REVIEW

Recent developments in solid lipid nanoparticle and surface-modified solid lipid nanoparticle delivery systems for oral delivery of phyto-bioactive compounds in various chronic diseases

Palanivel Ganesan[1,2,*]
Prakash Ramalingam[3,4,*]
Govindarajan Karthivashan[1,*]
Young Tag Ko[4]
Dong-Kug Choi[1,2]

[1]Department of Biotechnology, College of Biomedical and Health Science, Konkuk University, Chungju, Republic of Korea; [2]Nanotechnology Research Center and Department of Applied Life Science, Konkuk University, Chungju, Republic of Korea; [3]Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, University of the Sciences, Philadelphia, PA, USA; [4]College of Pharmacy, Gachon University, Incheon, Republic of Korea

*These authors contributed equally to this work

Correspondence: Dong-Kug Choi
Department of Biotechnology, College of Biomedical and Health Science, Konkuk University, Chungju 27478, Republic of Korea
Tel +82 43 840 3610
Fax +82 43 840 3872
Email choidk@kku.ac.kr

Abstract: Solid lipid nanoparticle (SLN) delivery systems have a wide applicability in the delivery of phyto-bioactive compounds to treat various chronic diseases, including diabetes, cancer, obesity and neurodegenerative diseases. The multiple benefits of SLN delivery include improved stability, smaller particle size, leaching prevention and enhanced lymphatic uptake of the bioactive compounds through oral delivery. However, the burst release makes the SLN delivery systems inadequate for the oral delivery of various phyto-bioactive compounds that can treat such chronic diseases. Recently, the surface-modified SLN (SMSLN) was observed to overcome this limitation for oral delivery of phyto-bioactive compounds, and there is growing evidence of an enhanced uptake of curcumin delivered orally via SMSLNs in the brain. This review focuses on different SLN and SMSLN systems that are useful for oral delivery of phyto-bioactive compounds to treat various chronic diseases.

Keywords: solid lipid nanoparticles, surface-modified solid lipid nanoparticles, chronic diseases, phyto-bioactive compounds, chitosan

Introduction

Solid lipid nanoparticles (SLNs) are lipid-based delivery systems that exist in numerous sizes, ranging from 30 to 1,000 nm. These can be developed using easily degradable lipids. SLNs have multiple advantages than other nano-delivery systems including bypassing the spleen or liver filtration with the particle size of 120–200 nm, lower chronic or acute toxicity due to physiological lipid, enhanced bioavailability and productivity, higher reproducibility, lower organic solvents usage in the preparation, protection of liable phytocompounds or drugs and possibility to incorporate both hydrophilic and hydrophobic compounds. Further, SLNs can be made with highly degradable lipids and hence are biologically safe systems which allow large-scale production, easy sterilization and long storage period. These advantages made the SLNs suitable for the oral delivery of various phyto-bioactive compounds, such as curcumin, resveratrol, quercetin and other polyphenols, to treat several types of chronic diseases.[1–6] Even though conventional SLNs have several advantages, there is a challenge to oral delivery of bioactive compounds,[4,7,8] that is, the burst release of the phyto-bioactive compounds in the stomach at a lower pH of about 1–3. To overcome this problem, the SLNs are subjected to surface modification to enhance the delivery of the phyto-bioactive compounds and to prevent the higher release in the stomach.[7]

Surface-modified SLNs (SMSLNs) were recently produced using heparin, albumin, polyethylene glycol and polysaccharides to control the oral delivery of phyto-bioactive compounds. Chitosan is highly degradable, presents lower immunogenicity and is suitable for controlled oral delivery of the phyto-bioactive compounds under various pH conditions.[4,9–11] The fate of SLNs and modified SLNs (MSLNs) administered through an oral delivery system is shown in Figures 1 and 2. The surface coating of SLNs with chitosan along with modifications in chitosan has many advantages in reducing the pH, such as a sustained release of the bioactive compounds, and a higher positive charge leads to a lower burst release of the SMSLNs. Coating the modified chitosan on SLNs results in the controlled release of these phyto-bioactive compounds in harsh gastric environments, which will be helpful to treat chronic diseases[7,8,12,13] by improving the efficacy of the therapy. Some SMSLN delivery systems, such as trimethyl chitosan (TMC), showed enhanced delivery of the compounds to the brain in an Alzheimer's mouse model. Further, modification of the chitosan and development of MSLNs are not cost effective. Other advantages of MSLNs including enhanced targeted delivery of the active compounds, ability to cross the blood–brain barrier in neuroinflammatory diseases and long-term storage with

bulk production make them an appropriate choice among the other nano-delivery systems. The recent surface modification of SLNs using chitosan and their applicability in chronic diseases are discussed in this review, focusing on SLNs and SMSLNs for oral delivery of the phyto-bioactive compounds and treatment in various in vitro and in vivo chronic disease models.

Role of SLNs in the oral delivery of phyto-bioactive compounds

SLN is a first-generation nano-delivery system that has been extensively used for sustained release in oral delivery of phytocompounds to treat various chronic diseases.[7,14–19] Recently, many new nano-delivery systems have been developed for oral delivery.[15–18] However, SLN has its own advantages in the bulk production, including a lower production cost, long-term stability and tolerability and biodegradability with lower toxic effects, along with enhanced oral delivery of phyto-bioactive compounds. Recently, sesamol-loaded SLN was developed with a particle size of about 120 nm, and it exhibited enhanced oral delivery for carbontetrachloride-induced hepatotoxicity in an animal model. The results confirmed that sesamol-loaded SLN has a higher protective effect than free sesamol, with lower irritation and no toxicity.[20] Further, the
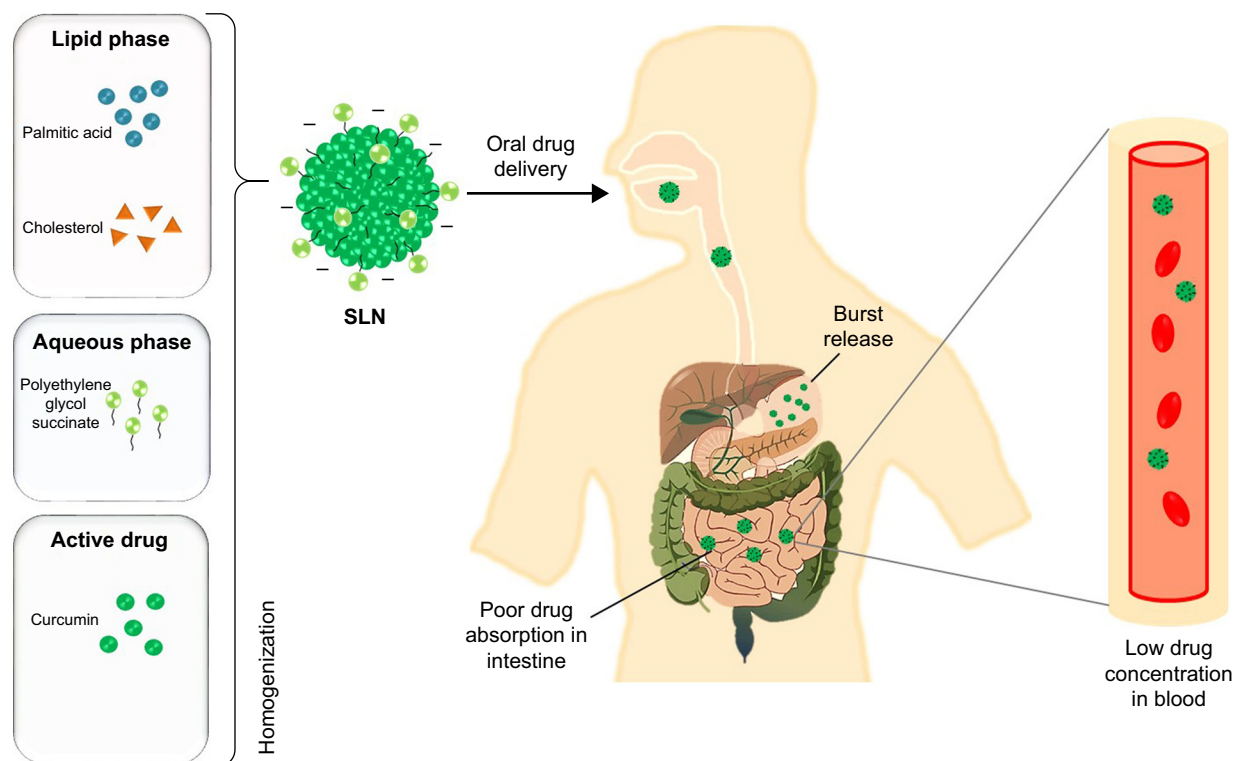

Figure 1 Schematic representation of the fate of SLN through oral delivery.
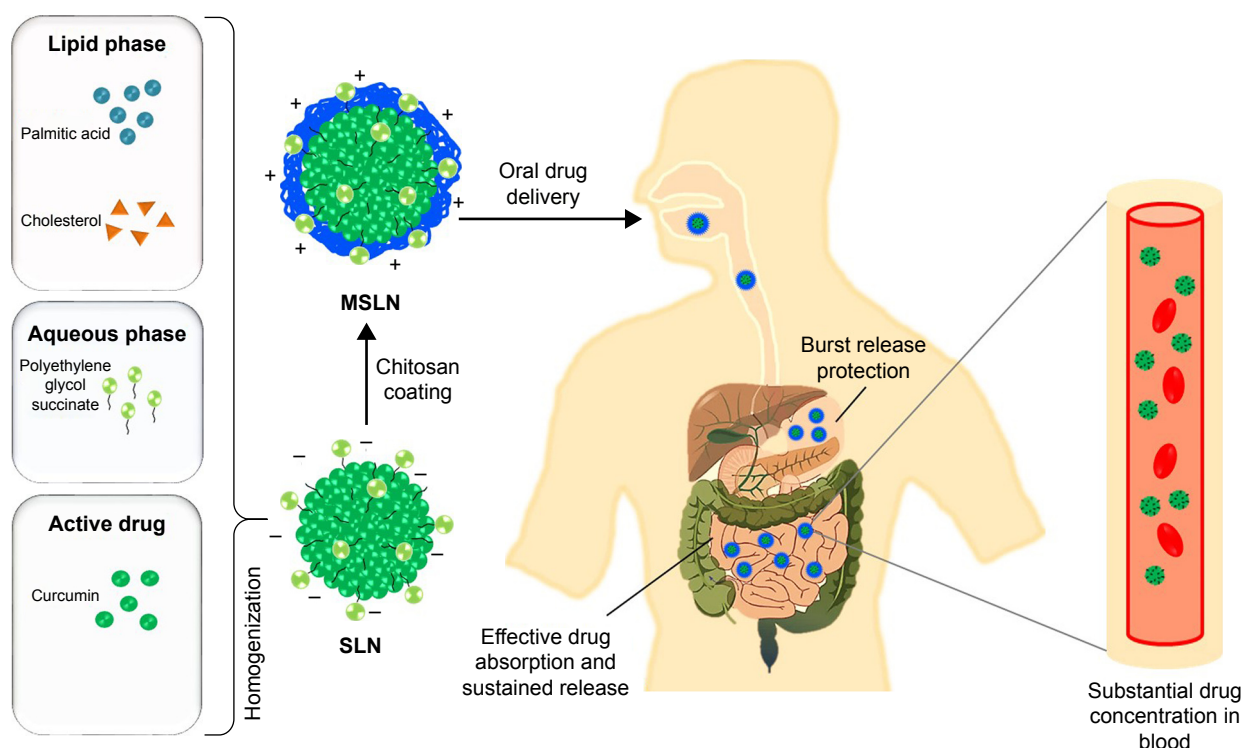**Abbreviation:** SLN, solid lipid nanoparticle.

Figure 2 Schematic representation of the fate of MSLN through oral delivery.
Abbreviations: MSLN, modified solid lipid nanoparticle; SLN, solid lipid nanoparticle.

antioxidant potential of sesamol-loaded SLN was higher than that of free sesamol through oral delivery.[21] Similarly, curcumin-loaded SLN was studied in the cerebral ischemia rat model, and the results indicated 16.4 times greater bioavailability of curcumin in the brain than with free curcumin. The brain bioavailability greatly increased along with a 90% increase in the cognition of the cerebral ischemic rat group.[22] Resveratrol was also studied for its sustained bioavailability through oral delivery via resveratrol-loaded SLN with a particle size of about 241 nm in male Wistar rats. Compared to free resveratrol, lipid core-loaded resveratrol showed two times higher bioavailability in the brain, kidney and liver.[23] Recently, quercetin-loaded SLN was developed with a particle size of about 172 nm, and a single oral dose showed 3.2 times higher bioavailability than free quercetin along with enhanced osteoprotective effect in a postmenopausal rat model.[24] Similarly, many other flavonoid-loaded SLNs were studied to assess their efficacy in the delivery of bioactive compounds. Owing to the higher-release behavior of SLN, puerarin-loaded SLN was studied for the cardioprotective effect through intragastric delivery, and it showed 3.1 times higher bioavailability than free puerarin.[25] The association of resveratrol with lipids was also studied in a stimulated gastrointestinal environment, and it was found to be stable with efficient delivery. Even though the lipid association of other phyto-bioactive compounds may be different, researchers are now highly focusing on modified SLNs for the sustained release of the phyto-bioactive compounds through oral delivery.

SLN formulation and production strategies for the improvement of oral delivery of bioactive compounds

For the enhanced oral delivery and stability of the phyto-bioactive compounds through SLNs, their composition of the formulation and their production methods play a critical role. SLN formulation in turns depends on the type of surfactants, lipids, phyto-bioactive compounds, cosurfactant and cryoprotectant which determines the stability and target reachability of the loaded phyto-bioactive compounds.[26] Various range of lipids like triacylglycerols, waxes, hard fats, palmitic acid and stearic acid are used to fabricate SLNs which have their own advantages as well as disadvantages. In case of curcumin loaded in several types of lipids, the entrapment efficiency increases with increase in the chain length of the hydrocarbon chain. Recently, Aditya et al studied the entrapment efficiency of curcumin in SLNs made with different lipids including

trimyristin, tristearin and glycerol monosterate and found that glycerol monosterate has greater entrapment efficacy than the other lipids.[26,27] Further, the entrapment efficiency of phyto-bioactive compounds like curcumin, resveratrol, or genistein also depends on the molecular weight of the type of compounds involved. Increase in the molecular weight decreases the entrapment efficiency of the compounds which in turn leads to lower oral delivery of the phytocompounds. In addition to the lipids selection, surfactants also play a critical role in the formulation of SLNs, by avoiding coalescence during solidification which in turn depends on the type of surfactant involved and its concentration.[28–30] Further, the production methods also determine the SLN loading capacity and stability of the phyto-bioactive compounds.[31,32] Various methods like emulsification solvent diffusion, emulsification solvent evaporation, high-pressure homogenization and microfluidization are involved in the production of SLNs. Owing to the lower degradation of sensitive phyto-bioactive compounds like curcumin, lower toxicity, enhanced stability and bulk production of the SLNs, microfluidization and high-pressure homogenization techniques are generally recommended in the production of phyto-bioactive compounds-loaded SLNs.

Absorption mechanisms of phyto-bioactive compounds loaded in SLNs and SMSLNs through oral delivery in various chronic disease models

Phyto-bioactive compounds loaded in the SLNs and SMSLNs need to be solubilized before absorption in the gastrointestinal tract when chronic diseases are treated through oral delivery.[33–38] The digestion of SLNs and SMSLNs by stomach enzymes results in SLN and SMSLN emulsion and formation of degradation products that form mixed micelles. These mixed micelles loaded with phyto-bioactive compounds can exhibit enhanced absorption due to their lower particle size.[18,39,40] In addition, surface modification results in the adhesion of SLNs to the intestine, which can result in longer or prolonged delivery to treat chronic disease. For the above reasons, SLNs loaded with phyto-bioactive compounds can pass through intervillar space or lymphatic system or Peyer's Patch without much loss in the active site of the bioactive compounds. In addition to the transportation of the bioactive compounds, some amount of coated nanoparticles are also transported through ileum absorption.[41–43] The absorption mechanisms and biodistribution in various organs are shown in Figure 3. Many recent studies have confirmed the enhanced absorption of bioactive compounds through SLNs or SMSLNs to treat diseases including diabetes, cancers,

neurological diseases and inflammations, and the effects of SLNs on a few of these diseases are discussed.

Anti-type 2 diabetic effect

Type 2 diabetes mellitus treatments with phyto-bioactive compounds are used in traditional medicinal systems in India, China and Korea. Various food-grade phytocompounds have shown an enhanced effect in preventing type 2 diabetes mellitus.[44–48] Curcumin-treated prediabetic patients have shown a beneficial effect in reducing the development of diabetes with 9 months of intervention, along with a higher improvement in the β-cell functions.[49] Similarly, a resveratrol supplementation can enhance the antidiabetic effect in humans with a dose of 1 g for 45 days.[50] Quercetin is another flavonoid compound that showed a higher antidiabetic effect in streptozotocin-induced diabetic rats. Even though these phyto-bioactive compounds showed a higher antidiabetic effect, a longer duration of treatment was needed. In addition, their efficacy and bioavailability when administered through oral delivery systems were very low. To improve the bioavailability through oral delivery, several macro- or nano-sized colloidal systems have been studied. Among them, SLNs showed an enhanced effect in treating type 2 diabetes through oral delivery. Recently, berberine-loaded SLNs with a particle size of 76.8 nm showed an improved bioavailability with a higher antidiabetic effect in a diabetic mouse model.[51] This study also confirmed that berberine-loaded SLNs improved the islet function and can thereby effectively reduce diabetes progression. In addition, the same research group also found that the bioavailability of the berberine in the liver was 20 times higher than in blood, which led to a reduction in diabetes-associated complications such as lipolysis enhancement and lipogenesis inhibition.[52] These studies confirm that delivery of the bioactive compound to the systemic circulation in a highly active way can enhance not only specific activities but also improve the associated complications. The bioavailability of certain other compounds such as curcumin, resveratrol, or quercetin was effectively enhanced through SLN delivery systems, but their activity in a diabetic animal model remains limited. Recently, surface-modified SLNs loaded with curcumin showed a 9.5 times higher bioavailability through oral delivery,[7] and they can be potentially applied to treat type 2 diabetes.

Anticancer effect

Phytocompounds have been used to effectively treat various cancers for longer periods of time.[53–56] However, this effect is not highly appreciable due to a higher loss of bioactivity
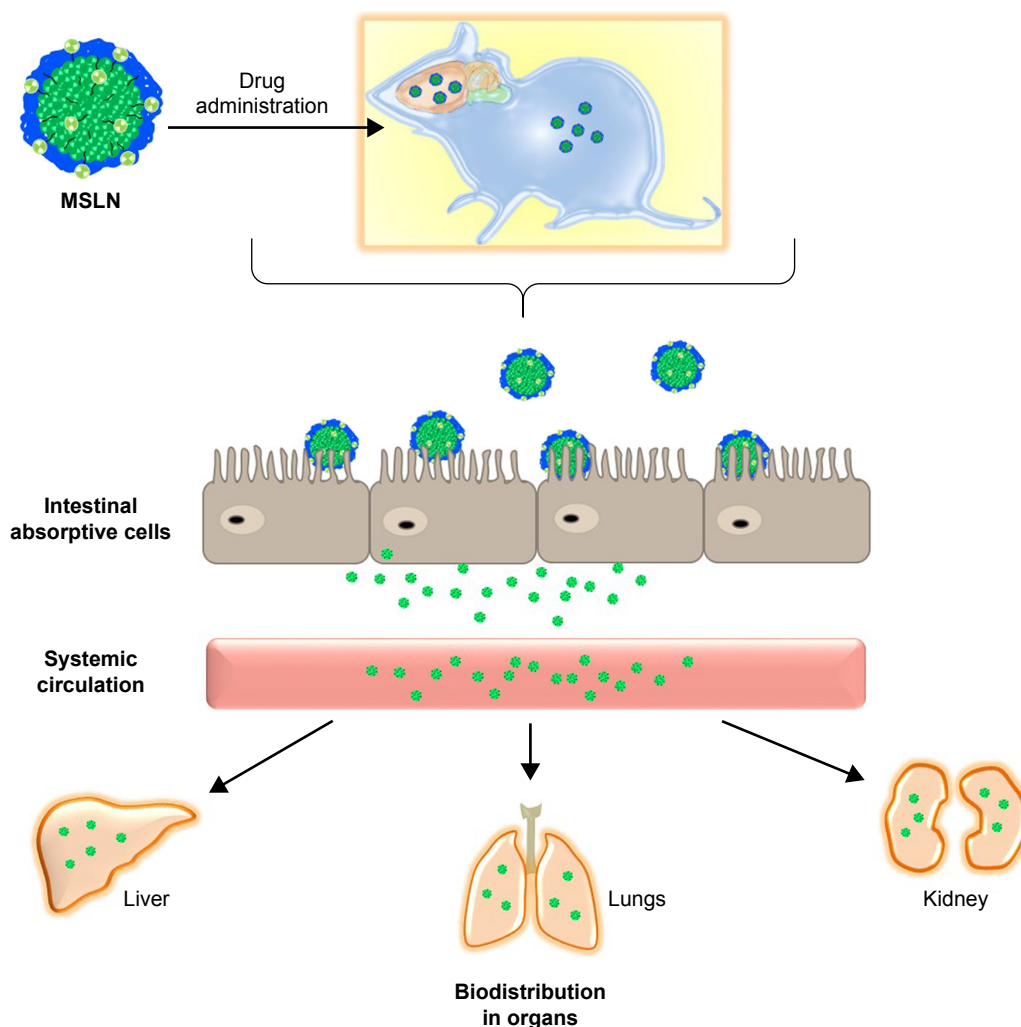
Figure 3 Biodistribution of phytocompounds loaded in MSLN through oral delivery.
Abbreviation: MSLN, modified solid lipid nanoparticle.

during oral therapy. Several synthetic medicines have also faced limitations for oral therapy, so lipid-based delivery of their active compounds has been extensively used to develop various cancer treatments.[57,58] SLNs have been extensively used in many studies to orally deliver bioactive compounds with an enhanced anticancer effect.[17,57,59–62] Genistein is a phytoestrogen that is extensively used for hormone-related cancers, and it has limited bioavailability. Recently, genistein-loaded solid lipid microparticles (SLMs) with a particle size of 6 µm were compared with SLNs with a particle size of about 120 nm in terms of their bioavailability. Surprisingly, SLMs showed a greater anticancer effect than the SLNs due to a slow disintegration in the intestine as well as the particles reaching the colon. In addition, different sizes of the particles can be used to alter the surface area of genistein to improve its activity. Smaller SLNs can be extensively absorbed in mesenteric vessels, leading to a higher absorption of the bioactive compounds rather than reaching the colon.[63]

In another study, curcumin-loaded SLNs were studied for their antitumor activity through intravenous administration, and curcumin showed a 1.25 times enhanced bioavailability.[62] Other research groups compared curcumin-loaded SLNs administered via intravenous or oral routes and showed 30 or 16.4 times higher bioavailability of curcumin, respectively.[22] Thereby, surface modification of SLNs with chitosan or modified chitosan could enhance the bioavailability of curcumin or other compounds in various organs through oral delivery. However, their applicability in various anticancer disease models is still limited. Many in vitro cell studies have shown an enhanced anticancer effect in various cancer models. Recently, berberine-loaded SLNs showed enhanced antitumor effect with a particle size of about 81 nm in MCF-7 cell lines.[64] Aloe-emodin is another phytocompound that can be loaded in SLNs, and when prepared with a particle size of about 88 nm, it showed an enhanced anticancer effect to treat breast and hepatoma cancer cell lines.[65] Resveratrol-loaded

SLNs with a particle size of about 96 nm showed an enhanced anticancer effect in HepG2 cells.[66] Similarly, oridonin-loaded SLNs with a particle size of about 108 nm showed an enhanced antitumor effect in MCF-7 cells.[67] Various research studies confirm that SLNs could be a potential carrier for various anticancer phyto-bioactive compounds, and further research on oral delivery of those anticancer phyto-bioactive compounds is necessary.

Antiobesity effect

The antiobesity effect of various phyto-bioactive compounds is well known to function through the inhibition of various cell signaling mechanisms, but these are very complex. In general, obesity is characterized by an increase in the deposition of fat storage adipose cells. A diet rich in various phytochemicals has shown an extensive reduction in the deposition of fat through complex mechanisms.[68,69] However, the concentration of certain phytochemicals reaching systemic circulation is very low. For instance, green tea catechin is a potential antiobesity compound, but its bioavailability is very low and is limited to 0.15 µM of the epigallocatechin gallate (EGCG).[70] In order to enhance the bioavailability of such phytocompounds, many lipid-based nanodelivery systems with SLNs or MSLNs have been developed to improve the delivery of the bioactive compounds with great potential for an antiobesity effect. Recently, EGCG was successfully loaded in SLNs with a particle size of about 300–400 nm, and it showed a higher stability and greater potential for oral delivery.[71] It could possibly be used in future as a delivery system to treat obesity-related complications. Zerumbone is another lipophilic compound that is most commonly found in ginger, and has shown an extensive antiobesity effect.[72] To date, there have been limited attempts to develop SLNs to deliver zerumbone for its antiobesity effect. Resveratrol is also a potential compound that has shown a higher antiobesity effect in various animal studies.[73] However, it requires a higher dose and prolonged supplementation. Recently, resveratrol-loaded SLNs and MSLNs were studied for their potential bioavailability. However, their roles in antiobesity have not yet been elucidated. Quercetin is another active compound that has shown significant potential for antiobesity in various animal studies. Recently, quercetin-loaded SLNs and chitosan-coated MSLNs were developed with a particle size of about 110 nm, and these showed an enhanced bioavailability of quercetin with a higher stability.[74] Further research is needed to focus on the oral delivery of SLNs and their antiobesity effect in animal models.

Anticardiovascular effect

Phyto-bioactive compounds such as resveratrol, curcumin, quercetin and diosgenins have shown an enhanced anticardiovascular effect through their cardioprotective activity. This cardioprotection is achieved through mechanisms such as antihyperlipidemia, antioxidation or platelet aggregation inhibition.[75–77] However, most phyto-bioactive compounds taken with the diet or through an oral delivery system have exhibited a lower bioavailability in systemic circulation.[78–80] Recently, many phyto-bioactive compounds showed an improved bioavailability through SLN or MSLN delivery systems, which can further improve their cardioprotective activity. Puerarin is among the most cardioprotective compounds, and its successful loading in SLNs resulted in a higher bioavailability in various organs, especially three times higher in the heart and the brain.[81] These studies confirm that a higher bioavailability and sustained release of these bioactive compounds can lead to a higher cardioprotective effect.[39,194] Furthermore, there is no change in the production of the metabolite when given orally. Very recently, flavonoid from *Dracocephalum moldavica* L. loaded in the SLNs with a particle size of about 104 nm showed an improved protective effect against myocardial ischemic–reperfusion injury. This could be a base study to prepare another phyto-bioactive compound-loaded SLN with cardioprotective activities.[39] Hydroxycitric acid (HCA) is a cardioprotective agent that was found in *Garcinia cowa*, and it undergoes much degradation during processing, leading to the loss of its cardioprotective activity when administered orally. Recently, HCA was successfully loaded in SLNs, which showed 1.3 times higher bioavailability than its free form.[82] Many phytocompounds loaded in SLNs or MSLNs are yet to be studied for their efficacy in oral delivery along with cardioprotective activity. Many other studies were conducted with a low-molecular-weight heparin-loaded SLNs or MSLNs with a much higher oral bioavailability to improve the cardioprotective activities.

Anti-arthritic effect

Phyto-bioactive extracts and compounds, such as green tea extract, pomegranate extract, curcumin, resveratrol, celastrol and gamabogic acid, have been extensively used to treat rheumatoid arthritis (RA).[83–85] These bioactive compounds showed an inhibitory mechanism against inflammatory mediators, thereby preventing cartilage destruction in various animal studies. Besides the protective effect of these bioactive compounds, their bioavailability through oral delivery system is a great challenge for their potential RA treatment.[86–88]

To overcome this, recently phytocompounds were loaded in SLNs and MSLNs which showed excellent bioavailability. Piperine-loaded SLNs with a particle size of about 128 nm showed excellent delivery of such compounds with potential anti-RA activity.[89] Similarly, hesperidin-loaded SLNs also showed a potential anti-RA effect with a particle size of about 279 nm in male Wistar rats. In another study, curcumin-loaded SLNs also showed an excellent delivery of curcumin in the RA-induced rats with potential anti-inflammatory or antioxidative mechanisms.[90] Other phytocompounds such as EGCG were also efficiently loaded in SLN systems and showed excellent bioavailability in animal models. This could also be potentially applied to treat RA. Many other bioactive compounds with potential anti-RA activities can also be efficiently loaded in SLN systems[91] for use in future treatments with nanomedicines. Furthermore, to improve the sustained release of the bioactive compounds, MSLNs can also be developed with specific bioactive compounds with higher anti-RA activities.

Anti-Alzheimer's effect

Phyto-bioactive compounds-loaded SLNs were recently used to treat Alzheimer's disease (AD), overcoming conventional limitations in treating neurodegenerative diseases.[92–96] Initially, SLN- or MSLN-loaded bioactive compounds were given intranasally or intravenously, and these showed extensive bioavailability in the brain, thereby preventing inflammation and further progression of AD.[97–101] Quercetin-loaded SLN with a particle size of about 200 nm was studied for its efficacy in the AD model, and it showed excellent delivery of quercetin to the brain with a higher antioxidative effect in brain cells.[102] The transport of bioactive compounds to the brain occurs through the endocytosis of the brain capillaries, and these compounds can thereby cross the blood–brain barrier. In a recent study, piperine-loaded SLNs showed enhanced bioavailability in the brain cells, and can thereby prevent a further prognosis of the AD. The study also revealed that piperine can enhance acetyl cholinesterase activity, reducing the formation of plaques and thereby improving cognitive activity.[96] Another study investigating ferulic acid-loaded SLNs against neurotoxicity found that ferulic acid can be extensively delivered to brain cells and can thereby prevent oxidation without any toxicity.[103] Curcumin is another potential compound that showed excellent anti-Alzheimeric effect in various in vitro and in vivo studies,[104–112] but it showed limitations in its bioavailability through oral delivery with a very low content in the brain, and could not achieve a significant potential effect. Therefore, many recent studies

were intended to improve the bioavailability of curcumin to the brain through oral delivery via SLNs.

Recently, curcumin-loaded SLN was studied for its potential effect in an aluminum-induced AD model. Curcumin-loaded SLN showed excellent delivery of curcumin to the brain, and the bioavailability of curcumin varied from 32 to 155 times in a dose-dependent manner with an enhancement in cognition and the biochemical parameters associated with it. In comparison with free curcumin, treatment with curcumin-loaded SLN showed 73% higher recovery of the biochemical aspects. This confirmed that curcumin-loaded SLN will be a potential delivery system for the oral delivery of curcumin for AD treatment.[113] However, to further improve the bioavailability, curcumin-loaded MSLN was recently developed, and it showed improved delivery of the curcumin for AD treatment. Recently, resveratrol has gained more interest to treat AD due to its greater neuroprotective effect, and many studies confirmed that resveratrol treatment significantly improved the cognition and biochemical parameters.[114–123] Recently, resveratrol-loaded SLN was studied for its bioavailability and brain delivery. Resveratrol was efficiently delivered to the brain and exhibited its potential bioactivity. To improve the sustained bioavailability, resveratrol-loaded chitosan-coated MSLN was also studied, which showed an enhanced and sustained delivery of resveratrol to the brain. In another study, resveratrol-loaded SLN with functionalized antibody showed excellent cellular uptake compared to normal SLN.[93] Many other phyto-bioactive compounds loaded onto SLNs or MSLNs are still in the development pipeline with a size suitable for effective transport through the blood–brain barrier, and these can result in higher protection of brain cells to overcome age-related degenerative diseases.[195]

Anti-Parkinson's effect

Parkinson's disease (PD) is another neurodegenerative disease that occurs most commonly in the elderly due to the loss of the dopaminergic neurons and the activation of microglial cells.[124–130] Phyto-bioactive compounds have shown an excellent anti-neuroinflammatory effect through various pathways.[131–141] However, they have limitations in oral delivery due to their extensive first-pass metabolism and difficulty in crossing the blood–brain barrier. Recently, SLN-loaded phyto-bioactive compounds have shown excellent bioavailability through oral delivery and a higher brain bioavailability.[107,132,142,143] Curcumin is a bioactive compound that has shown an anti-Parkinson effect in various in vitro and in vivo studies.[144–152] However, its brain bioavailability is limited. Recently, curcumin-loaded SLN was studied for

its efficacy and brain bioavailability. The bioavailability of curcumin-loaded SLNs or MSLNs in the brain was greatly enhanced,[7,8,12] which showed its potential for use in treating PD in future. Similarly, resveratrol-loaded SLNs or MSLNs also showed potential for delivery to the brain cells, and can also exert an anti-Parkinson effect. Many recent approaches assessed the brain bioavailability to exert a preventive effect against neuronal loss. Nevertheless, there is still a limited role for SLN- and MSLN-loaded phyto-compounds in PD animal models through oral delivery. Many new studies are currently in the pipeline to achieve an anti-Parkinson effect using SLN-loaded phyto-bioactive compounds to prevent neuronal loss and thereby ageing.

Antihepatic effect

Liver damage is associated with various chronic complications. The liver can be protected using dietary phyto-bioactive compounds,[45,153–166] but their potential for liver protection through oral delivery systems is very limited. However, SLN-loaded phytocompounds showed excellent bioavailability with enhanced liver protection.[1,20,52,93,167–170] Recently, *Ficus benjamina*-loaded SLN was studied against the hepatotoxicity, and the results showed a higher delivery of bioactive compounds with enhanced hepatoprotectivity.[171] Similarly, sesamol-loaded SLN also showed excellent hepatoprotection along with lower irritation when administered through oral delivery.[20,21,95,172] However, many phytocompounds that have shown excellent hepatoprotection have not yet been studied for their efficacy and bioavailability through SLN or MSLN delivery systems.

Chitosan-based surface modification of SLN delivery systems for the bioavailability of phytocompounds to the target organs

Owing to the higher release of SLN-loaded phyto-bioactive compounds in the stomach with an acidic pH, surface modification was effectively carried out with mucoadhesive polymers to enhance the sustained release of phyto-bioactive compounds

in SLNs.[4,173–175] Chitosan has various advantages over other polymers including lower toxicity, enhanced absorption and high mucoadhesive and antimicrobial properties which enhance the oral delivery of the phyto-bioactive compounds. In order to further enhance the absorption properties of the chitosan-coated SLNs, grafting of chitosan moieties was done through conjugation of amine and hydroxyl groups leading to functional chitosan like TMC.[7] SLN coated with TMC has excellent properties compared with chitosan which include higher mucoadhesiveness, enhanced delivery and low toxicity. Further, modified chitosan grafted with lipids showed target-specific delivery of the core compounds. For example, palmitic acid-grafted TMC-coated SLNs showed enhanced delivery of the different phytocompounds through controlled release by providing excellent surface environment through nanomicelles. Recently, Ramalingam et al studied the delivery of curcumin to the brain compared to that of free curcumin, chitosan-coated, non-chitosan-coated and TMC-g-palmitic acid-coated SLNs.[7] Among those, TMC-coated SLNs showed enhanced bioavailability of the curcumin in the brain cells. The same research group also found that resveratrol-loaded TMC-g-palmitic acid-coated SLNs showed 3.8 times higher bioavailability than the resveratrol suspension. In another study, N-carboxymethyl chitosan-coated SLNs showed enhanced bioavailability of curcumin in lymphatic cells. The uptake by the lymphatic cells and the oral bioavailability of the curcumin were found to be 6.3 and 9.5 times higher than that of curcumin suspension.[176] Based on the above studies, we can confirm that chitosan derivatives can be extensively used to improve the delivery of the phyto-bioactive compounds against various chronic diseases (Table 1).

SLN modified with chitosan and its derivatives, and its bioavailability through oral delivery
Chitosan-coated SLNs

Chitosan-coated SLN is the first-generation modified SLN developed to enhance the delivery of phyto-bioactive

Table 1 Phyto-bioactive compounds loaded in chitosan-coated solid lipid nanoparticles used in various disease models

Type of chitosan-modified solid lipid nanoparticles	Bioactive compounds	Disease models	References
Chitosan-coated solid lipid nanoparticles	Curcumin	Pancreatic cancer models	Thakkar et al[181]
	Resveratrol	Brain bioavailability studies	Ramalingam and Ko[13]
	Caffeic acid	Oral bioavailability studies	Fathi et al[183]
	Ferulic acid	Pancreatic cancer models	Thakkar et al[181]
Trimethyl chitosan-coated solid lipid nanoparticles	Curcumin	Brain bioavailability studies	Ramalingam and Ko[7]
	Resveratrol	Brain bioavailability studies	Ramalingam and Ko[12,13]
N-trimethyl chitosan-g-palmitic acid surface-modified solid lipid nanoparticles	Resveratrol	Brain bioavailability studies	Ramalingam and Ko[12]

compounds. Various properties of chitosan, such as high mucoadhesion, cationic nature, low toxicity and high bio-availability, have resulted in more researchers using this polysaccharide as a coating for SLNs to improve the delivery of bioactive compounds.[4,19,175,177] Chitosan-coated SLN was also used in other delivery routes including nasal, vaginal and skin, due to its enhanced and sustained delivery.[19,178–180] Based on the type of chitosan and lipids involved, the application and delivery routes vary. In oral delivery, chitosan-coated SLN is preferred for its mucoadhesion and sustained release. Although many commercial drugs have been extensively studied for use with chitosan-coated SLNs for sustained oral delivery,[174,177,180,181] there are few studies on phyto-bioactive compound loading. Recently, ferulic acid-loaded chitosan-coated SLNs were studied to treat pancreatic cancer, and these showed an enhanced effect via oral delivery. Similarly, chitosan-coated SLNs loaded with curcumin showed a sustained release of curcumin in various organs. Further-more, toxicity studies were conducted for certain drugs in combination with curcumin in chitosan-coated SLNs, and the results indicated no toxicity during pancreatic cancer treatment.[182] In another study, resveratol loaded in chitosan-coated SLNs also showed a higher bioavailability in animal models. Similarly, caffeic acid-loaded SLNs coated with alginate chitosan showed higher antioxidant activity and sustained release.[183]

TMC-coated SLNs

TMC-coated SLN is another modified SLN that overcomes the drawbacks of chitosan-coated SLN by increasing the solubility over a broad range of pH, improving the mucoad-hesion and achieving a sustained release of the bioactive compounds in the SLN during oral delivery.[184–186] Many early studies were conducted to deliver various drugs, including insulin, vaccines and proteins via sustained delivery with TMC-coated SLNs to enhance the biomedical effects in treating various chronic diseases.[187,196–198] Fewer studies were conducted on the delivery of phytocompounds through TMC-coated SLNs.[7,12] A recent study report on the delivery of curcumin to the brain through TMC-coated SLNs showed sustained delivery to the brain through paracellular transport, and this presents a potential treatment for AD models.[7] The same research group also performed a study with resveratrol as a core compound and found 3.8 times higher delivery of the resveratrol to the target organ through oral delivery.[12] These studies show a pathway for future studies of various phyto-bioactive compounds for sustained release via oral delivery and improved bioavailability to treat various diseases.

Hydroxypropyl trimethyl ammonium chloride chitosan (HACC)-modified SLNs

HACC-modified SLN is another modified chitosan-loaded SLN that was recently developed to improve the stability in the gastrointestinal environment for sustained release.[188–192] A recent study with docetaxel showed that HACC-modified chitosan administered orally exhibits a higher drug bio-availability via various absorption mechanisms including transcellular, paracellular and M cell uptake.[193] Interestingly, the study also found that HACC-modified SLNs showed a higher uptake of the drug in the Peyer's Patches than normal cells. The same research group also showed that HACC-modified SLNs with a uniform particle size achieved enhanced bioavailability with around 2.45 times increase of the drug through oral delivery.[187] In addition, the toxicity of the HACC-modified SLNs was also studied in Caco-2 cells, and the results showed no toxic effect and no irritation in the mucosa of the rats. This study confirmed that there is a chance of increase in the bioavailability of phyto-bioactive compounds like curcumin, quercetin and resveratrol through HACC-modified SLNs, which will be the scope for future studies on enhanced delivery. Figure 4 shows the mucoad-hesion and bioavailability of the phytocompounds loaded in the SLNs or MSLNs.

Challenges associated with SLNs and MSLNs in the food systems

Even though SLN and MSLN delivery systems try to accomplish the criteria required for the enhanced delivery of the phyto-bioactive compounds, it is not possible to use a single delivery system for all the phyto-bioactive compounds. However, both systems have unique advantages in both food and pharmaceutical applications like use of high food-grade lipids, bulk production with lower production cost and higher loading capacity in comparison to the food bioactive compounds. The incorporation of SLNs or MSLNs in the food particles, their physiological changes in the food systems during storage, and toxicity of these systems to the target organs are yet to be studied. The research in these aspects will increase the utilization of the SLNs or MSLNs in the food products. Food-based medicine will be a greater demand soon owing to the toxicity of various synthetic medicines. These systems could efficiently deliver the phyto-bioactive compounds along with the nutrients, and they will be helpful in the development of fortified food products or functional foods in future. In addition, MSLN development is not cost effective, and further research is necessary in the development of low-cost chitosan and modified chitosan for their effective usage and research in the toxicological
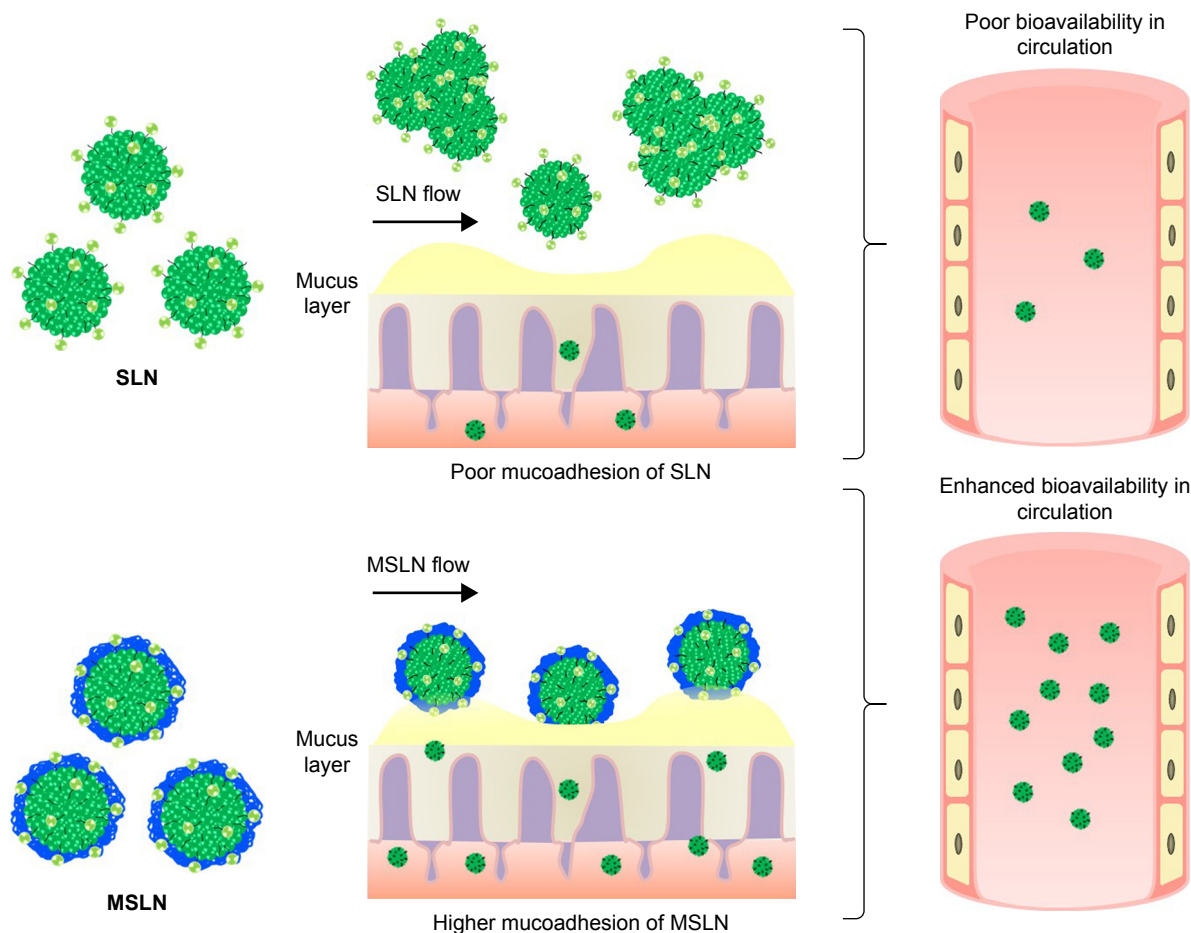
Figure 4 Schematic representation of mucoadhesion of SLN or MSLN through oral delivery.
Abbreviations: MSLN, modified solid lipid nanoparticle; SLN, solid lipid nanoparticle.

aspects could widen their applications in many other associated industries.

Conclusion

SLNs and MSLNs are promising colloidal delivery systems that help deliver phytocompounds to various organs, including the brain, via oral delivery. The bioavailability of these phytocompounds loaded in SLNs has been found to be about 5–10 times greater than that of their native form. Furthermore, the sustained release of these phyto-bioactive compounds through oral delivery can also be achieved through surface modification of the SLNs, which opens the way for development of many new phytocompounds loaded onto SLNs or MSLNs to treat various chronic diseases. The sustained and improved delivery of phyto-bioactive compounds via oral delivery is a focus of future development in nanomedicine.

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Disclosure

The authors report no conflicts of interest in this work.

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