sodium was applied for transdermal delivery, and a burst release with slow but sustained and constant dose release of the drug was obtained [165]. For example, flurbiprofen SLNs have shown 4.4-folds increase in bioavailability of the flurbiprofen and produced the desired levels of anti-inflammatory effects [166]. Drugs and other entities, *i.e.*, imidazole [40], triptolide [167], podophyllotoxin [168], vitamin-A [169], isotretinoin [170], DNA [171], flurbiprofen [172], glucocorticoids [173], sun-screen product, harmful UV-rays blocker, and 2-hydroxy-4-methoxybenzophenone (Eusolex® 4360) [174] have been formulated as SLNs lipidic carriers for topical delivery [175]. Cosmetics, anti-aging, and beauty products have also been formulated for better topical delivery as SLNs together with their different formulation variants [176,177]. Figure 11 sums up the various routes of SLNs-based drug administrations.

10 SLNs and cancer therapy: major thrust areas

Various classes of cytotoxic drugs have been incorporated into SLNs, *e.g.*, paclitaxel, DOX, mitoxantrone, methotrexate, camptothecin, SN38, etoposide, fluoro-deoxy uridine, retinoic acid, verapamil, and cyclosporin-A. These cancer-fighting drugs, when loaded in SLNs, have exhibited improved therapeutic efficacy, biodistribution, solubility, and better pharmacokinetics. The aloe-emodin, a drug used for treating many types of tumors, *i.e.*, liver, breast, and lungs, have demonstrated better efficacy with constant drug release profiles. SLNs formulations for targeting cancers [178] loaded with tamoxifen [179], camptothecin [180], and methotrexate as payload deliveries [110] are also reported.

10.1 Breast cancer

For breast cancers, several drugs, *i.e.*, mitoxantrone, paclitaxel, methotrexate, and aloe-emodin, have been clinically used. It has been observed that *in vitro* testing of cytotoxicity of the mitoxantrone, methotrexate, and aloe-emodin-loaded SLNs were higher than their free drug counterparts [181,182]. However, *in vitro* cytotoxicity evaluations did not exhibited much difference in

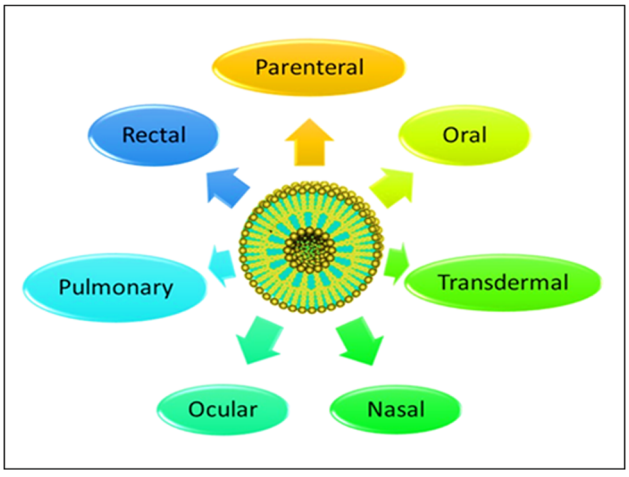

Figure 11: Various routes of SLNs administrations.

cytotoxicity levels for the paclitaxel-loaded SLNs and its free drug [182]. Docetaxel, a wide-spectrum, second generation anti-cancer drug, loaded onto SLNs showed enhanced inhibition of cancer tissue and the formulation was also effective at low dose as compared to the free drug administration [183]. Mitoxantrone formulated as SLNs for localized injection to control toxicity and improve bioavailability [184], and DOX prepared as SLNs formulation as a conjugate of soybean-oil-based anionic polymer to enhance the efficacy of the drug, are also reported [185].

10.2 Skin cancer

SLNs were effective in treating skin cancers, and were used as topical application for the purpose. DOX when loaded in cationic SLNs, the skin permeation of the formulation was enhanced by 4-folds. However, when similar SLNs formulation was delivered involving iontophoresis, the DOX's SLNs formulation's skin permeability enhanced 50-folds [186]. Similarly, the natural product, sesamol, when incorporated into SLNs, stayed longer in the epidermis with least fluctuations experienced in the epidermis [187].

10.3 Prostate cancer

Drugs loaded in SLNs restricted the tumor cell growth. The retinoic acid-loaded SLNs, when prepared by HPH method, showed initial burst release, and later sustained and nearly constant dose drug release in the *in vitro* condition with tumor growth inhibition at drug concentration levels of 150 µg/mL [188]. A comparison of Lipofectamine 2000® cationic SLNs (charge +40 mV in aqueous media) was found highly effective in treating prostate cancer. With about 100 nm in size, these SLNs did not lose the genetic substance against DNAase digestion, and exhibited transfection in prostate cancer cells [189]. A docetaxel and curcumin co-encapsulated lipid-polymer SLNs formulation for prostate cancer with enhanced anti-tumor activity was also lately reported [190].

10.4 Kidney cancer

Gallic acid ester derivatives have exhibited anti-metastasis and anti-apoptotic activity, and did not harm the surrounded normal cells. The *in vitro* and *in vivo* evaluations of the G8-loaded SLNs were found stable, and capable of treating the kidney cancer [191]. An *in vivo* and *in vitro* testing of 120 nm sized docetaxel-loaded SLNs showed improved cellular uptake, stability, enhanced cytotoxicity with lower toxicity to surrounding normal cells. SLNs were target-oriented with no side effects for the nearby organs and the normal cells. Thus, SLN formulations showed better therapeutic characteristics as compared to the free drug [192].

11 SLNs in Alzheimer's disease

Certain naturally occurring phenolics, *e.g.*, resveratrol, inhibited clustering of β-amyloid-protein, considered responsible for Alzheimer's disease pathogenesis, was SLNs formulated. The preparation avoided the first-pass liver metabolism and was stable for delivery and storage. The resveratrol SLNs were conjugated with antibody-like OX26 mAb for efficient transportation of the entrapped drug to the brain [193]. Galantamine hydrobromide was also able to cross the BBB as SLNs formulation [194]. The RVG-9R peptide, when mixed with BACE1 siRNA and formulated as SLNs, resulted in an efficient nasal drug delivery vehicle for treating Alzheimer's condition. Herein, the role of RVG-9R was to improve the transcellular pathway of neurons with cells penetration power. The BACE 1 siRNA was found to be effective in relieving the Alzheimer's conditions [195]. Brain targeted, polysorbate-80 coated piperine SLNs at 2 mg/kg dose levels for Alzheimer's disease are also reported [196].

12 SLNs for anti-tubercular therapy

Anti-tubercular drugs, *i.e.*, isoniazid, rifampicin, and pyrazinamide were formulated as SLNs, and employed to limit the high dosing frequency [197]. The formulation's nebulization in an animal model by incorporating these drugs as SLNs was also reported for enhancing their bioavailability and improving the therapeutic efficacy of the drugs [198].

13 SLNs and personalized medicine approach

Anti-cancer drug, docetaxel, appended with anti-FDFR-1-mAb was loaded into SLNs using tristearin after trying different formulation approaches. SLNs surface attachment of FGFR-1-mAb was analyzed by SDS-PAGE method, and

confirmed in comparison with the native anti-GFP-1 antibody. These SLNs preparation was used to effectively target the breast cancer cell lines and showed noticeable cytotoxicity of the formulation [199]. Formulation strategy as part of the personalized medicine for cancer treatment was also put forth [182,183].

14 Gene delivery

SLNs are among the most suitable delivery-carrier formulations for genetic materials transportation [200–202]. Incorporation of genetic material, their encased stability, and transport transitional safety, avoidance of carrier's toxicity, site-specificity, and targeted on-site delivery are comparatively feasible in comparison to structurally delicate liposomes and other nano-structures-based genetic materials delivery to the intended site. Delivery of diametric HIV-1 HAT peptide (TAT 2), delivery of peptidic material, plasmid DNA, and other nucleic acids as SLNs delivery modules, termed as geosphere formats have been reported, wherein SLNs surface was tagged with an antibody for site-specificity [203–205]. The delivery of non-viral, cationic SLNs complexed with a plasmid (shNUPR1) to inhibit the NUPR1 gene expressions, which are responsible for the growth of hepatocellular carcinoma and its chemotherapy resistance, was achieved in the *in vitro* conditions [206]. Examples of SLNs-based delivery for the CRISPR/Cas9 gene-therapeutics have been reported [207–211]. The *in vivo* deliveries, cell-lines based transfection efficiency, as well as biocompatibility of the gene therapy, have also been demonstrated [212,213].

Recent advances in gene and drug deliveries [214,215], breakthroughs in SLNs-based deliveries [216,217], self-assembling nucleic acid lipid NPs for gene delivery [203], toxicity and metabolism predictions for SLNs [218], orally delivered lipid drug (nicotine) complex [219], other drugs oral deliveries [220], anti-oxidants delivery [221], and patents information on SLNs delivery are amply available [222].

15 Natural products entrapped SLNs: toward alternative and traditional drug-based personalized medicine

SLNs-based delivery systems have been used to enhance the bioavailability, and therapeutic efficacy of certain bioactive natural products, plant extracts, and fractions (Figure 12) [223]. Ferulic acid, an example of broad range of bioactive natural products available from thousands of flowering plants, especially in the edible fruits and greens category, has been SLNs formulated. Biological and clinical recorded data for ferulic acid proved its anticancer, antioxidant, and cardio-protective activity. However, the oral bioavailability of the drug is poor due to its limited water solubility, and nano-structured lipid carrier (NSL), and SLNs have been used as a vehicle for the ferulic acid delivery to overcome its lower oral bioavailability, wherein the results of *in vivo* study demonstrated higher peak concentration (Cmax), and the area under the concentration–time curve (AUC) for the NSL and SLNs over the suspension of the aqueous free ferulic acid reflected the enhanced oral bioavailability of the ferulic acid [224].

Paclitaxel (Taxol®) and docetaxel oral bioavailability was also improved through their incorporations in SLNs.

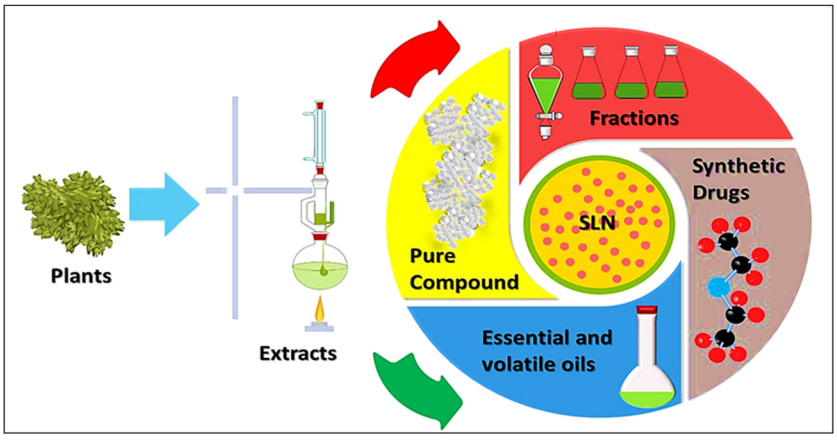

Figure 12: SLNs as the delivery carrier for natural products, extracts, fractions, pure compounds, and essential oils.

The paclitaxel-loaded hydroxypropyl-b-cyclodextrin-coated SLNs enhanced the uptake of paclitaxel by the Caco-2 cells by about 5.3-folds than the normal paclitaxel suspension [223]. Also, the bioavailability of docetaxel as an anticancer agent for treatment of breast and prostate cancers has been enhanced by their incorporations into SLNs formulations. Docetaxel-loaded SLNs coated with Tween 80, or D-α-tocopheryl poly(ethylene glycol) succinate (TPGS) showed a sustained docetaxel release as compared with the intravenous docetaxel formulation (Taxotere) delivery. The AUC of Tween 80 SLNs, TPGS SLNs, and Taxotere after oral administrations (20 mg/kg) were 7.0, 12.9, and 3.9 mg min/mL, respectively [223]. The intestinal absorption and associated oral bioavailability of the docetaxel in rats were further improved in TPGS SLNs, probably due to better inhibition of the drug efflux by TPGS 1000, along with intestinal lymphatic uptake activity [223].

GSH is one of the thiols that are naturally present in all body tissues. It is highly abundant in the hepatocytes, and plays an essential role in liver protection against free radicals led oxidative damages. The oral bioavailability of GSH is very limited, as the compound is degraded by γ-glutamyl transpeptidase which decreases the absorption level of the drug [224]. Dynasan-114-based solid lipid microparticles (SLM) loaded GSH was prepared with particle sizes of 250–355 μm, and with preserving the physicochemical properties of the GSH, as evidenced by FT-IR, DSC, and HSM analysis, the *in vitro* release studies using bio-relevant media showed that the Dynasan-114-based SLMs could efficiently release GSH in various intestinal fluids [225]. The amphiphilic lipid Gelucire® 50/13 based SLNs loaded GSH was also prepared to assess the delivery of the GSH to the primary cultures of HK leucocytes of *Sparus aurata* L. [226]. The formulated SLNs-GSH was stable for 3 months at the temperature of the fridge (4°C). However, on the biology level, the study of Trapani *et al.* [226] concluded no stimulant activity after incubation of HK leucocytes with SLNs-GSH preparation.

Curcumin, an efficient antioxidant natural product, obtained from Curcuma longa, family Zingiberaceae, has limited oral bioavailability attributed to its poor water solubility, lower absorption, and instability at physiological pH, rapid metabolism, and faster systemic elimination of the compound [117]. Curcumin-loaded SLNs composed of polysorbate 80, and soy lecithin to evaluate the brain delivery of the formulation, and its experimental paradigm of cerebral ischemia (BCCAO model) in rats were prepared [117]. The results proved an improvement in neurological scoring by 79%, and an increment of SOD, catalase, GSH, and mitochondrial complex enzymatic activities. The lipids peroxidation, nitrite, and acetylcholinesterase levels were also decreased by the administration of curcumin-loaded SLNs. In addition, Gamma-scintigraphy studies showed 16.4x and 30c-folds improvement in brain's drug bioavailability upon oral and intravenous administration of the curcumin-loaded SLNs *vs* the solubilized curcumin (C-S) [117]. Quercetin, a potent natural antioxidant, belonging to flavonoid class of plant-derived secondary metabolite, was formulated as SLNs of tripalmitin/lecithin lipid core, and with chitosan coat, exhibited better dispersion and release profile in the Caco-2 cells compared to the quercetin powder alone [227]. Also, compritol lipid based SLNs-loaded quercetin has been prepared to enhance the brain delivery and therapeutic effects of quercetin for use in the treatment of Alzheimer's disease [113,228]. The results obtained from the study revealed significant improvement in the memory retention among the rats that were administrated quercetin-loaded SLNs, as compared to the control, and free quercetin-treated rats [113]. Vincristine is one of the vinca alkaloids used as a chemotherapeutic agent in treatment of several tumors, *e.g.*, breast cancer, lung cancer, and leukemia. Vincristine's brain delivery and BBB permeability were improved by incorporating the drug within cetyl palmitate-based SLNs with the aid of dextran sodium sulfate (DS) [103].

Several other examples of the natural products loaded SLN formulations are available in the literature, and bioactive natural products, such as, chrysin [103], tocotrienol, cantharidin [222], quinine [229,230], and several other examples available in the literature were intended to improve the drug bioavailability, and therapeutic efficacy in the treatment of diseases was also formulated as SLNs. Also, SLNs formulation has been applied for several plant extracts, semi-purified fractions, and essential oils to achieve the same purposes of enhanced drug bioavailability, and improved therapeutic efficacy [231–235].

16 Surface-coated SLNs: developing targeted delivery specifics

Chitosan-coated-SLNs encapsulated with experimental dye were prepared for delivery to glioblastoma multiforme, a brain tumor type, and were found to provide efficient delivery to the site as compared to the non-chitosan coated SLNs. The coated SLNs were embedded in O-carboxy methyl chitosan containing nanofibers. The strategy was suggested as fit for the delivery of lipophilic anti-proliferative drugs to the brain tumor site [236].

In another experiment, hyaluronic acid coating of docetaxel encapsulating SLNs was prepared by utilizing the stearic acid, phosphatidylcholine, and hexadecyl trimethyl ammonium bromide. An *in vitro* delivery experiment confirmed the utility and efficacy of the preparation. Better cellular uptake, and cytotoxicity was observed against MCF7, MDA-MB-231, and MCF7/ADR cells [237]. Silk fibroin-coated SLNs were found to be better in ceramide's skin permeation owing to the positively charged fibroin and the negatively charged skin [238]. Docetaxel-loaded SLNs with chitosan coating were found to exhibit slower release of the drug, better cytotoxicity, and improved tumor inhibitions, as compared to the non-coated SLNs. Increased particle size and zeta potential charge inversion after coating was also observed [239].

Orally delivered, polysaccharide-coated SLNs were prepared for colon cancer delivery as a chemo/thermotherapy formulation. The super paramagnetic iron oxide NPs and DOX-loaded SLNs were coated and observed for their delivery to cancer cells which primarily avoided systemic drug absorption, and were delivered in an enhanced ratio than the uncoated SLNs. A coating of folate and then dextran were applied, and the coated SLNs provided enhanced residences for SLNs. The removal of outer dextran coating by enzymatic degradation, and the exposure of the folate coat provided better targeting and uptake. The oral delivery of the formulation confirmed its utility through enhanced function and bioactivity [240]. MCF-7 breast cancer cell's delivery of the chitosan and hyaluronan coated SLNs provided better targeting, uptake, and time and dose-controlled delivery, together with the facile release of the loaded drug, paclitaxel, thereby enhancing the chemotherapeutic value of the loaded anticancer drug [241]. Alginate-coated SLNs for oral insulin delivery is also reported [242].

For lung delivery through inhalation, SLNs coated with folate-grafted-PEG-chitosan derivatives were prepared, and the formulation provided delivery feasibility, improved pharmacokinetics, provided better pulmonary exposure, and prolonged lung residence of the coated SLNs with the very limited systemic distribution. For *in vitro* delivery, the coated SLNs feasibly reached the folate expressing HeLa and the M109-HiFR cell lines, and reduced the half-maximum inhibitory concentrations of the drug in M109-HiFR cell lines based activity evaluations [243].

The thiolated chitosan derivatives, obtained through amidation with the L-cysteine and 6-mercaptonicotinic acid in single and multi-capping procedures, were used to coat SLNs for evaluating their mucoadhesive properties. The cysteine-thiolated chitosan, 6-mercapto nicotinic acid-S-protected thiolated chitosan, and L-cysteine-S-protected thiolated chitosan were tested for their mucous interaction with the porcine intestinal mucosa, and the 6-mercapto nicotinic acid-S-protected thiolated chitosan was found most interactive in comparison to other chitosan derivatives and the pure chitosan, while its mucus diffusion was the least. This derivative also showed the highest retention in the intestinal mucosa [244]. Eudragit S100 coated SLNs were also prepared for delivery to the colon, and the optimal colon targeted parameters were achieved [245].

Folic acid trapped SLNs incorporating ferulic acid-*trans*-resveratrol coated with chitosan for targeted delivery to colon cancer cells toward enhanced apoptosis have been reported [246]. For oral adenocarcinoma cell lines delivery of the model drug, *trans*-retinoic acid, the phosphatidylethanolamine polyethylene glycol (PE–PEG) coating of the prepared SLNs provided reduced non-specific internalizations, enhanced delivery, as well as enhanced chemotoxicity effects as compared to the non-coated SLNs [247].

Magnetic and chitosan-coated SLNs delivering letrozole to cancer cell lines were also prepared, and it was found that chemotherapeutic efficiency was increased in several anti-cancer testing set-ups, *i.e.*, HUVEC (normal cell lines), MCF7 (breast adenocarcinoma), Hs 578Bst (breast carcinoma), Hs 319.T (infiltrating ductal cell carcinoma), UACC-3133 (infiltrating lobular carcinoma of breast), UACC-732 (inflammatory carcinoma of the breast), and MDA-MB-453 (metastatic carcinoma) cell lines [248]. Yet, in another development, chlorin e6 loaded SLNs with gastric cancer cell membrane attachments were prepared for the photodynamic therapy of gastric cancer [249]. The primal drug resistance in tumors was ameliorated through the hyaluronic acid coating of the DOX-loaded SLNs [250]. The chitosan coated *trans*-resveratrol, as well as ferulic acid, loaded SLNs in conjugation with folic acid, were tested, which showed better stability in a simulated acidic media and showed enhanced anticancer activity in HT-29 cell lines. The preparation also exhibited regularization of the expression of cyclin proteins, and also showed enhanced cell cycle arrests [251]. A comparative analysis of the nano-structured lipid carriers and SLNs with chitosan coating and fatty acid release revealed that the NLC showed more rapid digestion than SLNs due to the use of the liquid state lipid constituent. The free fatty acid release from chitosan-coated SLNs were nearly similar to the plain SLNs, and the chitosan-coated NLCs showed greater fatty acid releases than the uncoated NLCs. The information was proposed to be of important implications in the functional foods and beverages preparations to achieve lipid digestion controls in the GIT [252]. SLNs internalizations achieved through endocytosis were modulated by SLNs surface coatings. The PE–PEG coatings of the Epikuron 200, stearic acid, and sodium taurodeoxycholate-based SLNs provided targeted

cellular internalization of the preparation in oral adenocarcinoma cell lines which thereby reduced the non-specific internalization of the prepared SLNs and provided enhanced chemo-toxic effects as compared to the non-coated SLNs [253].

17 Toward SLNs-entrapped drugs' commercialization

It would be pertinent to discuss the commercial standpoint of SLNs formulated drugs from the continual market share and availability to public outlets. The current market share of nano-formulated drugs has reached over 50 billion USD which was at 50.32 billion in 2020 and is expected to reach over 88 billion USD by 2028 through growing at an expected rate of 7.3% annually. SLNs segment accounted for the major part of the revenue share for the first time in 2020 [254]. An increasing trend is expected and forecasted [255,256]. The COVID-19 situation has also contributed, and the marketed formulations, BNT162b2 vaccine (BioNTech and Pfizer) and mRNA-1273 vaccine (Moderna Inc.) developed as nucleoside-modified mRNA encoding the viral spike glycoprotein of SARS-CoV-2 encapsulated in lipid NPs, and lipid NP-encapsulated mRNA-based vaccine, which encodes the spike protein (S protein) of SARS-CoV-2, respectively, which have provided protection of the used RNA variants, were World health organization-endorsed, commercially available prescriptions.

18 Conclusion

SLNs as relatively new delivery vesicles have of lately attracted much attention with their versatility, functional, and bio-transport advantages, together with ease of preparation and stability, comparatively safe storage, as well as sustained drugs release profiles. The observation that natural lipids can be an encapsulating material has given SLNs an added advantage over other transport vehicles involved in targeted and specialized cellular delivery. The functional solid matrix of SLNs protected the embedded drug from the biochemically exposed physiological environments. and allowed sustained release with improved body tolerance and low toxicity to the organisms, along with delivery to different organs in a biocompatible manner. The surface coatings of SLNs also improved the delivery kinetics, bioavailability, and biological activity together with an enhanced biological half-life of the lipid vesicles, and the availability of the intact drugs at recommended concentrations. The feasibility of SLNs delivery to different cancers and barrier-constrained anatomical sites, especially the brain, and deliveries of the payloads to the kidneys, pancreas, bone marrow, lungs, heart, and other relevant organs, together with physiological conditions of various cancers and other ailments, have provided newer and better approach of drug delivery with enhanced bioaction by SLNs incorporated drugs.

19 Future developmental directions and newer prospects in delivery modules

The advancements and applications in personalized nanomedicines, superior biodegradability of the formulation, and non-allergenic formulations' development together with encapsulation/loading of multiple drugs of contrasting nature and structural classes, as well as the advancements in scale-up and industrial-scale productions, storage, and distant location transports, are some of the desired elements for sustained growth and outreach of SLNs-based drug delivery products.

Developments into SLNs-based products ranging from cancer nanomedicine to other disease segments, primarily in cardiovascular disorders, Alzheimer's and Parkinsonism, anti-tubercular, and the ongoing COVID-19 therapeutic developments as SLNs based formulations are also envisioned [257]. SLNs technology development and product patenting have been followed [94,258] toward encasing the developments in the field which is needed to speed up.

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