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Review Article

# Recent advances in oral delivery of drugs and bioactive natural products using solid lipid nanoparticles as the carriers

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ABSTRACT

Chemical and enzymatic barriers in the gastrointestinal (GI) tract hamper the oral delivery of many labile drugs. The GI epithelium also contributes to poor permeability for numerous drugs. Drugs with poor aqueous solubility have difficulty dissolving in the GI tract, resulting in low bioavailability. Nanomedicine provides an opportunity to improve the delivery efficiency of orally administered drugs. Solid lipid nanoparticles (SLNs) are categorized as a new generation of lipid nanoparticles consisting of a complete solid lipid matrix. SLNs used for oral administration offer several benefits over conventional formulations, including increased solubility, enhanced stability, improved epithelium permeability and bioavailability, prolonged half-life, tissue targeting, and minimal side effects. The nontoxic excipients and sophisticated material engineering of SLNs tailor the controllable physicochemical properties of the nanoparticles for GI penetration via mucosal or lymphatic transport. In this review, we highlight the recent progress in the development of SLNs for disease treatment. Recent application of oral SLNs includes therapies for cancers, central nervous system-related disorders, cardiovascular-related diseases, infection, diabetes, and osteoporosis. In addition to drugs that may be active cargos in SLNs, some natural compounds with pharmacological activity are also suitable for SLN encapsulation to enhance oral bioavailability. In this article, we systematically

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introduce the concepts and amelioration mechanisms of the nanomedical techniques for drug- and natural compound-loaded SLNs.



## 1. Introduction

Oral delivery is the most accepted drug administration route among the various delivery pathways because of its advantages: painlessness, easy self-administration, high patient compliance, and feasibility for outpatients [1]. Nevertheless, chemical and enzymatic barriers in the gastrointestinal (GI) tract hinder the effectiveness of oral drug delivery. The epithelial cell monolayer in the GI membrane also contributes to poor permeability for numerous drugs [2]. Some poorly soluble drug molecules are difficult to dissolve in the GI tract, resulting in low bioavailability. Novel and sophisticated drug delivery systems are necessary to conquer these limitations. By optimizing the formulations, the delivery efficiency and bioavailability can be ameliorated to promote the therapeutic potency with reduced side effects. The oral delivery improvement using nanocarrier systems has gained more attention recently [3]. Nanoparticles are defined as particles ranging in size from 1 nm to several hundred nanometers that can load drugs for efficient delivery. The drugs or actives can either be integrated in the core or matrix or attached to the surface of nanoparticles that have a high surface/volume ratio [4]. With respect to pharmacokinetics, the drugs in nanocarriers generally revealed prolonged circulation time, increased half-life, reduced clearance, and increased mean residence time (MRT) [5].

Among the different types of nanocarriers, solid lipid nanoparticles (SLNs) are at the forefront of the potential application in oral drug delivery systems [6]. SLNs are nanocolloids developed at the beginning of the 1990s by Schwarz et al [7]. They are used as alternative carriers to conventional colloids such as emulsions, liposomes, and polymeric micelles. Basically, SLNs are made of a solid lipid core with a monolayer phospholipid shell. The lipophilic moiety of phospholipids is embedded in the lipid matrix (Figure 1). Many drugs or diagnostics can be entrapped by SLNs, especially lipophilic ingredients [8]. The use of SLNs for oral administration is a promising approach for enhancing and controlling drug delivery. The solid state of the nanoparticulate matrix provides protection to chemically labile drugs and prolongation of drug release. SLNs show low cytotoxicity to mammalian cells, demonstrating an acceptable tolerance to the body. SLNs can be orally administered as aqueous dispersions or in the dosage forms of capsules, tablets, and pellets [9]. With the evolution of nanomedicine, the application of SLNs is expected to change the landscape of oral delivery. In this review, we highlight recent advances in the application of SLNs for oral delivery of drugs and bioactive natural compounds. We focus on the reports of SLN development during the past 5 years of orally administered drugs for therapy against cancers, central nervous system (CNS) diseases, cardiovascular (CV) diseases, bacterial/viral infection, and inflammation. The promising perspective in this emerging application is also discussed.

## 2. Nanocarriers for the oral route

The drugs should go through the stomach, intestinal lumen, the mucus membrane coating the intestinal epithelium, and finally the epithelium itself after oral administration. The inside of the stomach is composed of four layers; from the innermost layer to the outermost layer, these are the mucosa, submucosa, muscularis externa, and the serosa. The stomach is lined by a mucous membrane that contains glands (with chief cells) that secrete gastric fluid. The intestinal epithelium is made up of villi that vastly increase the surface region available for drug absorption [10]. Absorptive enterocyte cells and mucus-secreting goblet cells cover the villi, which are interspersed with the follicle-associated epithelium. The physiology of the GI tract can lead to poor absorption and availability of the drugs or actives because of the low mucosa permeability and drug degradation prior to absorption [11]. The multidrug efflux proteins such as P-glycoprotein rich in the epithelial cell membrane are another barrier for orally administered drugs. Some drugs or active ingredients show low aqueous solubility, and a high hepatic first-pass effect also limits GI absorption. The additional oral permeation challenges are chemical instability, a short half-life, and the effect of food [12]. Figure 2 summarizes the barriers and challenges for efficient oral delivery for administering drugs.

Nanomedicine offers improvement of oral delivery by bioavailability enhancement, adverse-effect minimization, and food-effect mitigation [13]. The nanocarriers can increase the dissolution rate of poorly soluble molecules in the GI tract. The poor stability in the GI tract can be overcome by

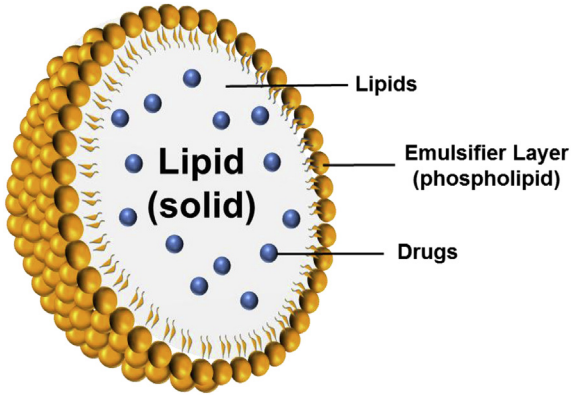


**Figure 1 – Structures of solid lipid nanoparticles (SLNs).**

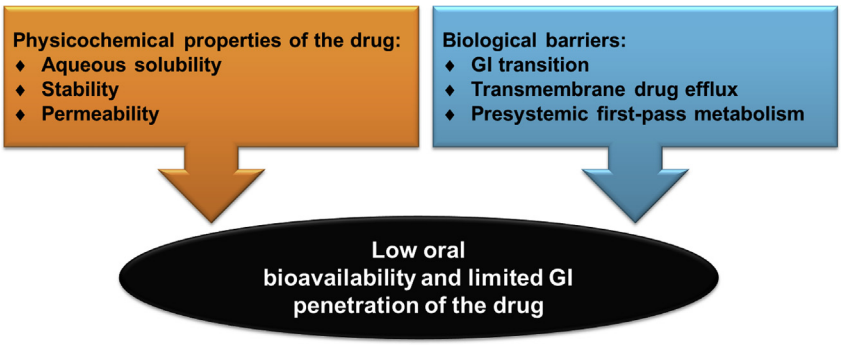


**Figure 2 – Schematic diagram of the challenges for oral drug delivery. GI = gastrointestinal.**

encapsulating the drugs in nanocarriers, thus rendering a protective impact toward chemical and enzymatic attacks in the tract. The designed nanocarrier systems provide intimate contact with the GI epithelium, prolonging residence time and revealing permeation enhancement for drug delivery [14]. The nanoparticles can at least to some extent transport into the mucus layer, releasing the payload. A presystemic metabolism functioning between the delivery system and the absorption membrane can thus be excluded. The nanocarriers are designed to modulate dimension, size, surface charge, surface property, and relative lipophilicity for preferentially penetrating across the GI membrane. Figure 3 illustrates nanocarrier strategies for ameliorating drug absorption across the GI tract.

Lymphatic drug delivery in the intestine is an alternative approach to bypassing first-pass metabolism. The lymphatic system forms a channel network throughout the body similar to blood circulation, but it is a one-way passage. The predominant categories of conduits in the lymphatic system are the capillaries, collecting vessels, lymph nodes, and ducts [15]. The total lymph flow amount is about 120 mL/h. The lymphoid system is found to be an efficient route for oral administration of lipids across the intestinal membrane. The lipid-based nanoparticles are considered to favorably transfer into the lymph [16]. The nanoparticles reach the lymphatic system via microfold cells (M cells). The enhanced lymphatic delivery decreases the first-pass effect and improves oral bioavailability owing to the lymph vessels draining directly into the thoracic duct and farther into the venous blood [17].

## 3. Structure of SLNs

SLNs are colloidal systems made up of a solid lipid core matrix, which is stabilized in aqueous solution by emulsifiers.

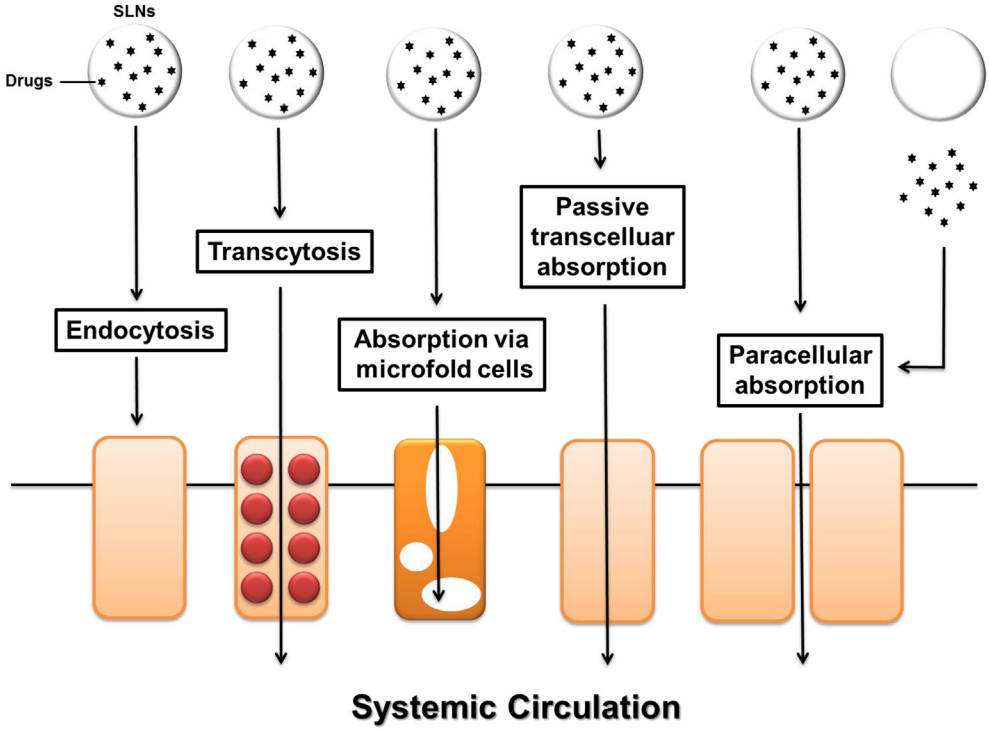


**Figure 3 – Schematic diagram of various routes for oral delivery of solid lipid nanoparticles (SLNs).**

This nanosystem provides advantages as a drug-delivery carrier, including stability, controlled release kinetics, tolerability, and protection of labile drugs [18]. The solid lipids commonly used in SLNs are glyceride mixtures, highly purified glycerides, or waxes that do not melt at body temperature. The safety of oral nanoformulations is a serious concern for their application [19,20]. A prerequisite for a new drug or formulation discovery is the confirmation of its safety when administered to the body. A balanced efficacy and safety is necessary when developing the nanomedicine for therapeutic application. The SLNs are developed by solid lipids and emulsifiers generally recognized as safe with respect to biocompatibility and nontoxicity. The lipid matrices are the natural or synthetic lipids that can be degraded, including triglycerides (trimyristin, tripalmitin, and tristearin), glyceryl monostearate (Imwitor), glyceryl behenate (Compritol 888 ATO), glyceryl palmitostearate (Precirol ATO 5), hard fat types (Witepsol), fatty acids (decanoic acid, palmitic acid, and stearic acid), waxes (cetyl palmitate, beeswax, and carnauba wax), and steroids (cholesterol) [8,21]. The drugs can be embedded in the voids of solid lipid matrix crystals. SLNs can encapsulate both lipophilic and hydrophilic drugs. Drug entrapment in the matrix depends on the types of solid lipids, drug solubility in the lipids, processing techniques, and polymorphic change in lipid crystals [22]. The emulsifiers or surfactants usually used for stabilizing the interface between the SLN shell and the aqueous medium are phospholipids (egg lecithin and soy lecithin), nonionic surfactants (Poloxamer, Pluronic, Brij, Tween, and Span), ionic surfactants (sodium cholate, sodium lauryl sulfate, stearylamine and trimethylammonium bromide), polyethylene glycol (PEG), and polyvinyl alcohol [23,24]. The lipids and surfactants are the two main materials used in SLNs. The materials cited in this section are basically safe for application.

Most of the materials for preparing SLNs are low cost with ease of scale-up for industrial production [25]. The solid lipid should be melted during the preparation process and then recrystallized at room temperature. There are several preparation methods for SLN production from the laboratory scale to the industrial scale. These include hot homogenization, high-pressure homogenization, ultrasonication, solvent evaporation, solvent emulsification–diffusion, microemulsion, double emulsion, supercritical fluid technique, and spray drying [26]. Figure 4 shows the preparation procedures

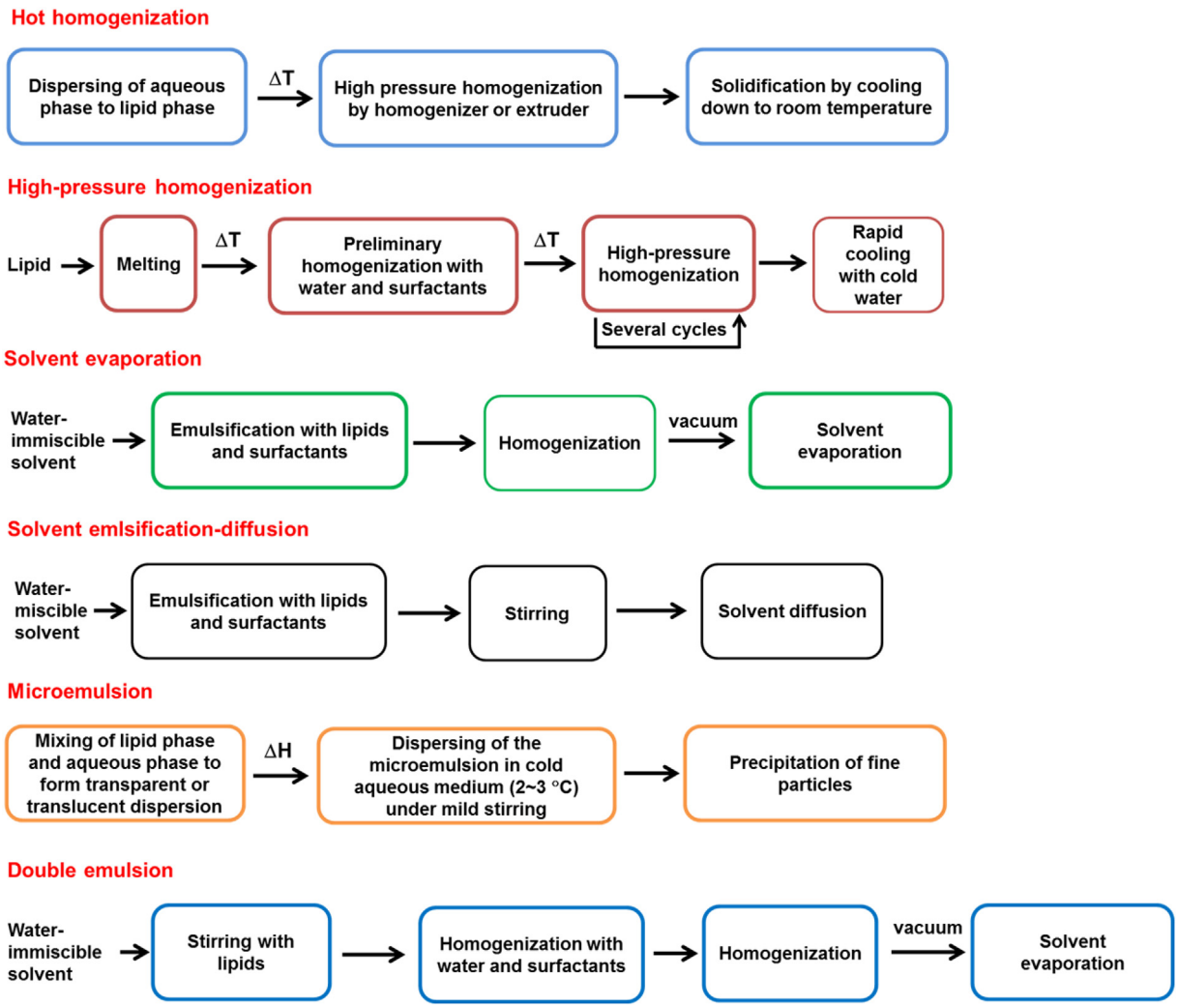


**Figure 4 – The general methods for preparation of solid lipid nano particles (SLNs).**

of some methods. The physicochemical characterization of SLNs after preparation is a critical step for quality control and prediction of stability, drug release, and therapeutic efficacy. Photon correlation spectroscopy can be used to determine the particulate diameter, polydispersity, and zeta potential of SLNs [27]. The imaging systems such as scanning electron microscopy (SEM), transmission electron microscopy, and atomic force microscopy are the tools used for observing the particulate size, surface morphology, and particle shape. The crystalline confirmation of the lipids inside SLNs significantly affects the drug loading and stability. The polymorphism of the lipids is detected by X-ray diffraction, wide-angle X-ray scattering, and X-ray photoelectron spectroscopy [28]. Differential scanning calorimetry and Fourier transform infrared spectroscopy are used to identify the drug–matrix interaction.

## 4. Application of SLNs as oral delivery systems

The drugs or actives should be solubilized to be absorbed by the GI system. In the lipid-based SLNs, the drugs are absorbed from the nanoformulations in the solid state [18]. Digestion of oral nanoparticles containing glycerides starts in the stomach by gastric lipase. The mechanical mixing of gastric fluid with amphiphilic products of lipid digestion results in the formation of crude emulsion. The SLNs are further digested in the intestinal fluid. The degradation products of lipids such as monoglycerides and fatty acids are able to promote intestinal drug transport by the production of mixed micelles with bile acids and subsequent uptake into the enterocytes [29]. The enormous effective surface area by virtue of the nano-sized SLNs can lead to an increased absorption rate. The tiny size of SLNs permits them to adhere to the GI mucus and also to enter the intervillar space, thus increasing the residence period for improved bioavailability. The surface-active capability of the emulsifiers can augment the drug absorption via the GI tract because of the altered GI membrane fluidity [30]. Cationic SLNs composed of cationic surfactants or lipids can be designed to ameliorate bioadhesion mediated by electrostatic interaction between the positively charged nanoparticles and the negatively charged mucosal surface [31]. SLNs have unique characteristics that make them promising candidates for lymphatic delivery of orally administered drugs [32]. The effect of emulsifiers on the preferential uptake of SLNs by Peyer's patch also improves the bioavailability of the oral drugs because of avoidance of first-pass metabolism.

SLNs can be digested in the GI tract. Thus, no translocation of intact nanoparticles to the circulation and other organs can be detected. Cai et al [32] demonstrated that no evidence supports absorption of integral SLNs via oral delivery. Contrary to this result, the *in vitro* experiment of SLN transcytosis into Caco-2 cell monolayers had suggested the transport of intact SLNs to the basolateral membrane side [33]. The internalization of SLNs is mediated via macropinocytosis, clathrin, and caveolae pathways. Li et al [34] reported that oral SLNs can be absorbed as intact nanoparticles through Peyer's patch and M cells in lymphoid follicles, especially in the ileum and colon.

## 5. Oral delivery of SLNs for treating various diseases

Recent applications of oral SLNs include therapies for cancers, CNS-related disorders, CV-related diseases, infection, diabetes, and osteoporosis. The use of SLNs provides enhanced bioavailability and controlled drug release. Such ubiquitous properties arise from the specific features of surface modification, increased GI permeation, and resistance to degradation [35]. The following describes the different therapeutic approaches of oral SLNs for drug and pharmacologically active ingredient therapy. The pharmacokinetics, tissue distribution, and pharmacodynamics of the nanoparticles are the main evaluation platforms used to define the therapeutic effect for our description.

### 5.1. *Cancers*

Nanomedicine is an efficient approach to promote the therapeutic benefit of anticancer drugs [36]. Intravenous drug administration for cancer therapy is inconvenient and painful for patients, leading to the requirement of regular hospital visits and low patient compliance. Oral chemotherapy would be preferable to intravenous delivery because it offers the benefits of improved compliance, low cost, and increased quality of life. Unfortunately, most anticancer drugs are not readily bioavailable via the oral route because of the harsh environment and permeation barrier of the GI tract [37]. For example, the oral bioavailability of paclitaxel has been found to be <1% [38]. Paclitaxel shows effective activity against ovarian, breast, and lung cancers as well as Kaposi's sarcoma. The oral availability of this drug is limited by cytochrome P450 activity and P-glycoprotein in the gut wall and liver [39]. SLNs as oral drug delivery systems are promising to solve the problems of oral anticancer drugs such as poor stability, healthy tissue toxicity, and high incidence of drug-resistant tumors [21].

Materials to improve the therapeutic advantages after oral administration can be applied to the surface of SLNs. Baek et al [40] had developed the surface-modified paclitaxel-loaded SLNs with hydroxypropyl-β-cyclodextrin (HPCD). This dextrin is known to solubilize the drugs and prevent oxidation of lipids [41]. The HPCD-coated SLNs showed a paclitaxel encapsulation percentage of 71% with a mean size of 251 nm. The Caco-2 cell uptake of paclitaxel from SLNs was 5.3-fold greater than the Taxol formulation. The $C_{max}$ and lymph node concentrations of SLNs (1.44 μg/mL and 11.12 ng/mg, respectively) were higher than those of the control solution (0.73 μg/mL and 0.89 ng/mg, respectively) after oral paclitaxel application at 25 mg/kg. Pooja et al [42] prepared wheat germ agglutinin (WGA)-coated SLNs to improve oral paclitaxel delivery. WGA can bind to *N*-acetyl-D-glucosamine and sialic acid presenting on the cell surface throughout the intestine, leading to prolonged residence time [43]. The *in vitro* anticancer activity against A549 lung cancer cells showed a half-maximal inhibitory concentration ($IC_{50}$) of 41 ng/mL and 165 ng/mL for WGA-coated SLNs and free paclitaxel, respectively. After oral administration at 25 mg/kg in rats, the area under the curve (AUC) of plasma concentration–time profiles

was higher for WGA-coated SLNs (30 μg h/mL) than conventional SLNs (16 μg h/mL) and the free control (8 μg h/mL). The inclusion of paclitaxel into WGA-coated SLNs led to doubling of MRT in contrast to the control solution.

Docetaxel is a second-generation taxane extensively used to treat breast, lung, prostate, and head/neck cancers. The development of an oral docetaxel formulation is hindered because of poor bioavailability. SLNs coated with Tween 80 or D-α-tocopheryl poly(ethylene glycol) succinate (TPGS) were prepared to improve the oral delivery of this drug [44]. The SLNs exhibited a sustained docetaxel release compared with Taxotere. The AUC of Tween 80 SLNs, TPGS SLNs, and Taxotere after oral administration (20 mg/kg) was 7.0 μg min/mL, 12.9 μg min/mL, and 3.9 μg min/mL, respectively. The superior bioavailability of TPGS compared to Tween 80 nanocarriers is attributable to the better inhibition of drug efflux by TPGS along with lymphatic uptake. No evidence of intestinal damage was visualized after SLN administration. Doxorubicin is an anthracycline antibiotic that can inhibit various malignant tumors. The major limitations of doxorubicin are its serious cardiotoxicity and hepatotoxicity [45]. Patro et al [46] investigated the oral bioavailability and toxicity of doxorubicin-loaded SLNs with an emulsifier system of soy lecithin and poloxamer 188. The SLNs exhibited increased the $C_{max}$ (6.7 μg/mL vs. 2.4 μg/mL) and reduced clearance (36 mL/h kg vs. 619 mL/h kg) when compared to free doxorubicin. The mean survival time of breast cancer-bearing rats increased from 34 days (positive control) to 47 days and 88 days in the free doxorubicin and SLN groups. Cardiac toxicity measured by the lactic dehydrogenase level was less in the SLN-treated group compared to the free control. Doxorubicin was included in PEGylated SLNs as mucus-penetrating nanoparticles for oral delivery across the GI mucus [47]. Modification of nanoparticles by PEG–stearic acid increased the hydrophilicity of nanoparticles with a rapid mucus-penetrating transport property [48]. The permeation ability of SLNs across the Caco-2/HT29 coculture cell monolayer increased after coating with PEG-stearic acid. The *in vitro* everted rat gut sac technique demonstrated that PEGylated SLNs could facilely penetrate mucus secretions. The pharmacokinetic data showed that the oral bioavailability of PEGylated nanosystems was 2.0- and 7.5-fold greater than conventional SLNs and free doxorubicin, respectively.

Vorinostat is a histone deacetylase inhibitor that efficiently induces cell cycle arrest and apoptosis for the treatment of cutaneous T cell lymphoma [49]. Tran et al [50] examined whether SLNs containing vorinostat could enhance multidrug-resistant cancer cells and oral delivery. The nanocarriers were spherical with a narrowly distributed size of about 100 nm, and were physically stable for at least 3 months. The SLNs were more cytotoxic than the free vorinostat in both sensitive (MCF-7 and A549) and resistant (MDA-MB-231) cells. The $C_{max}$ and AUC values of SLNs were 1.6- and 2.5-fold higher than those of the free drug by oral delivery at 30 mg/kg in rats. Hashem et al [51] evaluated the cytotoxicity and oral bioavailability of SLNs encapsulating tamoxifen, the drug for breast cancer management. The SLNs prepared using glyceryl monostearate and stabilized with poloxamer 188 showed an entrapment percentage of 90% for tamoxifen. The *in vitro* release profiles revealed an initial burst effect followed by a sustained drug release. The tamoxifen bioavailability could be increased to 1.6-fold by SLN administration.

Recent research indicates the usefulness of the compounds from natural resources for cancer prevention and treatment [52]. The antioxidant, anti-inflammatory, anti-apoptotic, vasodilating, and antimicrobial potentials of natural products are responsible for their anticancer effects [53]. γ-Tocotrienol is a natural form of vitamin E with a potential anticancer effect in breast malignancy. However, the effective oral delivery of γ-tocotrienol is very low (9%) [54]. SLNs were used as the formulations for γ-tocotrienol to improve the intestinal permeation [55]. The *in situ* rat intestine perfusion study demonstrated a 10-fold increase of γ-tocotrienol permeation compared to the control. The cellular endocytosis is the major contribution of γ-tocotrienol uptake from SLNs. Following the oral administration of 10 mg/kg γ-tocotrienol, SLNs increased bioavailability by 3-fold compared to the control group. Cantharidin is an anticancer active present in mylabris. It can inhibit tumor growth by interfering with the metabolism of nucleic acids and proteins. Cantharidin is shown to be poorly water soluble with low oral bioavailability in the beagle dog breed [56]. Dang and Zhu [57] used SLNs as the vehicles for oral cantharidin delivery. The mean diameter of the nanoparticles was 121 nm with a high cantharidin encapsulation of 94%. After a single oral dose of cantharidin at 0.1 mg/kg in rats, the relative bioavailability of SLNs to the free compound was 251%.

Ferulic acid is one of the most abundant antioxidants found in wheat bran. It shows anticancer potential in breast, skin, colon, and liver cancers [58]. The poor aqueous solubility of ferulic acid has led to unsatisfactory oral bioavailability. The limited bioavailability of ferulic acid can be overcome by SLNs. Zhang et al [59] prepared ferulic acid-loaded SLNs made with glyceryl behenate. The pharmacokinetic parameters showed a higher $C_{max}$ and half-life of SLNs (18.7 μg/mL and 4.6 hours, respectively) compared with those of aqueous dispersion (10.0 μg/mL and 2.1 hours, respectively), suggesting a sustained release from the lipid matrix. The *in vivo* imaging system also revealed a longer retention of SLNs in the small intestine than in the free control. Thakkar et al [60] combined ferulic acid and aspirin to be loaded in chitosan-coated SLNs for pancreatic cancer therapy. Chitosan-coated SLNs exhibited good stability in an acidic environment with the formation of a thick layer around the lipid core. This biopolymer coating also improved the mucoadhesion of SLNs [61]. The combination of low doses of free ferulic acid (200μM) and aspirin (1mM) inhibited pancreatic cancer cells MIA PaCa-2 and Panc-1 by 45% and 60%, respectively. A 5- and 40-fold dose decrease of ferulic acid (40μM) and aspirin (25μM) was found to show comparable cytotoxicity after SLN entrapment. In the *in vivo* pancreatic tumor xenograft mouse study, oral application of combined ferulic acid (75 mg/kg) and aspirin (25 mg/kg) in SLNs significantly suppressed tumor growth by 45% as compared to the control. Table 1 summarizes the profiles for anticancer therapy assisted by oral SLNs.

### 5.2. *CNS-related disorders*

CNS-related illnesses are a leading cause of disability and morbidity worldwide. However, the orally dosed drug

**Table 1 – Formulations of orally administered SLNs loaded with drugs or natural compounds against cancers and their benefits.**

| Active ingredient | Lipid type | Surface decoration | Average size (nm) | Outcomes offered by SLNs | Reference |
|---|---|---|---|---|---|
| Paclitaxel | Stearic acid | HPCD | 251 | Improved AUC in plasma and lymph node | Baek et al [40] |
| Paclitaxel | Monoglycerides, triglycerides, and stearic acid | WGA | 150–198 | Increased AUC and MRT | Pooja et al [42] |
| Docetaxel | Tristearin | Tween 80 and TPGS | 189–215 | Improved sustained release and AUC | Cho et al [44] |
| Doxorubicin | Precirol ATO 5 | soy lecithin and poloxamer 188 | 217 | Increased AUC and reduced cardiotoxicity | Patro et al [46] |
| Doxorubicin | Monostearin | PEG-stearic acid | 153–160 | Improved bioavailability and prolonged circulation time | Yuan et al [47] |
| Vorinostat | Compritol 888 ATO | None | ~100 | Enhanced $C_{max}$ and AUC | Tran et al [50] |
| Tamoxifen | Monostearin and stearic acid | Tween 80 and poloxamer 188 | 130–244 | Improved bioavailability | Hashem et al [51] |
| γ-Tocotrienol | Compritol 888 ATO | None | 105 | Increased intestine permeation and AUC | Abuasal et al [55] |
| Cantharidin | Monostearin | None | 121 | Improved bioavailability | Dang and Zhu [57] |
| Ferulic acid | Compritol 888 ATO | None | 86 | Increased $C_{max}$ and half-life | Zhang et al [59] |
| Ferulic acid | Stearic acid | Chitosan | 183–229 | Tumor growth suppression | Thakkar et al [60] |

AUC = area under the curve; HPCD = hydroxypropyl-β-cyclodextrin; MRT = mean residence time; PEG = polyethylene glycol; TPGS = D-α-tocopheryl poly(ethylene glycol) succinate; WGA = wheat germ agglutinin.

treatments for depression, anxiety, and schizophrenia are usually limited by low aqueous solubility, food effect, first-pass effect, and a short half-life [62]. Medication for psychotic diseases often needs repeated daily dose administration. This can lead to less patient compliance, the need for hospitalization, and high cost [63]. As such, the application of nanomedicine to CNS-related diseases is a viable option for maximizing treatment efficacy. Apomorphine is a mixed dopamine $D_1/D_2$ agonist for the treatment of Parkinson's disease approved by the U.S. Food and Drug Administration. The rapid degradation of apomorphine in the GI tract and the first-pass effect have resulted in a bioavailability of only 1.7% [64]. Tsai et al [65] developed SLNs for improving oral bioavailability and brain distribution of apomorphine. SLNs showed a bioavailability 13-fold higher than the reference solution at an oral dose of 26 mg/kg. Apomorphine distribution in the striatum, the major site of therapeutic action, also increased when using SLNs. In the rat model of Parkinson's disease induced by 6-hydroxydopamine, the contralateral rotation number increased from 20 to 115 after oral SLN administration.

Migraines are a debilitating headache disorder with symptoms of nausea, photophobia, and cognitive function impairment. Sumatriptan is the first drug approved by the U.S. Food and Drug Administration for acute migraine treatment. This drug undergoes incomplete absorption and first-pass metabolism, leading to a low oral bioavailability of 15% [66]. Chitosan-coated SLNs were used to encapsulate sumatriptan by using a solvent injection technique [67]. The nanoformulations showed a brain sumatriptan deposition of 5.28 μg/g in the pharmacokinetic study. The $AUC_{brain}/AUC_{plasma}$ of the drug was 4.5, indicating a targeting to the brain rather than plasma. The mouse model of photophobia demonstrated that the time spent in the lit chamber of a light/dark box was significantly increased by SLNs when compared to the free control. Rizatriptan is the second-generation antimigraine drug exerting selective vasoconstriction of the intracranial and extracerebral vessels. Girotra and Singh [68] investigated the brain targeting of SLNs for rizatriptan delivery. The *in vivo* study in rats exhibited an 18-fold increase of brain rizatriptan uptake after SLN delivery compared to the free drug at a dose of 5 mg/kg. The light/dark box study showed the improvement of photophobia by loading rizatriptan into SLNs.

Sulpiride is a selective antagonist of the central dopamine receptor used as an antipsychotic agent. In order to ameliorate the limited intestinal permeation, SLNs composed of stearic acid and Dynasan 118 were prepared for sulpiride delivery [69]. The drug permeability across the everted rat gut sac was 6.6 μg/cm$^2$ after 2 hours. The permeability was enhanced to 11.7 μg/cm$^2$ by SLNs. This can be attributed to the enhancement of the surface area, leading to a higher rate of dissolution and diffusion. Quetiapine is an antipsychotic drug with poor oral bioavailability (9%) because of the extensive first-pass effect [70]. An attempt to improve the oral bioavailability of quetiapine was performed by using SLNs [71]. The stable SLNs with a mean diameter of 175 nm and an encapsulation capacity of 92% were developed. The $C_{max}$ was 1.9 μg/mL for SLNs, whereas the $C_{max}$ for the aqueous suspension was 0.1 μg/mL. The oral bioavailability of SLNs increased 3.7 times

compared with the suspension. Venlafaxine is the first-line antidepressant for the treatment of major depressive disorders and anxiety. This drug is a substrate of P-glycoprotein that reduces penetration across the GI and blood–brain barrier [72]. Zhou et al [73] explored whether the venlafaxine efflux of P-glycoprotein could be reversed by SLN application. Mice were orally administered with SLNs containing venlafaxine (22 mg/kg) or free venlafaxine with verapamil. Verapamil is a P-glycoprotein inhibitor. The AUC of venlafaxine from the SLNs and verapamil-containing solution was 1.5- and 1.2-fold greater than that of venlafaxine alone, respectively. The AUC in the brain from SLNs was 1.5-fold higher compared to that in the venlafaxine solution.

Alzheimer's disease is a devastating and progressive neurodegenerative disorder characterized by amyloid-β (Aβ) accumulation and intraneuronal neurofibrillary tangles. Numerous natural compounds and plant extracts are effective against chronic inflammation in Alzheimer's disease [74,75]. Chrysin is one of the natural compounds inhibiting the neuroinflammation caused by Alzheimer's disease [76]. The therapeutic efficiency of chrysin is limited because of its compromised oral delivery. The lipid peroxidation and increased acetylcholinesterase in Aβ-injected rats could be restored by chrysin-loaded SLNs (5 mg/kg and 10 mg/kg) and the free compound (50 mg/kg and 100 mg/kg) [77]. The poor memory retention examined by radial arm maze training was recovered by treatment using SLNs at the lower dose compared to the free control.

Grape skins, mulberries, and peanuts are rich in resveratrol, a polyphenol reported to possess a wide variety of health benefits. Resveratrol is especially effective in the treatment of neurodegenerative illnesses such as Alzheimer's disease, Parkinson's disease, and brain ischemia [78]. As with most of the polyphenols, low aqueous solubility and poor GI absorption have limited resveratrol's therapeutic application. Pandita et al [79] entrapped resveratrol into SLNs to improve the oral bioavailability. SLNs prolonged resveratrol release up to 120 hours and followed Highchi kinetics. Resveratrol is sensitive when exposed to light. Resveratrol content in SLNs (86%) was higher than that in solution (36%) after a 6-hour ultraviolet light irradiation. The lipid formulation produced an 8-fold increase in oral resveratrol bioavailability in rats. The half-life was found to be 2.4 hours and 11.5 hours for resveratrol suspension and SLNs, respectively. *N*-Trimethyl chitosan was coated on the surface of SLNs to increase the retention and penetration of SLNs in the GI tract [80]. The *in vitro* release study of chitosan-coated SLNs revealed negligible resveratrol release in simulated gastric fluid and sustained release in simulated intestinal fluid. After oral dosing at 25 mg/kg, the bioavailability of resveratrol increased 3.8-fold compared to that in the aqueous suspension.

Curcumin is a lipophilic polyphenol derived from the spice turmeric from the ground rhizome of *Curcuma longa*. It has been reported that curcumin exhibits antioxidant, anti-inflammatory, antimicrobial, antiamyloid, and anticancer effects [81]. Of significant interest is curcumin's role in treating neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, and malignancy [82]. The oral bioavailability of curcumin is less than 1% because this compound has poor aqueous solubility and rapid metabolism [83]. Kakkar and Kaur [84] evaluated the effect of curcumin-loaded SLNs on Alzheimer's disease using the mouse model with treatment using $AlCl_3$, a neurotoxicant. Oral treatment of free curcumin (50 mg/kg) showed 15% recovery in lipid peroxidation and 22% recovery in acetylcholinestease with respect to the $AlCl_3$ treatment group. The SLNs demonstrated better results (97% and 73% recovery in lipid peroxidation and acetylcholinestease) at a dose of 50 mg/kg. Improvement in learning ability in the Morris water maze test was achieved by free curcumin and SLNs at the oral dose of 50 mg/kg and 1 mg/kg, respectively. Kakkar et al [85] further examined the brain distribution of curcumin with oral delivery of SLNs. Confocal microscopy was used to visualize the yellow fluorescence of curcumin. The presence of fluorescent nanoparticles in the plasma and brain indicated effective penetration of oral SLNs across the gut wall and the blood–brain barrier. The AUC for SLNs was 8.1 times higher than that of free curcumin. A 30-fold increase in brain curcumin accumulation was detected for SLNs compared to the free control. Ji et al [86] decorated curcumin-loaded SLNs with Brij 78 and TPGS to inhibit the P-glycoprotein efflux pump. In the *in situ* single-pass intestinal perfusion test, the effective permeability coefficient of SLNs + Brij and SLNs + Brij + TPGS was 1.3 times and 1.4 times greater than conventional SLNs in the jejunum. The *in vivo* pharmacokinetic experiment in rats showed the AUC for SLNs as 12.3-fold higher than in suspension.

Chitosan as a mucoadhesive polymer was coated on the surface of SLNs to improve oral intake [87]. The oral absorption of curcumin suspension (50 mg/kg) showed a $C_{max}$ of 0.28 μg/mL. This value could be increased to 1.04 μg/mL by SLN administration. The bioavailability of curcumin was increased by a factor of 6.9 after SLN delivery compared to suspension. Methylation of chitosan to *N*-trimethyl chitosan increases acid resistance and the mucoadhesive property [88]. *N*-Trimethyl chitosan-coated SLNs were developed to further ameliorate oral absorption [89]. Curcumin in chitosan-coated SLNs resulted in the release of 81% and 48% in simulated gastric fluid and simulated intestinal fluid, respectively. Release of curcumin from quarternized chitosan-coated SLNs was negligible (9%) in simulated gastric fluid and moderate (42%) in simulated intestinal fluid. The oral AUC of *N*-trimethyl chitosan-coated SLNs was 12.8 μg h/mL, which was significantly higher than free curcumin (0.3 μg h/mL), non-coated SLNs (6.0 μg h/mL), and chitosan-coated SLNs (6.9 μg h/mL). Another activity of curcumin on CNS-related disorders is the inhibition of cerebral ischemia [90]. Kakkar et al [91] assessed the effect of curcumin-loaded SLNs on the experimental platform of cerebral ischemic reperfusion injury in rats. γ-Scintigraphic study exhibited a 16-fold increase in brain AUC upon oral delivery of SLNs compared to the control solution. There was an improvement of 90% in cognition and 52% inhibition of acetylcholinesterase versus the nontreatment group. Table 2 depicts the oral delivery assisted by SLNs with the aim of CNS-related disorder treatment.

### 5.3. *CV-related diseases*

SLNs have been used orally, aiming at enhancing drug plasma concentration and prolonging circulation duration. These features are especially important for accomplishing better

**Table 2 – Formulations of orally administered SLNs loaded with drugs or natural compounds against CNS-related disorders and their benefits.**

| Active ingredient | Indication | Lipid type | Average size (nm) | Outcomes offered by SLNs | Reference |
|---|---|---|---|---|---|
| Apomorphine | Parkinson's disease | Tripalmitin | 63–155 | Increased bioavailability and brain distribution | Tsai et al [65] |
| Sumatriptan | Migraine | Tripalmitin | 192–301 | Improved $AUC_{brain}/AUC_{plasma}$ ratio and photophobia | Hansraj et al [67] |
| Rizatriptan | Migraine | Precirol ATO 5 | 220 | Improved brain uptake and photophobia | Girotra and Singh [68] |
| Sulpiride | Psychosis | Stearic acid and Dynasan 118 | 256 | Increased gut permeability | Ibrahim et al [69] |
| Quetiapine | Psychosis | Dynasan 118 | 175 | Enhanced $C_{max}$ and bioavailability | Narala and Veerabrahma [71] |
| Venlafaxine | Major depressive disorder and anxiety | Monostearin | 186 | Increased AUC in both plasma and brain | Zhou et al [73] |
| Chrysin | Alzheimer's disease | Stearic acid | 240 | Improved memory loss | Vedagiri and Thangarajan [77] |
| Resveratrol | Neurodegenerative disorders | Stearic acid | 134 | Increased bioavailability and half-life | Pandita et al [79] |
| Resveratrol | Neurodegenerative disorders | Precirol ATO 5 | 258 | Increased $C_{max}$ and AUC | Ramalingam and Ko [80] |
| Curcumin | Alzheimer's disease | Compritol 888 ATO | 135 | Reduced neuroinflammation | Kakkar and Kaur [84] |
| Curcumin | Alzheimer's disease | Compritol 888 ATO | 135 | Improved AUC and brain distribution | Kakkar et al [85] |
| Curcumin | Alzheimer's disease | Monostearin | 135 | Increased jejunum permeability and bioavailability | Ji et al [86] |
| Curcumin | Alzheimer's disease | Monostearin | 452 | Increased $C_{max}$ and AUC | Ramalingam et al [87] |
| Curcumin | Alzheimer's disease | Palmitic acid | 412 | Increased AUC and half-life | Ramalingam and Ko [89] |
| Curcumin | Cerebral ischemia | Compritol 888 ATO | 135 | Increased AUC in brain and cognition | Kakkar et al [91] |

AUC = area under the curve; CNS = central nervous system; SLN = solid lipid nanoparticle.

therapeutic benefits in treating CV-related diseases. Nimodipine is a calcium channel blocker used in the treatment of hypertension and stroke. Clinical studies demonstrate a low bioavailability of 4–13% for oral nimodipine [92]. Nimodipine-loaded SLNs were prepared with palmitic acid, poloxamer 188, and soy lecithin [93]. An accelerated stability test showed no significant change in size and polydispersity of the SLNs for 3 months. The bioavailability of oral SLNs containing nimodipine (8 mg/kg) was 2-fold greater than that of the solution in rats. Nisoldipine is another antihypertensive drug with low oral bioavailability. Dudhipala and Veerabrahma [94] developed optimal formulations of nisoldipine-loaded SLNs for improved delivery. The optimized SLNs were stable under refrigeration and at room temperature for 3 months. The pharmacokinetic study displayed a 2.2-fold increase in oral bioavailability by SLNs as compared with nisoldipine suspension. The pharmacodynamic study showed that SLNs could significantly reduce systolic blood pressure for a sustained period of 36 hours.

Candesartan cilexetil is a prodrug of candesartan, an angiotensin II type 1 receptor antagonist, used for hypertension and heart failure remission. This prodrug has poor aqueous solubility and low oral absorption. After inclusion of candesartan cilexetil (10 mg/kg) into SLNs using Dynasan as the solid lipid, oral bioavailability was enhanced more than 2.8-fold compared to the free control [95]. An extension of systolic blood pressure reduction was observed after SLN administration in hypertensive rats for 48 hours, whereas the period of blood pressure reduction was only 2 hours for the drug suspension. Zhang et al [96] elucidated the absorption mechanisms of candesartan cilexetil from SLNs. The pharmacokinetic study in rats indicated that the oral bioavailability and $C_{max}$ increased more than 12- and 27-fold after SLN incorporation, respectively. In the Caco-2 cell monolayer uptake, SLNs were distributed in the lysosomes and endoplasmic reticulum after internalization. The authors had suggested that SLNs could be internalized into the enterocytes and then diffused into the circulation via portal circulation and the lymphatic pathway. Carvedilol is an antihypertensive drug with a low oral bioavailability of 20% because of the first-pass effect. To improve the drug's oral delivery, SLNs were developed with *N*-carboxymethyl chitosan coating for protecting carvedilol in an acidic environment [97]. The polymer-coated SLNs had shown 5.2% of drug release in simulated gastric fluid for 24 hours. In simulated intestinal fluid (pH 7.4), the *N*-carboxymethyl chitosan on the SLN surface dissolved and the controlled release of carvedilol was detected. In the *in vivo* pharmacokinetics, the MRT was found to be 13.9 hours and 9.6 hours for polymer-coated SLNs and aqueous suspension, respectively. The AUC of polymer-coated SLNs was 6.3 μg h/mL, which was significantly higher than that of noncoated SLNs (2.9 μg h/mL) and the free control (2.0 μg h/mL).

Use of an iron supplement is an efficient way to treat the iron deficiency in anemia. However, the commercially available iron tablets often cause adverse effects on the GI system, resulting in constipation and blood in the stool [98]. Another concern is the high intersubject variability in iron absorption. This has led to the application of SLNs for oral iron delivery. Zariwala et al [99] prepared chitosan-coated SLNs for ferrous sulfate loading to test the Caco-2 absorption. The cell viability

after SLN treatment was >80% of the control cells. The Caco-2 iron absorption from chitosan-coated SLNs (643 ng/mg cell protein) was significantly higher than from noncoated SLNs (584 ng/mg cell protein) and the reference control (515 ng/mg cell protein). Hosny et al [100] assessed the *in vivo* pharmacokinetics of ferrous sulfate in SLNs. The iron-loaded SLNs exerted a biphasic release behavior, with a burst release within 30 minutes followed by sustained release. A 4-fold increase in oral iron bioavailability was achieved after oral administration of SLNs (10 mg/kg) in rabbits.

### 5.4. *Infection*

Infection can cause host tissues to react to organisms and the toxins they produce. Nanocarriers can be effective drug delivery systems for treating infections [101]. Among the different types of nanosystems, SLNs were widely applicable for carrying anti-infection drugs to treat bacterial, fungal, viral, and parasitic infection. Isoniazid is an antitubercular drug recommended by the World Health Organization for management of all forms of tuberculosis. A short half-life of 1–4 hours suggests the need for repetitive dosing that may result in hepatotoxicity and neurotoxicity [102]. Isoniazid-incorporated SLNs were developed to attain prolonged circulation retention and improved bioavailability [103]. The *in vitro* isoniazid release displayed a triphasic pattern comprising an initial fast release, followed by a hump and finally a delayed release. A significant amelioration of bioavailability in rat plasma (6 times) and the brain (4 times) was found after oral SLN administration compared to free isoniazid (25 mg/kg). The SLNs showed a 3-fold higher median lethal dose ($LD_{50}$) compared to the free drug in an acute toxicity study. Miconazole is a broad-spectrum antifungal drug with a low aqueous solubility of <1 μg/mL. Encapsulation of miconazole in SLNs showed a biphasic drug release with an initial burst and a following delayed release [104]. The SLNs showed better *Candida albicans* killing in the diffusion disk test, with the maximum inhibition diameter of 22 mm that was longer than the marketed capsule (14 mm). The *in vivo* pharmacokinetics in rabbits exhibited a 2.5-fold enhancement of oral bioavailability.

Lopinavir is a human immunodeficiency virus (HIV) protease inhibitor used in antiretroviral therapy. SLNs can act as a feasible carrier for lopinavir because of P-glycoprotein efflux and first-pass metabolism. The lopinavir-loaded SLNs composed of stearic acid were stable at 4°C for 4 months based on particulate size and the release profile [105]. Higher oral bioavailability was obtained for SLNs (2.5-fold) in comparison with lopinavir solution because of higher lymphatic delivery. In another study, Compritol 888 ATO was used as the solid lipid for preparing lopinavir-loaded SLNs [106]. The drug release showed a delayed pattern both in 0.1N HCl (pH 1.2) and phosphate buffer (pH 6.8). The SLNs could bypass P-glycoprotein efflux to reach systemic circulation, leading to a 3.6- and 4.9-fold increase in bioavailability and $C_{max}$ compared to solution. Efavirenz is a nonnucleoside reverse transcriptase inhibitor as the first-line antiretroviral drug to eradicate HIV infection. Gaur et al [107] investigated the enhanced oral bioavailability of efavirenz by SLNs. The optimized nanoformulations had shown good stability at 40°C for about 6 months. SLNs revealed a 5.3-fold increase in $C_{max}$ and an 11.0-fold increase in AUC compared to drug suspension after oral administration in rats. Makwana et al [108] further explored the absorption pathways of SLNs for delivering efavirenz. The profiles of lymphatic absorption and tissue biodistribution in rats indicated that a large amount of nanoparticulate efavirenz had bypassed the portal system and recovered in the lymph via chylomicron uptake. Reduction of hepatic uptake by SLNs (44.7%) demonstrated liver bypass and thereby the oral bioavailability enhancement. A great amount of efavirenz was observed in the spleen, a principal lymphatic organ.

Malaria continues to be a vast health and economic problem in tropical regions. Primaquine is the only available drug for combating the relapsing form of malaria. The oral absorption of this drug is low because of first-pass metabolism and excretion. The high-dose use of primaquine usually produces hematological- and GI-related toxicity [109]. Primaquine entrapment in SLNs exhibited a sustained drug release over 72 hours [110]. When the *Plasmodium berghei*-infected mouse was orally administered with SLNs at a drug dose of 2 mg/kg/d for 4 days, the suppression of 94% was achieved by SLNs, whereas only 72% suppression was found for the free control. Arteether is an artemisinin analog for treatment of multidrug-resistant malaria. SLNs were used to resolve the low stability in the gastric environment and the short half-life of arteether [111]. The cell viability remained >90% for SLNs against macrophages, indicating the safety of their application. The half-life of arteether SLNs was found to be 4.5 hours, whereas arteether in ground nut oil and water as the vehicles showed a half-life of 3.3 hours and 2.0 hours. SLNs could increase oral bioavailability compared to ground nut oil by 1.7-fold. Praziquantel is currently used to treat schistosomiasis, a parasitic disease caused by *Schistosoma*. Because of its limited effect on schistosomiasis, de Souza et al [112] incorporated praziquantel into SLNs to check the possible promotion of its therapeutic activity. In the experiment focused on *Schistosoma mansoni* inhibition, SLNs were more effective than the free drug, leading to parasite killing in less time. Contrary to the cases of enhanced intestinal permeation by SLNs, the designed SLNs for praziquantel revealed less permeation across the duodenal segment than the free drug in the everted gut sac transport study. This may be attributed to a reduced availability of SLNs in mucosal bulk. This suggested a reservoir role of SLNs for praziquantel to kill the parasites located in the mesenteric vein of the intestine. The parasite *Trypanosoma cruzi* causes Chagas disease, which remains a serious health problem. Carneiro et al [113] evaluated the *in vitro* and *in vivo* activity of 5-hydroxy-3-methyl-5-phenyl-pyrazoline-1-(*S*-benzyl dithiocarbazate) (H2bdtc) as a free active or incorporated into SLNs. H2bdtc-loaded SLNs efficiently reduced parasitemia in mice at a concentration 100 times lower than benznidazole, the currently available drug for treating Chagas disease. In the *in vivo* study, oral administration of H2bdtc (4 μmol/kg) in SLNs eradicated 70% of the parasites in circulation, whereas free H2bdtc and benznidazole killed only 48% and 15% of the parasites. SLNs also diminished inflammation and lesions produced by the free drug in the liver and heart (Table 3).

**Table 3 – Formulations of orally administered SLNs loaded with drugs or natural compounds against infection and their benefits.**

| Active ingredient | Indication | Lipid type | Average size (nm) | Outcomes offered by SLNs | Reference |
|---|---|---|---|---|---|
| Isoniazid | Tuberculosis | Compritol 888 ATO | 48 | Increased bioavailability and less acute toxicity | Bhandari and Kaur [103] |
| Miconazole | Fungi | Precirol ATO 5 | 23 | Enhanced antifungal activity and bioavailability | Aljaeid and Hosny [104] |
| Lopinavir | Retrovirus | Stearic acid | 181 | Increased bioavailability | Negi et al [105] |
| Lopinavir | Retrovirus | Compritol 888 ATO | 215 | Increased $C_{max}$ and bioavailability | Negi et al [106] |
| Efavirenz | Retrovirus | Monostearin | 125 | Increased $C_{max}$ and AUC | Gaur et al [107] |
| Efavirenz | Retrovirus | Compritol 888 ATO | 168 | Increased lymphatic uptake and bioavailability | Makwana et al [108] |
| Primaquine | Malaria | Stearic acid | 236 | Enhanced antimalarial efficacy | Omwoyo et al [110] |
| Arteether | Multidrug-resistant malaria | Monostearin | 100 | Increased bioavailability and half-life | Dwivedi et al [111] |
| Praziquantel | Schistosomiasis | Stearic acid | 506 | Enhanced parasite killing | de Souza et al [112] |
| H2bdtc | Chagas disease | Stearic acid | 127 | Enhanced parasite killing and diminished toxicity | Carneiro et al [113] |

AUC = area under the curve; H2bdtc = 5-hydroxy-3-methyl-5-phenyl-pyrazoline-1-(S-benzyl dithiocarbazate); SLNs = solid lipid nanoparticles.

### 5.5. *Diabetes*

Diabetes mellitus is one of the most common metabolic diseases worldwide. Hyperglycemia caused by diabetes is a serious pathologic condition producing neurological and CV damage. Diabetes is divided into two types: type 1 diabetes and type 2 diabetes. Type 1 diabetes occurs when the pancreas fails to produce sufficient insulin, giving rise to hyperglycemia. The patient requires a routine administration of insulin. Insulin absorption via the oral route is difficult because of acidic gastric pH, digestive enzymes, and the epithelial cells of the GI tract [114]. Researchers focus considerable attention on SLNs as the carriers to protect peptides and proteins known for their sensitivity to various environmental factors such as pH, temperature, and ionic strength [115]. Zhang et al [116] designed SLNs coated with stearic acid-octaarginine as carriers for insulin. Octaarginine is a cell-penetrating peptide that can facilitate cellular uptake of some drugs [117]. The size and insulin encapsulation of the octaarginine-coated SLNs were 162 nm and 77%, respectively. Octaarginine-coated and noncoated SLNs increased Caco-2 cell uptake by 2.3 times and 18.4 times, respectively. The SLNs containing octaarginine showed a significantly higher hypoglycemic effect (3-fold) in rats compared to noncoated SLNs. Ansari et al [118] developed SLNs composed of Dynasan 114 as the solid lipid matrix for oral insulin delivery. The permeability of insulin measured by the everted sac method showed a higher level of SLNs (14.8 μg/cm$^2$) than the insulin solution (8.0 μg/cm$^2$). SLNs provided better insulin protection from the GI environment as evident in the 5-fold higher bioavailability compared to the solution.

About 90% of diabetic patients are affected by noninsulin-dependent type 2. Glibenclamide is a second-generation sulfonylurea for type 2 diabetes treatment. The very low aqueous solubility is responsible for its limited oral bioavailability [119]. Gonçalves et al [120] developed SLNs coated with PEG to increase glibenclamide stability in gastric solution. The insulin release from SLNs obeyed a typical biphasic kinetic, where a complete release was achieved after 24 hours. The oral administration of free glibenclamide (5 mg/kg) in diabetic rats reduced the blood glucose concentration after 4 hours, and it then climbed quickly to the initially high level. Oral SLNs not only created a rapid onset of glucose lowering but also maintained the reduction for 8 hours after administration. Berberine is an isoquinoline alkaloid derived from *Coptis chinensis*. It is reported that berberine has the capability to treat diabetes by glycolysis stimulation and insulin secretion promotion [121]. Xue et al [122] encapsulated berberine by SLNs with a particulate size and entrapment efficiency of 77 nm and 58%, respectively. A single oral dose (50 mg/kg) in rats achieved a significant improvement of AUC by SLNs (179 μg h/L) compared to solution (86 μg h/L). Morphological analysis of the db/db mice indicated that SLNs potentially enhanced islet function and protected the islet from regeneration. *Andrographis paniculata* and its bioactive compound andrographolide have been reported to have antidiabetic and hypolipidemic activities [123]. Andrographolide is rapidly metabolized in the duodenum and jejunum to form sulfate conjugates [124]. The SLNs were prepared to load andrographolide with a high encapsulation percentage of 91% [125]. The oral bioavailability

and hypolipidemic activity of andrographolide was improved by SLNs because of the increase of solubility and stability in the intestine and the change of transport mode in Caco-2 cells. The bioavailability was increased 2.4-fold after andrographolide inclusion in SLNs.

### 5.6. *Osteoporosis*

Osteoporosis is a disease in which decreased bone strength increases the risk of a broken bone. It is the most common reason for a broken bone among the elderly and postmenopausal women. Oral raloxifen is approved for prevention and treatment of postmenopausal osteoporosis. Although 60% of raloxifen is absorbed orally, the absolute bioavailability is only 2% because of poor aqueous solubility and glucuronide conjugation [126]. SLNs for raloxifen delivery were prepared using Compritol 888 ATO as the lipid and poloxamer 188 as the emulsifier [127]. The release of free raloxifen was complete within 4 hours, whereas SLNs prolonged drug release up to 24 hours. The rats were orally administered raloxifen at a dose of 30 mg/kg. The bioavailability of SLNs was nearly 5 times that of free raloxifen. Tran et al [128] also prepared raloxifen-loaded SLNs to examine oral bioavailability and safety. The optimized SLNs showed an average size of 140 nm with ease of transport into the lymphatic system. $C_{max}$ and AUC were increased by 3.1- and 2.7-fold by SLN formulation compared to the free drug. The cytotoxicity against NIH-3T3 cells exhibited nontoxicity of the SLNs. Alendronate is a nitrogen-containing biphosphonate used for osteoporosis management. The challenge associated with oral alendronate is its low bioavailability (0.6 %) because of the difficulty of crossing the GI membrane [129]. The enteric-coated SLNs were designed to conquer this challenge to prevent alendronate contact with gastric mucosa [130]. The alendronate release percentage in 0.1N HCl was 5% and 85% for SLNs and commercial tablets, demonstrating the gastric resistance of the enteric-coated carrier. The drug release from SLNs occurred only at an alkaline pH. The pharmacokinetic determination of oral SLNs revealed that alendronate bioavailability increased 7.4-fold in rabbits.

Salmon calcitonin is a calcium-regulating peptide hormone secreted from the ultimobranchial gland of salmon. It is widely used in the treatment of postmenopausal osteoporosis. The oral bioavailability of calcitonin is <0.1% in rats and dogs [131]. SLNs encapsulating salmon calcitonin could increase Caco-2 cell uptake by 4 times compared to the free control [132]. The *in vivo* hypocalcemic effect in rats was better with prepared SLNs than with free calcitonin (17.4% vs. 2.0% reduction). The SLNs prepared with stearic acid and tripalmitin increased oral calcitonin bioavailability from 2% to 13%. Fan et al [133] prepared salmon calcitonin-loaded SLNs by coupling with peptide ligand CSKSSDYQC, which shows affinity with goblet cells on the epithelium, or IRQRRRR, which is a cell-penetrating peptide. The protective efficacy of SLNs on calcitonin against pancreatin was examined. Most of the free calcitonin was degraded within 15 minutes. A much slower degradation rate was found for SLNs. The permeability across the Caco-2 cell monolayer for nonconjugated, CSKSSDYQC and IRQRRRR SLNs was 2.1-, 5.9-, and 4.7-fold higher than that of the free control. The absolute bioavailability of CSKSSDYQC (12.4%) and IRQRRRR SLNs (10.1%) was greater than that of unmodified SLNs (5.1%), suggesting the effectiveness of peptide conjugation for the enhancement of oral protein delivery.

## 6. Conclusions and perspectives

SLNs are the colloidal systems for the delivery of labile drugs with controlled release kinetics. SLN-based carriers are compatible with the oral administration route because of nontoxic excipients and increased bioavailability. This review represents the research advancements that had been undertaken to establish the oral SLNs with respect to their unique properties. In the past 5 years, the oral SLNs have gained some advances in the therapy of cancers and CNS-related diseases, which are the increasing health threats around the world. For instance, SLNs could enhance the bioavailability of docetaxel by a 3-fold compared to the commercially available Taxotere. The PEGylated SLNs provided a 7.5-fold increase of oral bioavailability than free doxorubicin. With respect to the treatment of Parkinson's disease, a 13-fold increase of oral apomorphine bioavailability was achieved by SLNs compared with the free drug. The introduction of SLNs for improved oral delivery also promotes the possibility of natural compound application for disease management because the oral bioavailability and half-life of natural products are always low in the body.

Despite the advantages of oral SLNs for drug delivery, several challenges remain to be resolved for better application in the future. The particle growing and unpredictable gelation tendency are the storage problems in some cases. The burst drug release for some oral SLNs may cause toxicity concerns. However, the very slow drug release can lead to inefficient activity in treating the diseases. The development of the formulation design of novel SLNs to provide a feasible release profile is important. This depends on the cargo drugs selected in SLNs, because different drugs show different physicochemical characters, and on the interaction with the nanoparticles. Prolonged drug circulation is a common phenomenon for oral delivery of SLNs. However, the negative side of prolonged circulation is the slow tissue accumulation of the nanoparticles, including the targeted tissue. Again, the optimization of SLN formulations is necessary.

The SLNs as drug nanocarriers have the potential to achieve the broad objectives for treating various diseases. A wider collection of the lipid materials may be illustrated for SLNs in the future. The lipids from natural sources can be a major origin of the SLN lipid matrix. More patented dosage forms of SLNs can be expected in the near future. SLNs based on the optimized formulations should have a place in modern pharmaceutical products because of the capability of enhancing drug therapy. An innovative formulation of a drug can extend the life of patients. A novel delivery system for old actives would result in the reduction of side effects and more-effective treatment achievement. Although many oral SLNs have been developed for testing in cell-based and animal studies, clinical trials for drug delivery application are still limited. This may be because of the high cost of clinical trials and the unknown side effects that should be identified and

explored first. At least a 5-fold-improved oral bioavailability needs to be achieved in most cases to justify the use of nanocarriers from the commercial point of view, unless other convincing benefits can be gained. A better understanding of the full potential of SLNs and the progress from laboratory bench to large-scale commercialization is required. The introduction and description of the SLNs for oral delivery outlined in this review may give relevant information to investigators involved in designing feasible and efficient delivery systems for the treatment of various diseases.

## Conflicts of interest

The authors declare no conflicts of interest.

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