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Review Article:

Solid Lipid Nanoparticles as Innovative Carriers in Drug Delivery: A Review

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Abstract

Background: : Nanoparticle technology is a new drug delivery system with nano-scale-size. The solid lipid nanoparticles are dynamic systems adopted for formulating water-soluble and insoluble drugs in a colloidal carrier. Their matrix is solid lipids at room temperature and their size ranges from 10 - 1000 nm. Solid lipid nanoparticles have many privileges including protection of drugs from chemical, photochemical, and oxidative degradation. Also, they could be modified to be formulated as sustained-release or controlled-release dosage forms. Their limitations involve the low drug loading capacity with the possibility of leakage and damage during storage. The components of solid lipid nanoparticles are different but generally regarded as safe. Their preparation methods are numerous, ranging from the usual high-pressure homogenization to the green strategies. The most important applications of solid lipid nanoparticles include parasitic infection, cancers and brain diseases. The bioavailability and efficacy of drugs like praziquantel, nitazoxanide, and amphotericin B were greatly enhanced by solid lipid nanoparticles, improving treatment outcomes for conditions such as Leishmaniasis, toxoplasmosis, and schistosomiasis. In cancer therapy, solid lipid nanoparticles have been employed to target breast, lung, liver, and colon cancers, offering improved cellular uptake, increased cytotoxicity, and reduced systemic toxicity through surface decoration approaches. Furthermore, by overcoming the blood-brain barrier, solid lipid nanoparticles have shown a trustworthy promise in facilitating effective brain delivery of therapeutics for neurodegenerative disorders and brain tumors. **Aim:** This review highlights the solid lipid nanoparticles' privileges, limitations, components, preparation techniques and their most important applications. **Conclusion:** solid lipid nanoparticles applications in parasitic infection, cancers and brain disease could overcome the traditional drug delivery challenges. By reducing systemic toxicity, enhancing bioavailability, and improving targeting, they pave the way for more effective therapies.

1. Introduction

The diagnosis, treatment and prevention of different diseases in general require the administration of active pharmaceutical ingredients (APIs). These APIs are chemical compounds synthesized artificially or obtained from natural sources that are capable of producing direct effects on living cells and organs (1). Their effects on non-diseased body parts might lead to therapeutic problems including side effects, toxicity or therapeutic failure. This necessitates the development of delivery systems that target the API to the required site of action (2). Advanced drug delivery systems are sophisticated technologies that target the medication and depose it to the exact site of action inside the body to provoke the maximum therapeutic activity with the minimum undesirable effects (3). These new drug delivery systems could overcome the usual drawbacks encountered with the traditional drug delivery systems such as first-pass metabolism low drug stability, under optimum selectivity and decreased bioavailability (4–6). A wide range of sophisticated technologies could be adapted for the delivery of such

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systems such as those that depend on biomimetic techniques, intelligent drug devices, micro-needles devices, co-crystal systems, nanoparticles systems, nanoemulsions, smart hydrogels and others (7–11).

Nanoparticles are predominately defined by their surface- to- volume ratio which exceeds(60 m^2/ml) and are typically <100 nm in at least one dimension. Nevertheless, solid lipid nanoparticles (SLNs) up to 1000 nm have been formulated depending on application requirements and lipid composition (12,13). The classifications of nanoparticles are wide and variant. Some depend on the type of chemical components in the nano-metric scale that classifies the nanoparticles into three categories: organic, inorganic and carbon-based (14). Other classifications depend on the type of materials used in their production by which nanoparticles are classified into: polymer-based, non-polymer-based, and lipid-based nanoparticles. Solid lipid nanoparticles belong to the lipid-based category (15). SLNs are dynamic systems adopted for formulating water-soluble and insoluble APIs within a colloidal carrier. The matrix of the SLNs are solid lipids at room temperature and their sizes range from 10 up to 1000 nm depending on production methods and/or types of used excipients (15,16). The first SLN was produced by Müller in 1991. These first developed SLNs were prepared as tiny spherical particles consisting of lipids (that were solid at room temperature) which were able to form crystal lipid matrices perfectly. Additionally, it was possible to incorporate one drug or more between the fatty acid chains. These delivery systems offered relatively excellent stability for drugs with poor solubility and low bioavailability. Nowadays, SLNs are represented in different shapes including flat ellipsoid and disc-like geometry, as well as the traditional spherical shape. In most cases, the loaded drug was attached to the surface of the carrier matrix instead of the solid core that could be employed for a wide range of applications (17). This review covers recent advances in SLNs formulation techniques and materials, and provides a comparative analysis of conventional versus green preparation strategies. Also, the applications of SLNs in specific therapeutic areas are also explored to illustrate their broad utility. Finally, current limitations and challenges of SLNs systems are discussed as well. In this review, we conducted a systematic literature search (January 2015–April 2025) across PubMed, Scopus, and Web of Science, using keywords 'solid lipid nanoparticles', 'green synthesis', 'targeted delivery', and disease- specific terms.

1.1. The privileges and limitations of SLNs

SLNs could be loaded by both hydrophilic and lipophilic APIs (18). In contrast to liposomes, SLNs offer superior protection for sensitive APIs from chemical, photochemical and oxidative degradation which results from their ability to immobilize the drug and reduce its out leakage (19). Also, they protect the drug from degradable enzymes, first-pass metabolism and chemical decomposition. Their nano-sized diameter could shield them against the RES (Reticulo Endothelial System) cells endocytosis that might occur in the liver or the spleen (20). Other advantages of SLNs include their low toxicity as the excipients used in their production are generally regarded as safe (abbreviated as GRAS which is a term used to describe the excipients that are safely used in foods and drugs industry) (21). Compared to other polymeric nanoparticle systems, the carrier lipids used in their formulations are usually biocompatible and biodegradable (22). SLNs could be modified to be sustained release or controlled release dosage forms as they can control the release of the drug for up to several weeks through the coating of the SLNs with specific ligands (17,19,22). Also, they could be formulated to be administered by various routes including oral, rectal, pulmonary, nasal, ocular, dermal and injectable (23). In addition, SLNs could be applied as targeting systems with a relatively greater bioavailability at a specified site of action (particularly the brain) (20). Finally, SLNs are stable over one to three years which is a significant advantage compared to other similar systems (24).

On the other hand, the most significant limitation of SLNs involves their low drug loading capacity with the possibility of drug leakage and damage that could happen during storage. Another drawback is the limited number of hydrophilic drugs that are suitable candidates to be formulated as SLNs (25). Upon storage, lipid particles polymorphism and microbial growth had been occurred in some SLNs (26). At last, the coalescences and agglomeration of the dispersed particles might lead to lipid growth with unpredicted gelation and polymer transition rate. Accordingly, further researches are required to prevent and decrease these drawbacks and improve the SLNs quality (27).

1.2. Categories of SLNs

According to the methods of the drugs incorporation within the SLNs, they could be divided into three categories as illustrated in **Figure 1**.

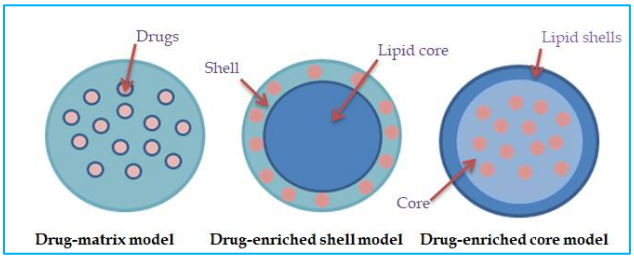

Figure 1. Categories of SLNs according to the drug incorporation methods*.

* (The figure was created using PowerPoint software and it was adopted from reference number (28)).

- Drug-matrix model: The first category involves the homogenous dispersion of the drug molecule within the lipid matrix of the SLNs. Cold homogenization usually prepares these nanoparticles without adding solubilizers (28).
- Drug-enriched shell model: This model depends on the thermal homogenization of the lipid-drug mixture. The mixture heated above the melting points of the lipid followed by rapid cooling of the mixture to room temperature. These rapid thermal changes would result in the formation of a shell around the drug particles

in the outer part of the SLNs with the precipitation of the lipid within their cores (16,28).

- Drug-enriched core model: The third model usually depends on the hot homogenization technique. The lipid material should be heated to the lipid melting point followed by the addition of drug molecules at a concentration near or above their saturation. Upon cooling of the mixture, the drug particles would precipitate in the core. Further cooling would make these lipid particles to form a membrane-like shell around the precipitated drugs within the core of the SLNs (15,27).

1.3. The SLNs components

The SLNs typically consist of solid lipids phase and an aqueous phase and this system stabilized into nanoparticles by the addition of surfactants. Other additional components, such as co-surfactants, cryoprotectants, charge modifiers, and preservatives, may be incorporated into SLNs depending on the drug targeting strategy and the selected preparation technique.(29,30).

A summary of all potential components for SLNs formulation is provided in **Table 1**. (29–32).

Table 1: A summary of the most common components for SLNs formulation.

			References
The typical components	**Solid lipids phase**	• **Fatty acids like:** Lauric acid, Dodecanoic acid, Palmitic acid, Oleic acid, Stearic acid, Behenic acid, Linoleic acid. • **Steroids like:** Cholesterol, and triglycerides. • **Waxes like:** Beeswax. • **Glycerides:** Mono and tri glyceryl stearate, Glycerol monostearate, Glyceryl trilaurate, Glyceryl trimyristate, Glyceryl tripalmitate. • **Hardened fat;** Witepsol.	(33,34) (35) (36) (37) (38)
	Aqueous phase	Distilled water.	(36)
	Surfactants	Phosphatidyl choline, Soy lecithin, Poloxamer, Polysorbate 80 (Tween 80).	(38–41)
The other additional components	**Co-surfactants**	Sodium lauryl sulfate, Sodium taurocholate, Sodium oleate, Sodium glycocholate, Butanol.	(42–44)
	Cryoprotectants	Gelatin, Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl alcohol, Polyvinyl pyrrolidone	(45,46)
	Charge modifiers	Dipalmitoyl phosphatidylcholine, Stearylamine Dicetylphosphate, Dimyristoyl phosphatidyl glycerol	(47,48)
	Preservatives	Antimicrobial like: Thiomersal, chitosan. Antioxidant like: vitamin E.	(49–51)

1.4. The preparation methods of SLNs

Different methods could be used in SLNs preparation. These range from conventional to green preparations to more complicated ones. The choice of the suitable preparation method depends mainly on the physical and chemical properties of the drug that is intended to be formulated as SLNs. However, the cornerstone in SLNs formulation is the synthesis of the microemulsion, emulsion or micellar solution (30,31).

1.4.1 Homogenization under high-pressure techniques

This method depends on the vigorous movement of a microemulsion under high pressure. This would produce high shear stress that causes the microparticles to break into nanoparticles. There are two general types of this technique, hot homogenization and cold homogenization. In the hot homogenization technique, the drug is incorporated into a melted lipid. After that, the mixture was dispersed using a high pressure homogenizer in a hot surfactant solution. Upon cooling of the mixture to room temperature, the lipid in the formed oil in water nanoemulsion would solidify and with the generation of SLNs (52,53). In contrast, the cold homogenization involves the addition of the drug in melted lipid which would be cooled rapidly by dry ice. the resulting cold mixture would be milled into micro sized particles and dispersed in a surfactant solution at or below room temperature. The applied high pressure homogenization would convert the formed nanoparticles into SLNs (30). The limitations of these two approaches include the high temperature in the first type which might cause drug degradation or migration to the aqueous phase during homogenization. The sudden cooling in the second one might result in the coalescence of particles (54).

1.4.2 Solvent-involving techniques

These techniques include numerous approaches that rely on the presence of organic solvent during SLNs preparation. They could be divided into the following:

A- Solvent-evaporation method

This method is based on the incorporation of the drug and the lipid phase in an organic solvent prior to the addition of the aqueous phase. Then the two phases would mix together while the solvent evaporates under low pressures or through lyophilization to produce SLNs. The main advantages of this method are its simplicity and its fast

and cheap production steps. However, the most significant limitation of this technique is its relatively poor efficiency for the entrapment of extremely hydrophilic medications. This problem could be solved by the encapsulation of the hydrophilic drug through a solvent emulsification technique (which is called the double emulsion technique). The hydrophilic drug dissolved in aqueous media containing an emulsifying agent to produce water in oil emulsion within the organic solvent. Upon the addition of this phase to the aqueous phase, the doubled emulsion phase would form with continuous mixing (as water in oil in water emulsion). The formation of SLNs was brought about by the evaporation of the solvent under high shearing stress. The SLNs that are produced by this technique are usually too large which could be considered disadvantageous (55,56).

B- Solvent-emulsification diffusion method

In this method, a water-miscible solvent is used to dissolve the drug-loaded lipid with sufficient stirring. This will represent the oil-organic solvent phase and be added to an aqueous phase containing surfactants under continuous mixing to form oil in water emulsion. The SLN s formation will occur upon the dilution of the formed emulsion with water in a ration of up to 10 times with the resultant diffusion of the organic phase through the continuous aqueous phase. SLNs will then be purified by passing through a dialysis membrane while the organic solvent will be removed by lyophilization (57–59).

C- Solvent-injection method

In general, this method is similar to the solvent-emulsification diffusion technique as the organic phase contains the drug-loaded lipid and the aqueous phase contains the emulsifiers or the surfactants. However, in this technique the organic phase will quickly injected by a needle into the aqueous phase with continuous stirring and under pressure (37). After the injection, two steps will lead to SLNs formation. The first one involves the reduction in the particle size by solvent diffusion into the aqueous phase with an increase in lipid concentration within the droplets. While the second step involves the impact of the emulsifiers in reducing the interfacial tension between the aqueous and the organic-solvent phase resulting in SLNs formation. The lipid particles produced by this technique are much smaller and more stable than the ones that are produced by the solvent involving techniques. In addition, this method is cost-effective process but the cornerstone is the solvent diffusion rate at the injection site that will control the reduction in the lipid particle size (60).

1.4.3 Microemulsion technique

This method depends on the heating of the solid lipid-drug phase above the lipid melting point. This mixture will be added to a previously heated aqueous-surfactant phase with gentle stirring to produce micro-emulsion. The hot micro-emulsion will be dispersed in an icy water with continuous stirring to produce SLNs. After that, the mixture will be filtered and the remaining water will be removed by lyophilization. The cornerstone in this technique is the type and amount of surfactants used and the ratio of hot micro-emulsion to water that should not exceed 1 to 50 (54,61,62).

1.4.4 Membrane contactor technique

This method is more complicated as it requires the use of a special membrane contractor module. The surfactant-containing aqueous phase should pass through the interior side of the membrane, while the hot lipid phase will be enforced by pressured vessels through the membrane pores from the outer side to the inner side. The resulting hot emulsion will be transformed into SLNs when the mixture is allowed to cool at room temperature. This method offers a controllable SLNs production with uniform particle size. However, their main drawback is that the difference in temperature between the aqueous and the lipid phases should maintained as comparable as possible to prevent premature lipid solidification (63).

1.4.5 The Green Strategies in SLNs preparation

The green strategies have been developed to decrease the environmental influences of the pharmaceutical industry (27). They afford more efficient and faster reaction with a better safety profile by excluding the need to use toxic organic solvents. Additionally, they produce a formula with higher solubility due to the lower polydispersity index and better particle size distribution. The green strategies could be used in SLNs preparation. For instance, ultrasound assisted methods use acoustic cavitation to form nanoemulsions at temperatures not exceeding 60 °C which ultimately reduce energy consumption and allow solvent free production. Whereas Microwave instruments accelerates lipid melting by uniform volumetric heating, while avoiding hot spots and solvent residues (54). Furthermore, supercritical fluid techniques are also used for the same purpose, it forms SLNs in one step, making use of tunable solvent power of supercritical fluids, eliminates the need to use toxic solvents and high shear processes (64). Producing SLNs using green strategies includes all following techniques:

A- Ultrasound-producing techniques

SLNs preparation by these methods involves the application of an ultrasound-producing apparatus like an ultrasonic bath, ultrasonic probe or ultrasonic high-speed homogenizer to produce an efficient mixing with particle size reduction to nanoemulsion size range with ultimate production of SLNs. The heated aqueous surfactant-containing phase will be added to the lipid drug-containing phase that was previously heated above the lipid melting point. After mixing, a coarse emulsion will be formed which will convert to a nano-size emulsion by the power of ultrasound-producing apparatus. The SLNs will produced

upon the dilution of the formed nanoemulsion with an ice-water bath (56,65). The produced emulsion may contain a wide range of particles sizes which is the main drawback of this technique. Filtration and lyophilization of the formed emulsion will increase particle size stability and decrease poly size distribution. The ultrasonic probe may cause metal contamination of the produced formula (66,67).

B- Microwave-producing technique

In this technique, a microwave-producing apparatus like a microwave tube is used to agitate and heat the micro-emulsion mixture by microwave energy which would increase mixing efficiency and decrease particle size and polydispersity (68). The oil drug-containing phase will be mixed with surfactant-containing aqueous phase to produce a micro-emulsion. The combined effects of the uniform mixing and heating obtained from the microwave rays would cause the micro-emulsion to be transformed into a nano-sized one. The heat will distribute equally in all directions producing more uniform size reduction and lower the polydispersity index. The SLNs will be formed by the cooling of the nanoemulsion in an ice-water bath (69,70).

C- Supercritical fluid technique

This is a novol environmental-friendly method for SLNs production. The most common type of this technique that is useful in pharmaceutical preparation is carbon dioxide approach. The types of particles produced by this method are smooth with small uniformly distributed particle sizes. Beside that, this method excludes the need to use toxic solvent as well as the application of high temperature and/ or high sheer stress in nanoemulsion formation. Therefore, this technique is more favorable for heat liable drug-loaded SLNs production (64,71). The main principle of the CO_2-supercritical fluid technique depends on the temperature-pressure phase diagram and the use of solvent and anti-solvent technique where the drug is soluble in the CO_2 solvent and both solvent and anti-solvent are miscible. An expansion will occur in the solution leading to the precipitation of particles with very low particle size (72).

A summary of the advantages and disadvantages of the SLNs different preparation techniques have been included in **Table 2**.

Table 2: A summary of the advantages and disadvantages of the SLNs preparation techniques.

Preparation technique	Advantages	Disadvantages	References
Homogenization under high-pressure technique			
• Hot homogenization	Low cost of production. and avoid the use of organic solvent.	Thermal damage.	(32,73).
• Cold homogenization	Used for thermally liable compounds.	High polydispersity index.	
Solvent- involving techniques			
• Solvent- evaporation method	Low cost of production. and the availability for single and double emulsions.	Thermal damage and large particle size.	(72).
• Solvent-emulsification diffusion method	Could be used to incorporate hydrophilic drugs.	Particle coalescences.	(74).
• Solvent- injection method	Production of stable small-size particles.	Require additional solvent removal.	(60).
Micro-emulsion technique	Avoid organic solvents and produce small-size particles.	High amount of surfactant is required. Stability problem upon storage.	(62,75,76).
Membrane contactor technique	Control over the size of the produced particles through the selection of the membrane size.	Not reproducible for large-scale production.	(32).
The Green Strategies techniques			
• Ultrasound-producing techniques	Avoid toxic organic solvents. Reduce shearing stress.	Possible metal contamination.	(77).
• Microwave-producing technique	Avoid toxic organic solvents. Uniform and controlled heat distribution. Produce purified SLNs with small particle sizes.	Cost process. High amount of aqueous phase.	(69,70).
• Supercritical fluid technique	Avoid toxic organic solvents. Reduce shearing stress. Used for thermally liable compounds. low polydispersity index.	Cost process. Multistep process.	(71).

1.5. Impact of particle characteristics on drug release

It has been shown that particle characteristics such as the crystallinity of the lipid matrix, particle size, and the surfactant's or ligand shell's thickness directly influence the release kinetics from SLNs. Pandey *et al.* noticed that SLNs smaller than 100nm exhibited burst release, releasing up to 30% of the drug load within the first hour, whereas larger particles > 500nm sustain drug release over several days (31). On the other hand, Duan *et al.* reported that α-to-β polymorphic transitions in the lipid matrix during storage can lead to drug expulsion and modify release profiles, highlighting the important influence of matrix crystallinity in the kinetics of diffusion (19). Moreover, Aldayel *et al.* reported that SLNs coated with chitosan form an additional diffusion layer which ultimately minimizes the initial burst release effect and reaches almost zero order release kinetic over two days (78).

1.6. Applications of SLNs

A summary of the different applications of SLNs is expressed in **Figure 2**.

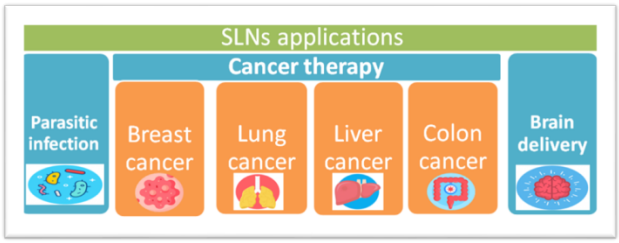

Figure 2. A summary of the SLNs applications*.
* (The figure was created using PowerPoint software).

1.6.1 SLNs in parasitic infections

Causes of liver damage can vary, and one common cause is parasitic infections. Their occurrence might be unexpected, which adds a burden in both diagnosis and treatment (especially in HIV and AIDS patients as well as travelers) (79).

Studies have been focused to deliver antiparasitic drugs as SLNs, such as Praziquantel (80–82), Nitazoxanide (NTZ) (83), and amphotericin B (AmB) (84,85), for improved therapeutic outcomes.

Treatment strategies for Leishmaniasis (both visceral and cutaneous leishmaniasis), a protozoal infection, involve the multiple administrations of toxic agents, which encounter side effects. To improve the absorption, stability, and bioavailability of the administered drugs, nanotechnology in general and SLNs particularly seem promising alternatives (80).

Parvez *et al.* (81) developed a novel carrier system to deliver AmB and paromomycin as oral therapy against visceral leishmaniasis (VL). The modified dual-drug SLNs (m-DDSLNs) were produced using 2-hydroxypropyl-β-cyclodextrin (HPCD) to incorporate both AmB and paromomycin. The *in vitro* tests (cytotoxicity assay and antileshmanial activity) were performed using mouse macrophage cell line J774A.1, whereas the *in-vivo* study utilized *L.donovani-infected* BALB/c mice. The results revealed that m-DDSLNs were less toxic, more biocompatible than conventional liposomal forms, and better uptaken by the infected macrophage. Unlike free AmB and paromomycin, m-DDSLNs significantly reduced the intracellular amastigotes (81).

It was shown that Artemisinin has antileishmanial activity against certain species, but a problem encountered during its administration which is the low bioavailability and the requirement for multiple-frequency administration (82). A study by Akbari *et al.* (83) included the delivery of artemisinin as SLNs to treat VL. In comparison to the free artemisinin, artemisinin-loaded SLNs showed superior antileishmanial activity in *L.infantum* infected BALB/c mice with a significant reduction in parasite burden in the spleen (85 ± 3.1 %), liver (84.7 ± 4.9 %) and hepatosplenomegaly (83).

Globally, it is estimated that 30- 50% of the population worldwide show positive serology for toxoplasmosis (84). Paromomycin (PM) is an aminoglycoside antibiotic with broad activity against bacteria and certain parasite species (85). Challenges such as short half-life encountered during its administration (86).

Khosravi *et al.* (87) prepared mannosylated SLNs and loaded them with PM (PM-SLN-M) to treat acute toxoplasmosis. To evaluate cytotoxicity, and the effect produced by paromomycin and the mannosylated PM-loaded SLNs on intracellular toxoplasma, an MTT assay was performed. It has been proven that the mannosylated PM-loaded SLNs have the lowest cytotoxicity than PM-SLNs and PM. Furthermore, *toxoplasma gondii* tachyzoites were significantly killed by PM-SLN-M. Accordingly, such findings proved that the PM-SLN-M has superior anti-toxoplasma efficacy and the lowest host cytotoxicity, even at high concentrations (87).

The same story applies to anthelmintic drugs, which is the need for targeted drug delivery to avoid side effects and excess administration of therapeutics. In 2024, a unique study by Sharma *et al.* (88) used Beeswax ethanolic extract to fabricate Albendazole SLNs (SLN-A) against the intestinal worm *Haemonchus contortus*. The extract is considered a lipid-based source used by the worm as food.

Although mortality rates are not so high with intestinal worm infections, they can cause various health drawbacks such as diarrhea and growth rate retardation. With its limited water solubility, Albendazole shows activity against these intestinal worms. *Haemonchus contortus* uses lipids as energy source and synthesizes parasite-specific lipids which are used in host invasion. Enhancement of albendazole entrapment efficiency along with an increment in its potency to about 50 folds (due to sustained release property) could be achieved by the formulated particles. Such outcomes would create a revolutionary change in anthelmintic therapy which besides the ability to reduce the dose of the drug, will reduce the side effects as well (88).

Schistosomiasis is a helminthic parasitic disease specifically caused by infection with trematodes, *Schistosoma* spp. (89).

Challenges occurred during schistosomiasis or bilharzia treatment. For instance, thelow bioavailability of the drugs of choice. Nanotechnology has emerged as a solution in general and SLNs in particular for such challenges (90). Adekiya *et al.*(91) conducted a study to develop and evaluate the stability of Praziquantel-loaded SLNs. Results revealed an elevation in entrapment efficiency and drug loading capacity and an increment in the stability of SLNs when Pluronic F127 is used as a stabilizer. Besides, in *Schistosoma mansoni*-infected mice, a single dose of the drug-loaded SLNs enhanced its antischistosomal post-infection efficacy dramatically.

1.6.2 SLNs in Cancer therapy

Cancer is still the most life-threatening disease that any person could face. The ability of any treatment to reach specific target sites either intracellular or intercellular and reduce their precipitation in other tissues is a key point in treating cancer. Traditional administration of medications is the most common way of drug treatment. However, it has many challenges, such as low drug solubility, specificity, and increased toxicity. Moreover, an increment in drug resistance to therapy, particularly multidrug resistance (MDR) is another obstacle facing cancer treatment (92). While liposomes, polymeric nanoparticles, and nanoemulsions remain important carriers, SLNs have emerged as a complementary platform offering distinct advantages in stability, biocompatibility, and scalable manufacturing since their development in the early 1990s (93).

A- Breast cancer

In recent years, nanotechnology has offered a better way for anticancer therapy. Breast cancer is the most common type of cancer that causes women's deaths annually. Different forms of treatment exist such as surgery, chemotherapy, hormonal, and radiotherapy being chosen according to many factors, for instance, the patient's tumor subtype (94).

The radiolabeled trastuzumab (TRZ), a humanized monoclonal antibody was loaded into SLNs. TRZ targets HER2, which upon binding to HER2 protein, will inhibit the epidermal growth factor reaching the cancerous breast cells, hence the immune cells can easily destroy them due to the inhibition of cell division. In this study, SLNs were formulated by high-shear homogenization and sonication. Dynamic light scattering measurements showed that the prepared formulations were around 100 nm in size with a negative charge. High radiolabeling efficiency along with stability results were obtained from radiolabeling studies. Apoptotic activity study results revealed that all SLNs formulations induced apoptosis effectively with higher activity contributed by those that contain TRZ (TRZ SLN-1 and TRZ SLN-2), compared to control groups. *In vivo,* pharmacokinetic study results showed that the treated TRZ-loaded SLNs exhibited a sustained release profile compared to free drug solution following parenteral administration in a rat model. Significant increments in pharmacokinetic parameters (C_0 and AUC_0-24) were observed with TRZ SLN-1 which could be attributed to the smaller particle size and the negatively charged nature of the particles compared to TRZ solution (95).

In 2022, Darabi *et al.*(96) succeeded in formulating dual-targeting SLNs containing doxorubicin against a triple-negative breast cancer cell (TNBC) line. Among all cases of breast cancer, it occurs in 15-20% of patients and is characterized by being an aggressive subtype with no curable treatment available. Anti-EGFR and anti-CD44 aptamers were attached to the prepared particles to target the latter two, which are highly expressed in this tumor subtype. Additionally, dexamethasone was decorated into the particle surface by chemical reaction to achieve better nucleus targeting by doxorubicin. Doxorubicin was almost completely released after 48 hours of incubation and the decorated SLNs with either EGFR or CD44 aptamers exhibited better cell proliferation inhibition.

A combination of Etoposide and quercetin as SLNs (QC-ETO SLNs) was conducted by Afarin *et al.* (97). Findings revealed inhibition of cell division and suppression of tumor activity following the exposure to either QC-SLNs alone or combined with ETO. An enhancement of apoptosis was observed with the QC-ETO SLNs. Furthermore, an increment in both bioavailability and controlling QC release was observed with these SLNs, making them a suitable choice for breast cancer therapy.

B- lung cancer

The most common type of cancer following breast cancer is lung cancer. It occurs in both men and women, causing a considerable percentage of mortality in both sexes, particularly men all over the world. Although the standard way of treatment is chemotherapy, the prognosis is still poor, with a 15% survival rate in five years (98,99).
Curcumin (Cur), popularly called turmeric, is well known for its various pharmacological actions, including anticancer effects. Its anticarcinogenic actions are owed to the ability of Cur to target multiple aspects, including growth and angiogenesis regulators and apoptotic genes (100). Rahman *et al.*(101).

formulated curcumin SLNs (Cur-SLNs) as a potential treatment for lung cancer. Cytotoxicity of the prepared particles was assessed against the A549 cell line. Results showed that curcumin SLNs exhibited more cytotoxic effects than plain curcumin suspension. Besides, an increment in cell uptake was achieved by the prepared Cur-SLNs adding to that their stability for up to 90 days following their storage.

Another study investigated the co-loading of paclitaxel and curcumin as SLNs to treat lung cancer. Both *in-vitro* and *in-vivo* studies were conducted using A549 cell lines and BALB/c mice, respectively. The *in-vivo* study results

reported a twelve-fold reduction in tumor volume with no alteration in the body weight of the investigated mice. Moreover, this co-delivery achieved synergy and higher cytotoxicity (indicating its potential in lung cancer therapy), enhancement of the anticancer effect and improved targeting by these SLNs (102).

C- liver cancer

Hepatocellular carcinoma (HCC) is the most commonly occurring form of liver cancer. Liver cancer is considered the fifth leading cause of death by cancers (103). Traditional forms of treatment include surgery and chemotherapy. Chemotherapy is still facing the problem of resistance caused by MDR, providing only symptomatic relief with no eradication cure. On the other hand, surgery is not successful in patients in the advanced stages. Ultimately, targeting such types of tumors becomes necessary, either passively or by active targeting (104).
6-Mercptupurine (6-MCP) was successfully formulated as SLNs with improved solubility and bioavailability. A cytotoxicity study against HCC was performed on the (HEP3B) cell line. Results showed that the optimized formulation had a significant cytotoxic effect compared to the pure 6-MCP (105).

Surface decorations of SLNs could enhance specific receptor targeting. Polyethylene glycol (PEG) modification of SLNs co-loaded with organic capped superparamagnetic iron oxide NPs (SPIONs) and sorafenib to examine their efficiency in drug delivery and specific liver accumulation driven by magnetic implants. Extensive characterization of the prepared particles was made as entrapment efficiency, imaging properties, and drug loading. Results showed that the generated magnetic field had led the PEG-modified (sorafenib/ SPIONs) SLNs to exhibit better organ accumulation (106). On the other hand, SLNs surface modification by glycyrrhetinic acid (GA) and/or folate (FA) has been conducted by Xu *et al.* (107) to encapsulate the anticancer agent Cantharidin (CTD).

Best tumor targeting was achieved by the decorated SLNs, using the HepG2 hepatocellular carcinoma cell line with less cytotoxic effect on the hepatocyte cell (L-02) line. Additionally, better tumor inhibition was exhibited by the modified SLNs as shown by *in-vivo* study results. Overall, both GA and FA ligands targeted the HepG2 cells effectively.

D- Colon cancer

High incidence rates of morbidity and mortality have been reported to be caused by colon cancer which represents a major health concern around the globe (108). It is characterized by the occurrence of uncontrolled growth of neoplasm cells both in the rectum and colon. Although surgical removal is still the mainstay of tumor therapy, other modalities including chemotherapy, immunotherapy, and radiation are of value in ceasing tumor growth and removing circulating neoplasms (109).

To achieve a targeted effect on the recepters present in the epithelium of the colon surface, Ahmed *et al.*(110) conducted a study to prepare SLNs loaded with irinotecan (IRN) and daidzein (DZN) and the surface modified with hyaluronic acid (HA) and bovine serum albumin (BSA). *In-vitro* cell line studies on HT-29 demonstrated that the prepared SLNs exhibited a more cytotoxic effect (only at 75 µg/ml), indicating that SLNs uptake was by endocytosis (receptor-mediated) process.
Furthermore, apoptosis was inhibited by 56% and a histopathological study confirmed that the decorated SLNs (HA-BSA) restored the normal colon architecture and mucosa. Due to low stability, water solubility, and high volatilization, Moghimipour *et al.*(111) formulated thymol as SLNs (Th-SLNs) using the microemulsion method. They were characterized by atomic force microscope (AFM), Fourier-transformed infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC).
Additionally, cytotoxicity and hemolysis studies were also conducted. AFM images showed that the prepared particles were spherical. Both DSC and FTIR graphs illustrated the loading of thymol into SLNs. Moreover, Th-SLNs had a significantly higher cytotoxic effect on the HT-29 cell line when compared to the free thymol and blank-SLNs, which in turn confirmed that the prepared SLNs undergo successful endocytosis by the cancerous cells and also higher stimulation of apoptosis as well. Hemolytic analysis confirmed the hemocompatibility of the prepared SLNs.

1.6.3 Brain delivery of drugs

Disorders in the brain, such as brain tumors, neuroinflammation, and neurodegenerative diseases (NDDs) are abundant worldwide causing a considerable percentage of morbidity and mortality.
Neurodegenerative disease examples include Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), epilepsy, dementia, Multiple Sclerosis (MS), brain stroke, and headache. Medical therapy for these neurological disorders is complicated due to the presence of the blood-brain barrier (BBB), which creates vital boundaries between blood in the circulation and neuronal environment that avoid or even inhibit the passage of foreign materials, immune cells, and toxic metabolites to the CNS (112,113).

The BBB maintains normal homeostasis and ion movement in the brain. Although BBB possesses all these advantages, it still represents an obstacle to drug entry into the CNS even if it became penetrable during many neurological disorders such as (PD, AD, and MS) (114). Nanotechnology paved the way to deliver drugs to the brain, overcoming the BBB and chemotherapy is faster growing to find solutions that alleviate the neurodegeneration process in NDDs.

Various treatment options are available for Alzheimer's disease, a massive NDD characterized by the accumulation of the intercellular protein segment amyloid-beta (Aβ) and intracellular condensation of tau proteins twisted fibers. Although neurotransmitter regulation of acetylcholine and

glutamate remains the mainstay of therapy, other researchers studied the reduction of oxidative stress in animal models with AD as a form of treatment to reduce the cognitive and memory impairment associated with the disease.

Resveratrol (RSV), a natural polyphenol stilbene compound, has an antioxidant character and has been formulated as SLNs to attenuate neurodegenerative symptoms by Khishvand *et al.* Morphologically, the particles were spherical and not aggregated. *In-vivo* study results showed that RSV-SLNs were more efficient in reducing lipid peroxidase and elevating glutathione levels in brain samples. Histopathologically, it has been demonstrated that RSV-SLNs cause a reduction in neural deficits and improved AD- symptoms when compared to free RSV (115).

Dimethyl Fumarate (DMF) is encapsulated in SLNs in inhalational therapy. It explored the potential to alleviate central nervous system (CNS) and lung inflammatory response in MS using animal models induced with autoimmune encephalomyelitis (EAE). Being an immune disease, MS is characterized by chronic inflammation in the CNS with demyelination.

DMF is approved as an effective oral therapy with neuroprotection and anti-inflammation. However, severe gastrointestinal side effects result from oral administration causing less therapy adherence by patients. In this work done by Pinto *et al.* EAE mice treated with DMF-loaded SLNs by inhalation demonstrated a reduction in weight loss, clinical scores, and CNS vascular permeability. Levels of pro-inflammatory cytokines TNF-α and IL-17 were reduced while an increment in FOXp3 levels in the spinal cord occurred. These results suggested that inhalation therapy with DMF-SLNs could be a promising approach in treating MS, reducing CNS inflammation and progression of the disease (116).

The nose-to-brain approach is also used as cargo to cross the BBB and a shortcut to deliver medications to the brain by an olfactory pathway which serves as a gateway for drugs to enter the CNS. Haloperidol (HPL), is an antipsychotic drug used to treat multiple psychiatric disorders such as mania, schizophrenia, and hyperkinesia. It was formulated as SLNs that target the brain by Yasir *et al.* through the intranasal route. SLNs were prepared using the emulsification diffusion technique with glyceryl behenate as the lipid and tween 80 as the surfactant. Extensive characterization was performed and results showed that the optimized formula (HPL-SLNs 6) achieved significant brain targeting, with the brain AUC_0 -∞ higher (2.7 times) than HPL- solution (HPL-sol) when administered intravenously, and 3.66 times higher when HPL-sol was given intranasally (117).

Friedreich ataxia (FRDA), is an autosomal recessive hereditary disorder caused by frataxin deficiency and characterized by mitochondrial dysfunction and oxidative stress; Diazoxide (DZX), a vasodilating agent used in the treatment of hypertension, showed promise in the treatment of preclinical-models, however, its efficacy is limited due to its poor penetration to the brain implicated by the BBB and toxicity caused by the required high dose. Arduino *et al.*(118) conducted a study to formulate DZX as SLNs to enhance BBB penetration and reduce toxicity. The prepared particles were characterized, and the *in-vitro* BBB model demonstrated an improved permeability compared to free DZX. Furthermore, at only 1 µM concentration, an enhancement of cell viability was demonstrated by FRDA fibroblast cells. Moreover, SLNs-DZX treatment significantly reduced total and mitochondrial reactive oxygen species (ROS) levels compared to controls and empty SLN-treated cells. Such findings highlight the importance of the SLNs approach in treating FRDA, providing an improved BBB penetration, reduced toxicity, and effective reduction of oxidative stress.

The significance of SLNs in brain tumor therapy cannot be overlooked. In adults, Glioblastoma multiforme (GBM) represents the most aggressive and predominant tumor of the CNS characterized by poor prognosis and invasive nature. Multiple modes of therapy exist, with no definitive cure. This clarifies the urgent need for innovative therapeutic strategies (119). To be effective in GBM treatment, anticancer should penetrate the BBB effectively. So nanotechnology generally and SLNs in particular offer a possible solution.

These nanoparticles showed biocompatibility enhancement, and less systemic toxicity when compared to conventional delivery approaches and other anticancers used to treat GBM. A study conducted by Kadari *et al.*(120) to formulate SLNs decorated with angiopep-2 (A-SLNs) which is a ligand that targets the lipoprotein receptor-related protein 1 (LRP1), which is overexpressed in both brain endothelial and glioma cells, to enhance the delivery of docetaxel. This modification resulted in the enhancement of cytotoxicity and cellular uptake and an increment in apoptosis in U87MG human glioblastoma and GL261 mouse glioma cells compared to non-modified SLNs.

Furthermore, *in-vivo* pharmacokinetic and biodistribution studies confirmed superior brain accumulation and targeting of (A-SLNs) when compared to Taxotere, a commercially available docetaxel formulation. These findings highlight the potential of angiopep-2-decorated SLNs as a targeted drug delivery platform for GBM therapy. A summary of all the above mentioned SLNs formulations with their drug-loaded, main components and method of production are arranged in **Table 3**.

Table 3: A summary of the most common SLNs formulations with their drug-loaded, main components and method of production.

Type of disease	Drug-loaded	The main components of SLNs.	The method of Production	References
SLNs in parasitic infections	Amphotericin B Paromomycin	**Lipid Phase:** glyceryl monostearate and soya lecithin. **Surfactants:** PEG 400 and Tween 80. **Stabilizer:** polyvinyl alcohol and PEG 400.	Emulsion formation and solvent evaporation method.	(81)
	Paromomycin sulfate	**Lipid Phase**: stearic acid or cetyl palmitate. **Surfactants**: Tween 80 and Span 85.	1. Microemulsion technique. 2. Solvent diffusion technique.	(86)
	Paromomycin sodium	**Lipid Phase**: tristearin (1% w/v) and soya lecithin. **Surfactants**: Tween 80. **Charge modifier:** stearyl amine.	Solvent injection method.	(87)
	Albendazole Rhodamine B	**Lipid Phase**: beeswax. **Surfactants**: Poloxamer 407.	Double emulsion technique	(88)
	Praziquantel	**Lipid Phase**: Compritol and lecithin. **Stabilizer:** Pluronic F127.	Solvent injection co-homogenization techniques	(91)
SLNs in cancer therapy	Tamoxifen citrate	(**Lipid Phase** Glyceryl Palmitostearate. **Surfactants**: Cremophor.	Hot emulsification method.	(94)
	Radiolabeled trastuzumab	**Lipid Phase**: stearic acid and lecithin.	High shear homogenization and sonication techniques.	(95)
	Doxorubicin hydrochloride	**Lipid Phase**: glycerol monostearate and soy lecithin. **Surfactants**: Tween 80. **Cryoprotectants:** manitol.	Double emulsification and the solvent evaporation technique.	(96)
	Etoposide and Quercetin.	**Lipid Phase**: Compritol, oleic acid and lecithin. **Stabilizer:** polyvinyl alcohol .	Ultrasonic producing techniques and homogenization method.	(97)
	Curcumin	**Lipid Phase**: glyceryl monostearate. **Surfactants**: Tween 80.	Emulsification–ultrasonication method.	(101)
	Paclitaxel and Curcumin.	**Lipid Phase**: Compritol or Stearic acid. **Surfactants**: Tween 80.	High pressure homogenization.	(102)
	6-Mercaptopurine.	**Lipid Phase**: Precirol ATO5. **Surfactants**: Tween 80. **Stabilizer:** polyvinyl alcohol .	Double emulsion-solvent evaporation method.	(105)
	Superparamagnetic iron oxide nanoparticles and Sorafenib.	**Lipid Phase**: Cetyl palmitate. **Surfactants**: Tween 80.	Hot homogenization method.	(106)
	Cantharidin.	**Lipid phase:** glycerol monostearate and egg yolk lecithin. **Stabilizer:** Pluronic F68.	Emulsion ultrasonic dispersion method.	(107)
	Irinotecan and Daidzein isoflavonoid drugs with hyaluronic acid and bovine serum albumin surface coated.	**Lipid Phase**: stearic acid. **Surfactants**: Tween 80.	high-shear homogenization.	(110)
	Thymol.	**Lipid Phase**: glycerol monostearate and stearic acid. **Surfactants**: Tween 80.	Microemulsion method.	(111)
SLNs in Brain delivery of drugs	Resveratrol.	**Lipid Phase**: glycerol monostearate. **Surfactants**: Tween 80.	Solvent emulsification-evaporation technique.	(115)
	Haloperidol.	**Lipid Phase**: glyceryl behenate. **Surfactants**: Tween 80.	Emulsification diffusion technique.	(117)
	Diazoxide.	**Lipid phase:** cetyl palmitate. **Stabilizer:** Pluronic F68.	Nanoprecipitation technique	(118)
	Docetaxel.	**Lipid phase:** glycerol monostearate and Stearic acid.	Not mentioned.	(120)

2. Conclusions

In conclusion, solid lipid nanoparticles (SLNs) offer significant advantages over traditional drug delivery systems, including improved bioavailability, reduced systemic toxicity, and the unique ability to cross biological barriers such as the blood–brain barrier. They can be formulated in various forms using key components such as solid lipids, surfactants, and an aqueous phase, and can be produced through a range of versatile techniques. The findings of this review highlight the transformative potential of SLNs in addressing diverse clinical challenges. Notably, their applications in parasitic infections, cancer, and brain diseases demonstrate the ability to overcome many limitations of conventional drug delivery methods.
However, challenges such as low drug loading capacity, instability during storage, and difficulties in large-scale production require further investigation. Future research should focus on developing optimized SLN formulations for hydrophilic drugs and adopting environmentally friendly manufacturing techniques. By addressing these challenges, SLNs have the potential to emerge as next-generation drug delivery systems, offering improved patient compliance and therapeutic outcomes across a wide range of diseases.

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الجسيمات النانوية الدهنية الصلبة كطرق مبتكرة في التوصيل الدوائي: مراجعة تحليلية

الملخص:

خلفية: تقنية الجسيمات النانوية هي نظام جديد لتوصيل الأدوية بمقياس نانوي .الجسيمات النانوية الدهنية الصلبة هي أنظمة ديناميكية معتمدة لصياغة الأدوية القابلة للذوبان في الماء وغير القابلة للذوبان في الماء باستخدام ناقل غروي .القالب عبارة عن دهون صلبة في درجة حرارة الغرفة ويتراوح حجمها من 10إلى 1000نانومتر .تتمتع الجسيمات النانوية الدهنية الصلبة بالعديد من الامتيازات بما في ذلك حماية الأدوية من التحلل الكيميائي والتحلل الكيميائي الضوئي والتأكسدي .أيضا ، يمكن تعديلها لصياغتها كأشكال جرعات مستدامة الإطلاق أو مسيطرة الإطلاق .تتضمن المحددات انخفاض قدرة تحميل الأدوية مع إمكانية التسرب والتلف اثناء التخزين .تختلف مكونات الجسيمات النانوية الدهنية الصلبة ولكنها تعتبر عموما آمنة .طرق تحضيرهم عديدة ، بدءا من التجانس المعتاد بالضغط العالي إلى الاستراتيجيات الخضراء .تشمل أهم تطبيقات الجسيمات النانوية الدهنية الصلبة العدوى الطفيلية والسرطانات وأمراض الدماغ .تم تعزيز التوافر البيولوجي وفعالية الأدوية مثل البرازيكوانتيل والنيتازوكسانيد والأمفوتريسين ب بشكل كبير من خلال الجسيمات النانوية الدهنية الصلبة ، مما أدى إلى تحسين نتائج العلاج لحالات مثل داء الليشمانيات وداء المقوسات والبلهارسيا .في علاج السرطان ، تم استخدام الجسيمات النانوية الدهنية الصلبة لاستهداف سرطانات الثدي والرئة والكبد والقولون ، مما يوفر امتصاصا محسنا للخلايا ، وزيادة السمية الخلوية ، وتقليل السمية الجهازية من خلال مجال الزخرفة السطحية .علاوة على ذلك ، من خلال التغلب على الحاجز الدموي الدماغي ، أظهرت الجسيمات النانوية الدهنية الصلبة وعدا جديرا بالثقة في تسهيل تقديم علاج فعال للدماغ لعلاج الاضطرابات التنكسية العصبية وأورام المخ. **الهدف**: تسلط هذه المراجعة الضوء على امتيازات الجسيمات النانوية الدهنية الصلبة وقيودها ومكوناتها وتقنيات التحضير وأهم تطبيقاتها. **الاستنتاج:** يمكن لتطبيقات الجسيمات النانوية الدهنية الصلبة في العدوى الطفيلية والسرطانات وأمراض الدماغ التغلب على تحديات توصيل الأدوية التقليدية .من خلال تقليل السمية الجهازية ، وتعزيز التوافر البيولوجي ، وتحسين الاستهداف ، فإنها تمهد الطريق لعلاجات أكثر فعالية.

الكلمات المفتاحية: الجسيمات النانوية الدهنية الصلبة؛ الاستراتيجيات الخضراء؛ علاج السرطان؛ العدوى الطفيلية؛ توصيل الدواء إلى الدماغ.