REVIEW ARTICLE

Unraveling the Therapeutic Prospects of Solid Lipid Nanoparticles for the Treatment of Parasitic Diseases

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Received: 18th December, 2023; Revised: 21st January, 2024; Accepted: 06th March, 2024; Available Online: 25th March, 2024

ABSTRACT

Parasites induce a spectrum of illnesses, ranging from mild to severe, often causing significant global outbreaks. Existing antiparasitic drugs exhibit toxicity and notable side effects. Nanocarriers offer a promising solution by mitigating these issues through reduced side effects, enhanced target delivery, and additionally regulated prolonged active ingredient release. Solid lipid nanoparticles (SLNs), a subset of lipid nanoparticles (LNPs), have gained prominence for their favorable attributes. SLNs present themselves as a feasible option among colloidal carriers, offering an optimal release rate, stability, and precise target delivery. Their potential to deliver natural antiparasitic products is particularly noteworthy. Recent advancements in utilizing nanoparticles to enhance SLN stability and loading capacity are also explored in this review. The narrative encompasses SLN development, preparation methods, characterization, and the incorporation of drugs for combating parasitic diseases, offering insights into the evolving landscape of antiprotozoal SLN-saturated medications.

Keywords: Nano-sized carriers, SLN formulations, Drug administration, Protozoans, Helminthic parasites.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.1.64

How to cite this article: Singh H, Singh M, Singh N, Jain H, Goel H, Chawla V. Unraveling the Therapeutic Prospects of Solid Lipid Nanoparticles for the Treatment of Parasitic Diseases. International Journal of Drug Delivery Technology. 2024;14(1):447-462.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Nanobiotechnology spans a spacious range of disciplines, including electrical devices, nutriments, workstation science, drugs, strength, transmission, transit, and the atmosphere.[1-3] Significant advancements in nanobiotechnology have enabled precise regulation and utilization of components by nanometric dimensions. Tiny materials, characterized by dimensions smaller than 100 nm, play a pivotal role in various applications.[4] In biomedicine, nanotechnology is primarily employed for designing and developing nanocarriers that can effectively deliver therapeutic agents with precision.[5,6] Nanodrug, an intersection of nanotechnology, biological, and pharmaceutical research, is instrumental in screening and the administration of drugs, aiming to enhance efficacy and reduce toxicity[7,8] for improved medical outcomes.[9,10]

Colloidal particles, solid nanocarriers ranging in diameter between from 10 to 1000 nm, consist of the two synthetic and natural polymers, presenting a potential alternative to liposomal colloidal carriers.[11] Many medicinal agents are linked to tiny particles to modify pharmacokinetic (PK) and/or PD properties of drugs.[12,13] Numerous nanometer-sized medication preparations has been granted authorization among health-related studies.[14,15] Approved and investigational drug types include ultrafine crystal preparations, lipid nanocarrier, non-carbon-based nanoparticles (NPs), polymerized, Metallic compounds, dendrimeric materials, micelle-based systems and polypeptides.[16-18] Liposomes and polymers are the predominant NPs employed in proven formulations,[14-17] with liposomes playing a crucial role in efficient smart drug administration.[19] The success of drug delivery relies on sustained release and stability at the nanometer scale.[20,21] Liposomal colloidal drug carriers, known for their dimensions, assurance, capacity to entrap diverse drugs with biological compatibility and serve as cost-effective alternatives to polymer compounds.[22] Solid nanoparticles of lipid (SLNs), a subset of lipid nanoparticles, offer diverse therapeutic applications, positioning them as usual messengers to conventional colloidal micro particles.

Pathogens or parasites, encompassing protozoa or helminths, are widespread contributors to digestive tract disorders, malnourishment, iron deficiency and allergic reactions. Primary contact involves ingesting contaminated food, water, or vectors.[23-25] Table 1 summarizes effectively treating a diverse range of medically and veterinary significant parasites poses a critical challenge. Conventional drugs for

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pathogenic diseases are often costly, toxic, and prone to undesirable side effects.[26-28] Consequently, the pursuit of developing efficient drugs for parasitic disease treatment is ongoing. Nanotechnology has been integrated into the pharma field to create effective drug dosage forms for several pathogenic conditions like *T. gondii* infection,[29,30] Kala-azar (Visceral *Leishmania*),[31-36] Trypanosomel infection[41] as well as plasmodium infection.[37-40] Encapsulating standard medications within nanostructured carriers, like lipidic carriers, offer the potential to design new drug therapies in addition to increased efficacy and lower toxicity in inhabitant organisms than conventional drugs. The present review study explores broad factors, formulations, and evaluation strategies of SLNs to deliver. plant-based product or molecules, for the effective therapeutic management of parasitic infections in humans.

Table 1: An overview of medically significant parasites and the associated diseases they cause.

Parasite Name	*Disease Caused*	*Body Area Affected*
Plasmodium falciparum, P. vivax, P. malariae	Malaria	Red blood cells, liver, spleen
Entamoeba histolytica	Amoebiasis	Intestines
Giardia lamblia	Giardiasis	Small intestine
Trypanosoma brucei gambiense, T. brucei rhodesiense	African sleeping sickness	Nervous system, lymph nodes, blood
Trypanosoma cruzi	Chagas disease	Heart, digestive system, nervous system
Leishmania donovani, L. infantum, L. major	*Leishmania*sis	Skin, mucous membranes, internal organs
Schistosoma mansoni, S. haematobium	Schistosomiasis	Intestines, bladder, lungs, liver
Fasciola hepatica	Fascioliasis	Liver, bile ducts
Taenia solium, T. saginata	Taeniasis	Intestines
Echinococcus granulosus, E. multilocularis	Hydatid disease	Lungs, liver, other organs
Ascaris lumbricoides	Ascariasis	Intestines
Trichuris trichiura	Trichuriasis	Intestines
Enterobius vermicularis	Enterobiasis (Pinworm infection)	Intestines, perianal area
Toxoplasma gondii	Toxoplasmosis	Various organs, fetus (in pregnant women)
Trichomonas vaginalis	Trichomoniasis	Vagina, urethra (men)

Key facets of Solid Lipid Nanoparticles: Compositional Architecture and Functions

Over the years, various colloid vesicles, including liposomes, polymer microspheres and emulsifying systems has been designed.[42-44] Surrounded by these innovative formulations, Lipid-based nanoparticles obtain garnered significant attention as a substitute to novel colloidal delivery systems for resultant therapeutic outcomes.[45] In the early '90s, Lipid-based nanoparticles were presented as conventional colloidal delivery systems,[46] with sizes ranging from 50 to 1000 nm, positioning them as sub-micron colloidal vehicles.[44] The notable advantages of SLNs include an abundant area at the surface, enhanced durability, and higher drug entrapment attributes, which contribute to improved pharmaceutical efficacy.[47] Additionally, SLNs exhibit superior control over release compared to liquid lipids, making them particularly advantageous for parenteral drug delivery applications.[48] Lipid arrangement, composed of physiological lipids, decreases SLN unwanted effects and enhances the penetration and absorbing of hydrophobic drug candidates in the GI tract.[49,50] SLNs consist of solid containing core of lipid exhibiting higher melting point encoated by phospholipids as a safer surfactant boundary.[51,52] This lipid component in SLNs encompasses fatty acids, saturated monoacid triglycerides, waxes and partial glycerides. To ensure safety and efficacy of this carrier system, the toxicological profile of SLNs acts crucially for production as well as application. Based on the encapsulation site of drug molecule, SLNs exhibit three different dimensions classified by their production methods: (1) Shell-enriched with Drug model 2) Core- enriched with Drug model (3) Homogeneous matrix model depicted in Figure 1.[53]

Toxicological profile holds significance in the development and function of SLN systems.[54,55] Prior to pre-clinical and clinical studies, a thorough toxicological assessment involving both *in-vitro* and *in-vivo* assays is necessary.[56]

SLNs potentially carry a variety of drug molecules, leveraging their advantages like suitability, biodegradability, and tiny size, making SLNs suitable for drug delivery to the liver.[57,58] Owing to their enhanced solubility and dissolution rate, SLNs can expedite the initial phases of drug action as shown in Figure 2.[53]

New advancements in the field of SLNs highlights its potential application for lingual and sublingual routes, CNS delivery, parenteral delivery, delivery, dermal delivery, and serving as vectors for gene transfer.[49,59-62] Another advantage of SLNs lies in their ability to modulate drug release profiles.[42] Factors influencing drug delivery from SLNs include particle shape and size, concentration of surfactant and polymorphism of SLNs.[48,63] The solid structure of SLNs comprises compatible ingredients that shield therapeutical components from chemical disruption. Additionally, the initial burst of drug from SLNs can extend bioavailability and minimize bursts by enhancing drug solubility in the water phase.[64,65]

Various technologies are employed to perform the characterization of SLNs. Such as TEM, SEM, STM, FFEM, AFM, and DLS.[66,67] The amount of drug entrapped can be analysed using UV spectrophotometry and HPLC.[68]

The site of drug carriers within SLNs can impact its release. Specifically, the drug release from the inner core of SLNs is more rapid than when the therapeutic drug carrier is present in the lipid nucleus. The advantages of SLNs are assessed through

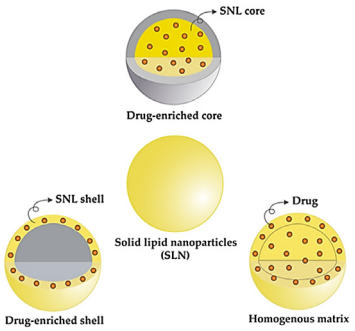

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Figure 1: Classification of SLN models representing the drug distribution in the lipid core

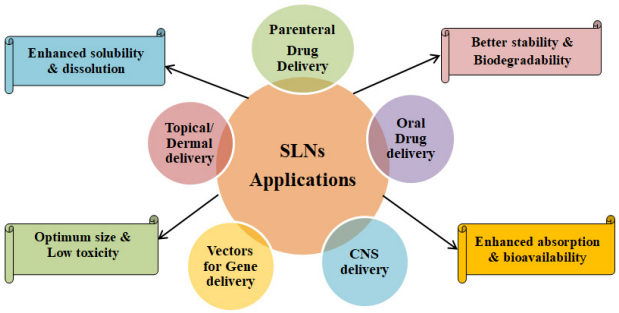

Figure 2: Potential SLN applications for diverse routes of drug delivery

in-vivo and *ex-vivo* assays, including the characterization of drug entrapment efficiency,[69] determination of the % of drug release,[70] pharmacokinetic model,[71] animal studies,[72,73] PDI,[74] zeta size and potential,[75] thermo-gravimetric analysis,[76] and cell lines using MTT colorimetric assay.[77]

Production of Solid Lipid Nanoparticles

Numerous formulation approaches have been developed to prepare SLNs as reported in Table 2.[78,79] Adopting an appropriate composition and developing of the technique depends on factors like particle size that are crucial for improving drug entrapment of therapeutic agents. SLNs are formulated using lipids, emulsifiers, and solvents, often involving precursors like emulsions, micro emulsions, and micelle solutions. Hot homogenization, melt dispersion,[80] phase inversion temperature (PIT),[81] and solvent evaporation-diffusion from emulsions[82] are some of the fundamental emulsion methods. The coacervation method[83] is frequently employed for microemulsions, whereas microemulsion dilution and chilling procedures are typical for microemulsions.[84] Other methods are instrument-specific and include the membrane contactor method,[85] spray-drying, spray-congealing[86] and electrospray. Notably, the most popular preparation methods for SLNs formulations targeting antiparasitic drugs are often reported to be high shear homogenization, hot and cold homogenization, ultrasonication or homogenization, emulsification/evaporation, microemulsion, double emulsion method, and solvent evaporation/diffusion from emulsions.[87-89]

In addition to traditional preparation methods, recent innovative technologies have been explored for liposome preparation. These include the membrane contactor method, microfluidic channel method, dense gas methods, and freeze-drying of monophase solutions.[90] Green technologies are one of these innovative methods that have several advantages for biomedical research. Conventional synthetic nanomaterial development can be expensive and less ecologically friendly, which can create hazardous compounds.[91] During the ten-year period from 2003 to 2014, the implementation of green technologies led to a 7% decrease in the manufacturing of hazardous products, including methyl isobutyl ketone, trichloroethylene, and hydrochloric acid.[92] As demonstrated by Mozafari *et al.* introduction of the bioactive carrier Tocosome, lipid nanoparticle synthesis has included green technology.[93] This molecule is the result of a manipulative and enhanced heating technique known as the "*Mozafari method*".[94] However, green technologies have been investigated for specific parasitic and harmful diseases, such as malaria,[95-105] but their use in the formulation of lipid nanoparticles for parasitic diseases is limited, necessitating more precise developments.

Incorporation of natural and herbal polymers into Solid Lipid Nanoparticles

Throughout human history, herbal therapy has also developed to treat a wide range of illnesses and ailments.[106,107] Numerous applications have emerged as a result of the benefits of herbal remedies over time.[7,108] In order to improve molecular size, boost bioavailability and biocompatibility, and reduce possible toxicity, herbal compounds are now incorporated into nanostructured systems.[10,109-111] Nanotechnology is essential When it comes to lessening harmful effects and enhancing the targeted distribution of herbal products.[112-114] SLNs have attracted attention in the field of drug delivery in the past few years,[115-118] with the goal of improving the oral bioavailability[119] and efficacy of traditional herbal medicine. Furthermore, SLNs demonstrate stronger antioxidant application and function as stable carriers for plant extracts.[120] Artemisinin, extracted from *Artemisia annua*, is a well-known herbal remedy prescribed for malaria treatment. Recently, it has been shown that artemisinin-based combination treatments (ACTs) can reduce adverse effects and increase treatment efficacy for malaria. SLNs have been used in several studies as carriers for antimalarial medications, such as artemisinin.[121] In order to boost effectiveness, artemisinin and its derivatives (dihydroartemisinin, artemether, and artesunate) are combined with other commercial and unrefined medications.[122,123] Combination therapy, such as the enclose of artemether and lumefantrine in SLNs, is now recommended against unilateral for parasite malaria prevention and treatment.[124] For instance, Attama *et al.*,[38] utilized SLNs to significantly package the antimalarial drugs artemether and lumefantrine as the primary therapy for malaria management. The aforementioned approach sought to address biophysical problems, improve

accessibility, and lessen adverse reactions. SLNs had been titled using the compound coumarin 6 to track cell-based consumption through *Plasmodium*-infected cell types in living cells investigations demonstrated excessive parasitic infections removal using lesser opposite effects, indicating SLNs to be an ensuring strategy for enhancing the productivity during conjunction rehabilitation for the malaria parasite. Dwivedi and others[39] stuffed a different artemisinin by derivative, arteether (ART), through SLNs for oral medications. The effectiveness of ART-SLNs manufacturing was evaluated through trapping productivity via high-performance liquid chromatography and cellular damage consequences were assessed via MTT analysis upon the J774A.1 organism graph, revealing an organism's sustainability across 90%. Omwoyo and colleagues.[37] introduced DHA, a synthetic form of artemisinin receptor, into SLNs to determine its antimalarial effectiveness and get around issues such bad biophysical character and dissolution in water. The SLNs-crowded DHA, produced by fast speeds homogenization and single-emulsion solvent evaporation techniques, exhibited a dimension range of 150 to 500 nm. Consistency and continuous absorption of drugs were observed for more than 90 days and then 20 hours, respectively. In culture and in rodent assays revealed at IC50 using 0.25 ng/mL *via* 97.24% chemo-suppression at 2 mg/kg/day. These results underscore the excellent potential of SLNs formulation for clinical applications.

Recently, several reports have highlighted resistance against artemisinin.[125-128] Luteolin, a biological constituent, has emerged as a potential solution to contradict artemisinin-resistant *P. falciparum*.[129] Luteolin disrupts the parasite's life cycle by inhibiting lipid metabolism, impeding the growth of novel organelle components and the formation of juvenile trophozoites (ring stage).[130,131] Due to the superior biological compatibility of luteolin, it has been utilized for incorporation into SLNs PEG by hot homogenization, freeze homogenization, and hot-micro emulsion ultrasonic methods.[40] Consequently, luteolin isolated using Solid lipid nanocarriers via PEG alteration demonstrated enhanced absolute bioavailability, accompanied by reduced transport as well as elimination of the constituent

T. gondii, a different approach frequent microorganism that infect individuals, is the object of recent treatment studies. Nemati *et al*.[30] produced Indian lilac (neem) extract-loaded SLNs by dual emulsification technique & assessed thier toxoplasma antagonist effect. This study outcome revealed that SLNs serve as lipid vesicles for neem oil, extend liberation, and exhibit tolerable Toxoplasma inhibition and minimal cellular toxicity.

Chitosan (CS), an organic biopolymer comprising units of NAG (N-Acetyl-D-glucosamine) and D-glucosamine, exhibits fascinating characteristics and is widely utilized in pharmaceutical fields, particularly in drug delivery applications.[132,133] Recently, interest in innovative formulations that combat microorganisms by using biological sources and non-toxic materials has increased[134] CS has shown promise as a coating material for the delivery of different types of nanoparticles, including SLNs.[135,136] CS-covered SLNs have been effectively prepared for treating multiple conditions.[22,137,138]

The anti-parasitic potential of CS to counter parasites such as *Leishmania, Trichomonas, Plasmodium,* and Toxoplasma have been preclinically investigated.[139] Teimouri *et al*., demonstrated the high effectiveness of CS against *T. gondii*, proposing its use as a substitute botanical therapy in toxoplasmosis management.[140] Laboratory and animal studies revealed total mortalness the RH variant microorganisms and the rates at which their development is inhibited in abdominal animals. CS also displayed considerable influences on *P. berghei*,[141] displaying potential antimalarial activity at different concentrations. To counteract chloroquine (CQ) expulsion from the acidic environment within the parasite phagosome, chloroquine microparticles, employing CS encapsulation, weakened *P. berghei* disease in male Swiss rodents. The nanoparticle formulation demonstrated greater strength in protecting against deoxyribonucleic acid damage, oxidizing strain, and inflammatory response in infected mice.[141]

Chitosan's antiparasitic efficiency was investigated against *T. gallinae* trophozoites, exhibiting a high mortality rate and inhibiting trophozoite viability compared to the control group.[142,143] Yet, limited analysis has explored the composite of chitosan using SLNs in ectoparasitic diseases. Furthermore, chitosan has demonstrated antiparasitic effectiveness in an artificial environment using a 50% effective concentration (EC50) counteracting promastigote-stage parasites and amastigote-stage parasites of various *Leishmania* species.[144-147] Recent findings also suggest therapeutic and vaccine purposes for chitosan and its derivatives in treating and preventing similarly integumentary and internal *Leishmania* species. Trade CS is proposed as a suitable aspirant for additional research concerning integumentary and internal *Leishmania* species therapy.

In a research conducted by Jain and colleagues [36] they studied the use of chitosan-coated SLNs as an immuno adjuvant therapy for *Leishmania* infection. By combining SLNs with CS, a natural resin, and loading them with amphotericin B (AmB), they were able to activate macrophages, eliciting immunological reactions like tumor necrosis factor-alpha and interleukin 12 counter *Leishmania* species. The SLNs preparation with the solvent emulsification-evaporation technique and cellular toxicity research conducted in mice demonstrated a favourable safety profile. These findings suggest that AmB-loaded SLNs, serving as a secure and efficient platform, hold promise for the treatment of *Leishmania* infections through both therapeutic and immunotherapeutic approaches.

Medicinal effectiveness of Antiprotozoal Agents Encapsulated into SLNs

Plant-based Drugs has evolved as healing method beneficial to infection throughout living history.[106,107] Gradually, plant-based Drugs' advantages have led to various applications' development.[7,108] Plant-based compounds are integrated into nanosized systems to enhance molecular mass, higher biological

Table 2: Approaches to SLN fabrication and Their Pros and Cons

Approaches	*Benefits*	*Drawbacks*
Accelerated shear homogenization	Generation about micro dispersions using solid lipid. Widespread distribution and ease of handling	Breakdown of powder, particularly for delicate or heat-sensitive powders Excessive wetting leads to sizable lumps forming, resulting in less granular compressibility.
Thermal homogenization	SLN-suspended particles formed avoiding the need of solvents.	Deposition of medications through nanotechnology. Lack of polar drug encapsulation Not appropriate for pharmaceutical compound that react to heat Minimal concentration of drugs in the SLN
Refrigerated homogenization	Tackling an array of issues related to thermal homogenization greater dimensions of particles as well as a wider range of dimensions	An operation consuming an excessive amount of effort Dispersions of polydisperse Lack of sustainability
ultrasonic vibration Homogenization	Usual across all laboratory	Increasingly distributed tiny particles that cross the micron level
Emulsification/ Evaporation	Remain cautious of warmer temperatures	Toxicity problems due to solvent residues
Micro emulsion formats: (1) strategy for dispersing micro emulsion; (2) strategy for freezing micro emulsion	Spontaneous Low-energy required Efficient Scalable Biocompatibility Economical	Opaque in nature
Super critical solution	Excellent absorption efficacy of compounds with supercritical CO^2 Solution having a large compression factor which includes liquid and gas characteristics	Restricted
The dual emulsion technique	Straightforward Suitable for managing parameters used in processing Protecting pharmaceutical compounds that are polar and highly lipophilic	Particles of enormous size can be produced with this method of production.
Spray evaporation	The capacity to adjust and manage a range of characteristics The preferred technique for drying a variety of materials that are heat-sensitive	Irregular Non-spherical
Solvent based methods	Acquire compounds that have issues with equilibrium and bioavailability. Lukewarm activity	
Precipitation technique	Affordable Capability to regulate SLN size Preparation of microspheres and microcapsules	Particle size is influenced by lipid concentration
Evapo-diffusion	Scalable Use less energy	Outdated Explore more about solvents made from organic materials Enquire regarding excessive amounts of lubricants. Complicated
Phase transition temperature technique	Significant Greater tolerance Specificity Polydispersity	Very limited applications for thermosensitive molecules.

Membrane contactor technique	Easy Rapid 3. Scalable	to cross-link rarely A modest number of particles are produced. Utilizes a substance
Electrospray	Easy Affordable Safe Effortless	-
Green technologies	Easy Affordable	Fine-tuning Regulation of crystal structure and morphology
Solvent infusion techqniue	Effective Adaptable Straightforward Produces both hydrophobic and hydrophilic Progressive	Organic solvents and is not easily scaled up

availability, bioinertness& lower potential toxigenicity.[10,109-111] Nanotechnology performs a decisive taskin reducing adverse effects and improving the targeted transportation of plant-based items.[112-114] Recently, SLNs have garnered focus in the field of medication distribution,[115] aiming to improve the effectiveness[116-118] and boost the efficiency of oral drug uptake [119] of indigenous plant based drug. Additionally, SLNs serve as reliable carriers for phytoextracts, exhibiting improved anti-oxidant capacity.[120]

Artesunate (a derivative of artemisinin), extracted from Artemisia annua, is a well-known herbal remedy prescribed for malaria treatment. Artemisinin-based combination protocols have recently been generated to enhance efficiency and minimize side effects in malaria treatment. Numerous studies have utilized SLNs formulations as vehicles for antimalarial medicines, including artemisinin.[121] Artesunate and other artemisinin derivatives are incorporated using other economic medicines for improved efficacy.[122,123] Combination therapy, such as the encapsulation of artemether and lumefantrine in SLNs, is now desired a cross-single-drug therapy for plasmodium infection.[124] To illustrate, Attama and contributors.[38] Artemether and lumefantrine, which are used to treat malaria, were encapsulated using SLNs. The mentioned approach aimed to reduce adverse effects, increase absorption rate, and address pharmacokinetic disparities. SLNs were tagged with coumarin 6 to monitor cellular absorption within *Plasmodium*-infected cells. Animal trials demonstrated a significant reduction in parasitemia alongside decreased adverse effects, suggesting that SLNs hold promise as a technique to improve the efficacy of malaria combination therapy. Dwivedi and other colleagues.[39] Developed SLNs were used to administer another artemisinin derivative, arteether (ART). The effectiveness of the ART-SLNs preparations was assessed by determining its encapsulation efficiency with high-performance liquid chromatography. Cytotoxic changes were assessed using MTT analysis on the J774A.1 cellular lineage reveals a biological cell potential above the 90% mark. DHA, a subclass of artemisinin, was encapsulated into nanocarriers in a study by Omwoyo and colleagues[37] in order to evaluate its antimalarial activity and get over obstacles, including poor water solubility and adverse pharmacokinetic properties. The single-emulsion solvent evaporation and fast speeds homogenization techniques used to create the SLNs impregnated with DHA showed a dimension array ranging from 150 to 500 nm. The formulations exhibited endurance and continual drug release for up to 90 days and across 20 hours. In an animal model and under experimental conditions experiments showed an IC50 of 97.24% chemo-suppression at 2 mg/kg/day with 0.25 ng/ml. These results underscore the excellent potential of SLNs formulation for clinical applications.

Recently, several reports have highlighted resistance against artemisinin.[125-128] Luteolin, a biologically active substance, has emerged as a potential solution to eliminate artemisinin-resistant *P. falciparum*.[129] Luteolin disrupts the parasite's life cycle by inhibiting lipid synthesis, impeding the generation of novel cell components and the growth of juvenile trophozoite (ring stage).[130, 131] Due to the admirable physiological compatibility of luteolin, it has been injected into SLNs- polyethylene glycol with thermal or freeze homogenization and hot-microemulsion ultrasonic methods.[40] Consequently, the Antioxidant compound encased by SLNs using polyethylene glycol adjustment demonstrated the enhanced proportional bioavailability, reduced spreading, and endorsement regarding the segment.

T. gondii et al., further endemic protozoan parasites, is a target for the creation of novel treatments. Nemati and other.[30] grown nimbafat-coated SLN with the dual emulsification technique & assessed their toxoplasma eradication. The study findings revealed that SLNs, assuming the role of lipid vesicle transporter for neem oil, extended extract delivery, exhibited decent Toxoplasma inhibition and minimal cytotoxic effects.

Chitosan (CS), a native biological polymer made up of NAG and glucosamine units, possesses intriguing aspects and finds wide-ranging drug applications, notably in drug delivery.[132,133] Recently, Novel formulations that combat germs by using organic sources and non-toxic chemicals have drawn more and more attention.[134] CS is establishing itself to be a viable method of delivering and coating several types of nanoparticles, such as solid lipid nanoparticles.[135,136] Chitosan-loaded SLNs

have been effectively developed to manage various health conditions.[22,137,138]

Inverse effects of chitosan opposed to parasites such as *Leishmania, Trichomonas, Plasmodium*, and *Toxoplasma* have been noted.[139] Teimouri *et al*.,[140] demonstrated the high effectiveness of CS against *T. gondii*, proposing its use as substitute native drug in toxoplasmosis therapy. In a mouse peritoneal cavity, the rate of expansion decreased by RH strain microorganisms, which was shown to be completely mortal in an animal model under experimental settings. *P. berghei* was significantly affected by CS as well, showing possible antimalarial action at various doses. Using CS encapsulation to prevent chloroquine (CQ) from being effluxed from the parasite's acidic digestive vacuole, male Swiss mice with *P. berghei* infection were less susceptible to nanoparticle chloroquine (NCQ) infection. The nanoformulation demonstrated greater potency in protecting against DNA damage, oxidative stress, and inflammation in infected mice.[41]

Chitosan's antiprotozoal action was underlined against trophozoites of the parasite *Trichomonas gallinae*, exhibiting a high mortality rate and inhibiting trophozoite viability compared to the control group.[142,143] Yet, limited investigation has investigated chitosan's union using SLNs in parasitical contagions. Furthermore, CS has demonstrated laboratory-based anti*Leishmania* action with a 50% effective concentration (EC50) as opposed to motile and non-motile models of various *Leishmania* species.[144-147] Recent findings also suggest therapeutic and vaccine purposes for chitosan and its derivatives in treating and preventing skin-related and gut *Leishmania* together. Market-oriented CS is proposed as a suitable prospect for extended analysis on skin-related and gut *Leishmania* medication.

In an investigation,[36] chitosan-loaded SLNs were applied as an immune modulator cytotoxic treatment for *Leishmania*l disease. The mixture of SLNs using chitosan as a novel synthetic resin, coated with an antifungal drug, caused macrophage enabling, triggering host defenses like Cytokine TNF and cytokine IL12 instead of *Leishmania*. The formulation of SLNs was carried out with the solvent emulsification-evaporation method, and cell-toxic investigation in mice uncovered proper well-being data. The results indicate the entity AmB-SLNs, as a secure and efficient medicament dosage system, could be valuable in anti*Leishmania*l treatment and Immunologic therapy.`

Medicinal Effectiveness of Anti*Leishmania*l Drugs Encapsulated in SLNs

In order to enhance the therapeutic qualities and effectiveness of commercial antiparasitic medications, such as praziquantel,[98,101] paromomycin,[29,32,34,35] nitazoxanide,[148] tanespimycin (17-AAG),[31] and AmB,[32,36,149] investigations have utilized SLNs to serve as a vehicle.

Protozoans

Accessible information points to adverse effects, virulence, and resistance to trade medicines in various parasitical protozoan transmission.[150,151] To address the drawbacks of existing substances for parasitical protozoa transmission, Lipophilic preparations have been proposed to improve therapeutic agent absorption rate and efficiency.[152,153] Parvez and others[32] Planned a therapeutic agent-transmission structure to reduce therapeutic agent harmfulness and enhance absorption of Amphotericin B and Post-meridiem as opposed to core *Leishmania*sis through orally controlled double drug solid lipid nanoparticles. These solid lipid nanoparticles, altered using 2-hydroxypropyl beta-cyclodextrin, demonstrated decreased toxicity and adverse effects and improved efficiency balanced with lipid-based models. The 2-hydroxypropyl beta-cyclodextrin alteration enhances SLNs' engage by afflicted phagocytes, inhibiting intracell non-motile stage progress.[32] Additionally, B12-stearic acid complex-coated Amphotericin B-loaded SLNs were developed to improve oral transportation absorption and AmB utilization,[33] achieving an efficiency of up to 94% using lower toxic. Adjustment of molecular chaperone 90 kDa was suggested to suppress the progress of *Leishmania* spp.[154] Pires *et al*.[31] loaded SLNs with tanespimycin (17-AAG), an Hsp90 inhibitor, demonstrating potential as delivery systems for eliminating intracellular *Leishmania*. Kharaji *et al*.[34] developed PM sulfate-loaded SLNs that were opposed to L. major and L. tropica, showing enhanced effectiveness using lower toxicity. Heidari-Kharaji and others.[35] reported the safety and efficacy of post-meridiem opposed SLN preparations counter to L. major in infected BALB/c mice, suggesting its use in treating cutaneous *Leishmania*sis. Additionally, Khosravi *et al*.[29] created post-Meridiem mannosylated SLNs at larger dosages than PM and showed strong anti-intracellular *T. gondii* activity and minimal cell damage.

Helminths

Categorization of anthelmintic drugs according to their mode of action.

Helminths is a eukaryotic organisms with intricate structures with the muscular system, nervous system, digestive system, and reproductive system), can affect various human tissues, including the liver, blood, and intestine.[156] Clinically, helminths are categorized into the following classes: cestodes (tapeworms), nematodes (roundworms), and trematodes (flatworms), distributed worldwide.[157]

Anthelminthic drugs disrupt the cell morphology, rigidity, metabolism, and Neuromuscular tones of helminths, leading to damage and expulsion from the host's intestine.[158,159] anthelmintics are categorized into anticestodal, antinematodal, and antitrematodal medicines according to their mode of action. Helminthicide medicines could react using gluconeogenesis and respiratory enzyme modulation, which may lead to neuromuscular action being blocked. The following action can lead to the render in the susceptible to the immune cells of the host.[160-163]

Metabolism disruption

Benzimidazoles (BZD) which are albendazole (ABZ), mebendazole, thiabendazole, and triclabendazole are a group of agents with improved therapeutic efficacy used against various

parasitic worms such as *A. lumbricoides, T. trichiura, E. vermicular*, *Necator americanus,* and *Ancylostoma duodenale*. They primarily inhibit tubulin polymerization, interfering with gluconeogenesis and microtubule polymer formation. This damages cytoplasmic tubulin filaments, impairs glucose assimilation in juvenile and mature parasite phases and significantly consumes parasite glycogen by mebendazole.[164] Niclosamide treats tapeworms by inhibiting oxidative phosphorylation and transportation of electrons, impairing Adenosine triphosphate production.[165] The nerve system and the glycolytic pathway of *F. hepatica*, may be affected by Clorsulan, which inhibit phosphoglycerate kinase.[166,167] The well-known antibacterial and anthelmintic agent, Bithionol, may interfere with the production and formation of ATP oxidative phosphorylation, resulting in the inhibition ATP formation in parasites.[164]

Nervous and muscular system disruption

Imidazothiazoles, nicotinic anthelmintics, act as acetylcholine receptor agonists, may leads to the flaccid paralysis of worms causing by inhibiting neuromuscular depolarization. Piperazine mimics GABA receptor-blocking Cl channels (a family of chlorine channels), inhibiting motor neuron activation in soil-transmitted helminths (STH). Tetramisole, Pyrantel-pamoate, and Morantel-tartrate target nicotinic AChRs, resulting in spastic paralysis. Pyrantel pamoate, broad-spectrum anthelmintic, having the therapeutic action of degenerating neurological and muscular blockers, paralyzing parasitic organisms by releasing Acetylcholine and inhibiting cholinesterase.[159]

Cell Membrane Integrity and Destruction

mostly, anthelmintic drugs act by inhibiting cell- wall outer layer usually, the protective layer and paralyzes helminths by causing intracellular Ca^{2+} leakage. In cestodes, anthelmintic medication causes paralyzing muscle effects and tegumental dysfunction. Following PZQ treatment, teguments disruption occurs due to a significant influx of Ca^{2+}, resulting in death and expulsion.[172-174] When used to treat loiasis, filariasis, and tropical eosinophilia, diethylcarbamazine immobilizes bacteria and modifies their surface structure, which causes them to move from tissues and improve their interaction with the immune system.

Therapeutic effectiveness of anthelmintic drugs encapsulated in SLNs

Various groups of anthelminthic drugs are developed, each tailored to address specific classes of helminths. For example, the recommended treatment for tapeworm infections and schistosomiasis is praziquantel, whereas the main medications for soil-transmitted helminths are mebendazole and albendazole. Furthermore, ivermectin and diethylcarbamazine are used to treat filarial infections.[175]

Gastrointestinal absorption sites for anthelmintic drugs and role of SLNs

Anthelmintic drugs exhibit distinct absorption sites in the gastrointestinal tract.[176] Mebendazole accumulates in the intestine, targeting the enormous gastrointestinal worms like whipworms, hookworms, and ascarids.[177] In contrast, pyrantel pamoate, chosen for ascariasis, hookworm, pinworm, along with trichostrongyliasis infections, is within the lumen of the intestine.[159] Currently, available anthelmintic medications have issues with quick disintegration, low absorption, and insoluble in water.[178] Specific administration using a combination of traditional treatment and nano carriers has been utilized to tackle these problems and fight anthelmintic resistance.[179-180] High surface-to-volume ratio nanoparticles enhance dissolution rates and surface area, overcoming solubility and bioavailability limitations. Small and large intestine helminths utilize lipids from digestive fluid for metabolic activities, making SLNs exhibit marvelous lipid carriers for anthelmintic drugs like albendazole (ABZ), praziquantel (PZQ), and albendazole sulfoxide (ABZS).[181-185]

Enhancing Anthelmintic Efficacy through SLNs Formulation

Ivermectin and nitazoxanide (NTZ) serve as potent anthelmintic drugs, extensively utilized for trichinosis treatment.[148] Anticipating future drug resistance, the need for novel, stable, and biocompatible therapeutic agents has emerged. Hassan and other researchers prepared SLNs brimming using nitazoxanide utilizing a modified thin-film hydration method, demonstrating increased effectiveness toward the muscular and intestinal stages of trichinosis in murine hosts.[148] This approach, commonly employed for liposome preparation, holds promise for enhancing drug delivery.

Albendazole (ABZ), a widely used and prescribed benzimidazole for various Worm infections, has demonstrated efficacy against various helminths.[103] Sharma along with additional researchers produced SLNs laced with ABZ to combat the GI parasitic organism worm the human parasite (Ha) contortus. Utilizing a double emulsion technique, this formulation aimed to enhance ABZ effectiveness, reducing required dosage and minimizing side effects.[103]

Hydatidosis, caused by Echinococcus tapeworm larvae, is typically treated with benzimidazole derivatives. ABZ, being lipophilic, is effective against cystic echinococcosis (CE). However, systemic side effects pose challenges. A study focused on the SLN loaded with ABZ and ABZ sulfoxide formulations to improve agents permeation across hydatid cloned membranes, demonstrating enhanced release, improved conductivity and efficacy in contrast with standard drugs.[100] Ultrastructural changes were investigated, showing increased effectiveness of SLNs-loaded Albendazole and Albendazole sulfoxide in tiny, fertile cysts.[99]

Toxocara canis and *T. catis* are the causes of the disease toxocariasis, is treated with ABZ. Kudtarkar *et al*. employed by the lipid nanoparticles to prepare ABZ-loaded SLNs, exhibiting effective drug delivery and therapeutic outcomes in animals harboring *T. canis* worm infection. [105]

Abedi along with additional researchers created Electromagnetic SLNs loaded albendazole, incorporating (Fe_3O_4) NPs as carriers to enhance efficient drug delivery.[182]

These advancements in SLN formulations showcase their potential to improve anthelmintic drug efficacy.

Optimizing Praziquantel (PZQ) Efficacy Through Nanoformulation

Despite reported disadvantages such as poor water solubility with low digestive system penetration, along with the requirement over substantial dosages,[186] PZQ remains a first line medication to worm pathogens with the recommended option for schistosomiasis chemotherapy.[187-189] However, its effectiveness is compromised in high-endemic areas, particularly during oral administration. Nanoformulations of PZQ have been explored to address these challenges.

The intestinal penetration, toxic effects, and effectiveness of PZQ-loaded SLNs towards adult *S. mansoni* were evaluated by Souza *et al*.[98] With reduced cellular toxicity than free PZQ, the spherical PZQ-SLNs, measuring 500 and 1000 nm, showed improved efficacy against *S. mansoni* by the use of high-shear homogenization and micro-emulsification techniques. This points to PZQ-loaded SLNs as a possible method of controlling schistosomiasis.

Similar to this, PZQ-SLNs were developed by Radwan *et al*. [97] to improve absorption and antischistosomal effectiveness towards *S. mansoni* infection in mice. The SLN formulations were made by homogenizing at high shear and micro-emulsifying, exhibited sizes ranging between 87.32 and 302.3 nm. Treatment with SLNs-PZQ significantly reduced the number of worms and total mature eggs in *S. mansoni*-infected mice, indicating improved therapeutic outcomes. Pharmacokinetic assessments further demonstrated increased PZQ absorption among individuals infected with *S. mansoni*.

Xie and colleagues [102] employed a novel strategy to increase treatment efficacy against dogs infected with E. granulosus: they loaded PZQ inside hydrolyzed castor oil-SLNs. Utilizing heat homogenization and ultrasonication procedures, the study found that PZQ with SLNs exhibited improved therapeutic activity, even at a lower dose of 0.5 mg/kg compared to the clinical application dose of 5 mg/kg. The average nanoparticle size was 263.00 ±11.15 nm.

Andrade[101] for the purpose of treating *S. mansoni* infections, SLNs loaded with PZQ were created using the high-cut homogenization approach. A study using SEM microscopy revealed spherical PZQ-loaded SLNs that ranged in size from 500 to 1000 nm. PZQ-loaded SLNs exhibited outstanding parasiticidal activities against mature *S. mansoni* worms *in-vitro*, highlighting their potential to optimize treatment outcomes.

Future perspectives in nanodrug formulation for parasitic diseases

As we witness the emergence of novel drugs, the nano technology and nano science are the more emering fields spanning a wide spectrum of communicable and non-communicable diseases. Nanoparticles, or materials at the nanoscale, have gained popularity due to their best-suited approaches and ease in drug delivery, leading to a significant rise in interventional studies exploring nanoparticle-based medications. Site-particular medication administration holds the promise of reducing systemic toxicity, overcoming certain distribution, and addressing disadvantages associated with conventional drugs.

Moreover, the progression in nanomaterial-based drug delivery systems for parasitic infections remains a priority for ongoing research. Clinical trials utilizing SLN based formulations for the cure of parasitic diseases are limited, highlighting the need for an expanded arsenal of nanodrugs tailored to combat these infections. Furthermore, in tandem with advancements in herbal medicine, SLN formulations present an alternative avenue to enhance particular distribution and mitigate the detrimental impacts of phyto lysates and their ingredients.

The utilization of SLN formulations in immunizations stands out as a potential focus for future research. Incorporating SLNs with adjuvants has the potential to boost immune system reactions during immunization, This may prolong exposure to the immune system, enhancing overall immunogenicity, especially given the instant disruption of adjuvants in the body.

Despite the rapid progress of novel drug approach and its applications in nanodrug formulation, a growing disparity exists between developed and developing countries. Limited facilities and technology in poor countries impede their effective participation in building up nanotechnology-based drugs to meet their specific needs. To bridge this gap, several suggestions are proposed: fabricating budget- friendly novel medications with minimal cost of higher consistency and efficacy of administration; involving non-governmental organizations in investing and providing resources for designing and fabricating effective nanodrugs; utilizing cost-friendly components like Plant- based extraction and technological advances to reduce the overall expense for developing new medications to combat infections caused by helminths and developing a central corporation for help research and development forfuther approaches innovations, thereby increasing the accessibility of nanodrugs in less-developed regions to address their unique challenges.

CONCLUSION

In conclusion, the application of SLNs as nano vehicles for antiparasitic drugs presents a promising avenue in the field of pharmaceutical drug delivery systems. The spectrum related to illnesses caused by parasites, ranging from mild to severe, necessitates innovative and effective drug delivery systems. SLNs, characterized by their optimal discharge ratio, and reliable passage, emerge as viable surrogates among nanocarriers. The review delves into the evolution of SLN development, emphasizing preparation methods, characterization techniques, and the incorporation of drugs to combat parasitic diseases. The advantages of SLNs, including their higher area of the surface, enhanced reliability, and higher drug delivery attributes, contribute to improved therapeutic efficacy. Their potential to deliver natural antiparasitic products is particularly noteworthy, offering a sustainable approach for

the management of parasitic infections. Recent advancements in utilizing nanoparticles to enhance SLN stability and loading capacity underscore the dynamic nature of this field. The comprehensive overview of SLN structures, applications, and characterization methods provides valuable insights into the evolving landscape of antiparasitic SLN-loaded drugs. As nanotechnology performs a fundamental task in biomedicine, integrating SLNs as carriers in favor of antiparasitic drugs opens up new possibilities for efficient and targeted treatment. The successful development of SLN-loaded drugs could potentially address the challenges posed by conventional chemical drugs, offering a safer and more effective alternative in the fight against parasitic infections. This review contributes to the ongoing dialogue on nanotechnology's role in advancing drug delivery systems for parasitic diseases and underscores the importance of continued research in this area.

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