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Application of nanotechnology to improve the therapeutic benefits of statins

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Hyperlipidemia is defined as an elevated level of lipids and lipoproteins in the blood and is considered to be a significant risk factor for accelerating the process of atherosclerosis and, consequently, cardiovascular disease. The level of cholesterol, especially low-density lipoprotein cholesterol (LDL-C), is commonly elevated in hyperlipidemia and represents the primary therapeutic target. Statins are a group of drugs that function by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and are extremely efficacious in reducing elevated LDL-C in the serum and preventing atherosclerotic cardiovascular disease. However, statins have some limitations, such as poor aqueous solubility, low oral absorption, and, consequently, limited bioavailability when administered by the oral route. The field of nanotechnology is now well developed and some of these newer nanotechnology strategies offer systems with enhanced aqueous solubility of the statin, increased absorption, bioavailability, and controlled release of the statin at the site of administration. Here, we discuss nano-sized drug delivery systems to enhance the therapeutic potential of statins.

Introduction

Cardiovascular disease is a major cause of death, worldwide. Hyperlipidemia is one of the most important risk factors in the development and progression of cardiovascular disease and is characterized by elevated plasma lipoproteins, including LDL-C and triglycerides (TGs) [1]. Statins are the most common medication prescribed to lower plasma lipids and decrease the risk of developing cardiovascular disease. Statins primarily target LDL-C and the degree to which statins lower LDL-C generally ranges from ~10% to ~40% [2].

However, statins have low oral bioavailability primarily because of their limited aqueous solubility and some have a considerable molecular weight. Additionally, significant numbers of patients develop drug-related adverse effects. Improved bioavailability of statins has potential to reduce the adverse effects and toxicity associated with higher statin plasma concentrations [3], and efficient delivery systems may improve this bioavailability. Here, we summarize novel drug delivery systems and their therapeutic utility for statin delivery.

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Properties of statins

Statins inhibit HMG-CoA reductase, thereby lowering elevated LDL-C and reducing the incidence of cardiovascular disease [4]. Statins also moderate the plasma concentrations of other lipids, including TG and high-density-lipoprotein cholesterol (HDL-C) [5].

Interactions between HMG-CoA and HMG-CoA reductase cause conversion of HMG-CoA to L-mevalonate, the rate-limiting step in cholesterol synthesis. Competitive inhibition of HMG-CoA reductase by statins reduces cholesterol synthesis in the hepatocyte, upregulation of hepatocyte LDL-receptor expression, and reduced circulating plasma LDL-C levels [6].

Natural statins, such as lovastatin (LOV), pravastatin, and simvastatin (SIM), are closely related in chemical structure, whereas the structural features of artificial statins allow more interactions with HMG-CoA reductase, thereby altering their lipophilicity and function [7]. The major challenge in formulating a therapeutic statin derivative is to obtain a stable formulation with enhanced bioavailability following oral administration [8].

Atorvastatin, fluvastatin, LOV, and SIM are comparatively lipophilic molecules, whereas rosuvastatin is more hydrophilic [9]. Statin absorption from the small and large intestine is impacted by the dose and dissolution rate in the intestinal lumen, transit time, and permeability across the intestinal mucosal membrane. All statins are absorbed in the range of 30–98% following oral administration, reaching peak plasma concentration (T_{max}) at ~4 h [10].

Newer statins demonstrate poor systemic bioavailability, exhibiting increased first-pass metabolism [7]. Given that the liver is the target organ for statins, an effective first-pass uptake into hepatocytes can be therapeutically beneficial. The systemic bioavailability of cerivastatin is >60%, whereas for fluvastatin it is 19–29% [9].

All statins are hepato-selective for HMG-CoA reductase inhibition, which is a benefit given that the liver is the greatest contributor to endogenous cholesterol production. Lipophilic statins enter endothelial cells by passive diffusion more efficiently than do hydrophilic statins because of extensive first-pass uptake. Possible pathways for permeation of hydrophilic statins into extrahepatic cells, such as endothelial cells, is the organic anion transporter (OATP-C), which also allows hydrophilic statins to enter hepatocytes [11]. Pravastatin, cerivastatin, pitavastatin, rosuvastatin, and atorvastatin are some human OATP1B1 substrates belonging to the OATP group [12]. In hepatocytes, other drug carriers, including multidrug resistance protein, breast cancer resistance protein (BCRP), and the bile salt export pump, can result in efflux of the parent drug or the metabolite [13] and represent crucial mechanisms for statin clearance and metabolism [14].

TABLE 1

Pharmacokinetic properties of statins

Property	Statin							
	Atorvastatin	**Cerivastatin**	**Fluvastatin**	**Lovastatin**	**Pitavastatin**	**Pravastatin**	**Rosuvastatin**	**Simvastatin**
Dose (mg)	40	0.3	20–40	40	2	40	20–80	40–60
Dose form	Open acid	Open acid	Open acid	Lactone	Open acid	Open acid	Open acid	Lactone
Optimal time of consumption	Any time during day	Evening	Bedtime	With meals morning and evening	Any time during day	Bed time	Any time of day	Evening
Absorption (%)	30	98	98	31	80	37	50	65–85
T_{max} (h)	2–4	2.5–3.0	0.5–1.5	2–4	1.0–1.8	0.9–1.6	3–4	1.3–2.4
Bioavailability (%)	12	60	10-35	<5	>60	18	20	<5
Solubility	Lipophilic	Lipophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Main metabolic pathway	CYP3A4	CYP3A4	CYP2C9	CYP3A4	CYP2C9	CYP3A4	CYP2C9	CYP3A4
Lipid-lowering metabolites	Active	Active	Mainly inactive	Active	No	Mainly inactive	No	Active
IC_{50} (nM)	15.2	13.1	17.9	2.7–11.1	6.8	55.1	12	18.1
Hepatic excretion (%)	>70	–	>68	>70	–	46–66	90	78–97
Renal excretion (%)	2	<30	6	30	<2	60	10	13
Clearance (1 h^{-1}, kg^{-1})	0.25	0.20	0.97	0.26–1.10	–	0.81	–	0.45
Half-life (h)	11–30	2–3	0.5–2.3	2.5–3.0	11	0.8–3.0	20	1.9–3.0
Production method	Synthetic	Synthetic	Synthetic	Fungal fermentation	Synthetic	Fungal fermentation	Synthetic	Fungal fermentation

Statin metabolism occurs largely via cytochrome P450 (CYP450) enzymes [12]. The CYP3A4 isoenzyme metabolizes most drugs, including LOV, SIM, and atorvastatin [12].

CYP2C9 metabolizes fluvastatin, whereas CYP2C19 metabolizes rosuvastatin. By contrast, pravastatin, pitavastatin, and rosuvastatin are not metabolized by CYP450 [15]. In general, lipophilic drugs are more susceptible to oxidative metabolism using CYP450 [16].

Most statins are eliminated in the bile after being metabolized in the liver [11]. Hepatic clearance of statins is controlled through carriers located on the basolateral membrane of liver tissue. Canalicular efflux carriers P-glycoprotein (P-gp) and multidrug resistance-related protein 2 are two major ATP-dependent efflux pumps for secreting statins into the bile.

Urinary excretion of statins is minimal, with the exception of pravastatin, where up to 60% of intravenously administered pravastatin is excreted in the urine [17]; tubular secretion, primarily mediated by the OAT3 carrier, is the major pathway responsible for the renal elimination of pravastatin. Except for atorvastatin and pitavastatin, statins have very short elimination half-lives (0.5–3 h) (Table 1).

Absorption and bioavailability

Statins have recently been evaluated in the prevention of a variety of diseases, including osteoporosis, Alzheimer's disease, stroke, cardiac diseases, and diabetes, as well as offering benefit post organ transplantation [18]. Statins have potential neuroprotective and neurorestorative effects on cerebrovascular disease, such as ischemic stroke, and in neurodegenerative diseases such as Parkinson's disease. The beneficial effect appears to be mediated through a reduction in cholesterol level and enhanced anti-inflammatory, anti-thrombotic and antioxidant functions [19–24]. Moreover, statins can contribute to the management of multiple sclerosis (MS) through immune modulation and anti-inflammatory functions [25]. Adverse effects, including myopathies, neuropathies, memory impairment, raised liver enzymes, lightheadedness, and depression, were observed with high-dose statins [3]. Statins are most frequently administered orally, once daily. However, oral administration presents several challenges; bioavailability is typically low because of first-pass metabolism by the liver and clearance within the gastrointestinal tract.

Reasons for the low oral bioavailability of statins also include limited cell permeability and limited aqueous solubility [26]; thus, the dose must be increased to compensate, creating risk for adverse drug effects [3]. Current studies have focused upon improving bioavailability and increasing efficacy, often utilizing novel delivery methods [3]

Low water solubility has been overcome through the development of new formulations [27]. Controlled-release statin formulations improve absorption, allowing increased accessibility of the statin to hepatocytes and reducing exposure of peripheral tissues to the statin, thereby reducing adverse effects.

Nanotechnology to enhance statin bioavailability

Nanotechnology has enabled the production of nano-sized systems and functional nanomaterials with diverse applications. Nano-sized drug delivery systems optimize the delivery of drugs with challenging pharmaceutical properties [28], and include nanocrystals, polymeric nanoparticles (NPs), solid lipid NPs (SLNs), liposomes, and micelles (nano-sized drug delivery systems or nanocarriers) (Fig. 1).

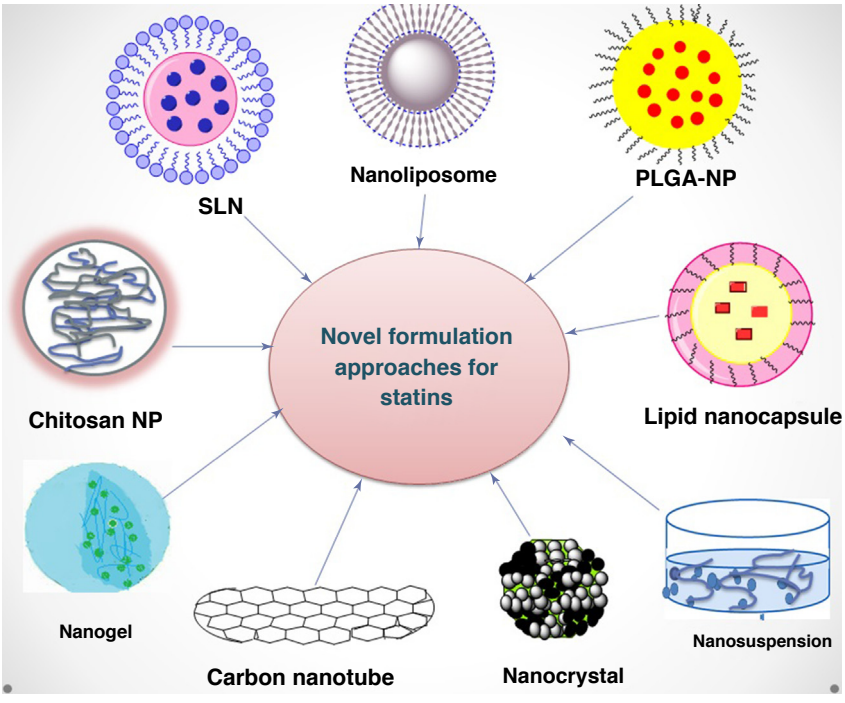

FIGURE 1

Formulation approaches for enhancing the delivery of statins. Abbreviations: NP, nanoparticle; PLGA, Poly(D,L-lactide-co-glycolide) acid; SLN, solid lipid nanoparticle.

Nanotechnology enhances the oral bioavailability of statins by increasing their uptake by absorptive endocytosis. The controlled release of drug helps to reduce fluctuations in the plasma concentration, minimizing adverse effects. Drug incorporated into NPs can diffuse through a cell membrane, increasing drug efficacy by enabling access to receptors in the target tissue [29]. Nanotechnology can also improve drug effectiveness, safety, and patient adherence, and reduce treatment costs.

Nanocarriers can be biodegradable and/or biocompatible, enable site-specific drug delivery, and can provide stimulus-sensitive release in response to triggers such as pH and temperature. Carriers and/or formulations include liposomes, nanofabricated materials, metals, and polymeric-based systems.

Nanoparticles

NP technology is a well-accepted formulation method for poorly water-soluble drugs. Being <1 mm in size, the intracellular localization of NPs is augmented, an advantage over microparticles.

Most nanotechnology-based techniques aim to increase the oral bioavailability of poorly water-soluble drugs [30]. NPs have been formulated with SIM using a novel evaporation technique in which volatile solvents were evaporated from an oil-in-water microemulsion. Resulting NPs can be incorporated into solid dosage forms (tablets). X-ray diffraction showed that the formulation, initially amorphous, was partially converted to crystalline form after storage at room temperature (RT) These tablets displayed remarkable improvement in dissolution profile compared with conventional tablets [31].

Lipid NPs in the form of SIM-tocotrienol lipid NPs were prepared by the incorporation of a tocotrienol-rich fraction (TRF) into the NPs, entrapping SIM within nano-compartments; the *in vitro* SIM release profile exhibited 20% release over 10 h followed by a plateau. Particle size was unchanged despite storage at RT for 6 months, efficacy remained intact and the NPs showed anticancer activity following verification of their antiproliferative impacts on malignant +SA mammary epithelial cells (a cell line taken from an adenocarcinoma of a BALB/c female mouse) [32].

Kouhi *et al.* formulated SIM nanocomposite nanofibers with poly-(ε-caprolactone)-loaded (PCL) bioactive glass (BG) NPs using an electrospinning technique. The BG NPs in the compound improved the crystallinity amount of PCL nanofibers; in addition, the results of differential scanning calorimetry revealed that SIM was scattered in the molecular situation via the PCL matrix. SIM release rate in PBS and nanofiber biodegradation were affected by BG concentration. The SIM nanocomposite nanofibers were used for treatment of degenerative disorders and showed controlled drug delivery, with formation of a glass–tissue interface on the nanofiber surface in the biological fluid, which is beneficial for bone regeneration [33].

Using a NP-mediated pitavastatin delivery system, Oda *et al.* reported improvement in collateral arterial circulation in an exercise-induced rabbit model of chronic hind limb ischemia, a platform potentially beneficial for treating severe organ ischemia [34].

Solid lipid nanoparticles

SLNs provide a favorable method for the delivery of poorly water-soluble drugs, such as statins. SLNs are spherical with a drug-lipid solid core stabilized using surfactants or stabilizers, allowing for long-term storage. Preparation includes emulsification by homogenization of the molten solid lipid containing the drug at elevated temperature. SLNs provide prolonged drug release, increased oral bioavailability of lipophilic medications, improved biocompatibility, lower toxicity, increased biodegradation, and increased drug encapsulation efficiency [35], making them an attractive sustained-release drug-targeting system for statin administration. SLNs administered orally can bypass first-pass metabolism by taking advantage of intestinal lymphatic drainage.

SIM-loaded SLNs were produced by hot melt emulsification and optimized based on the levels of surfactant, lipid, and SIM load; optimized formulations, prepared from solid lipids such as glyceryl behenate and glyceryl palmitostearate with Tween 80 as the surfactant, exhibited >96% SIM entrapment efficiency with average particle size <200 nm.

Pharmacodynamic studies of SIM-containing SLNs showed significant reduction of serum total cholesterol plus increased bioavailability [36]. Bioavailability of LOV was enhanced by oral administration in SLNs. LOV-incorporated SLNs, prepared using ultrasonication followed by homogenization at elevated temperature, produced particles of size range 60–119 nm with negative zeta potential and increased oral bioavailability compared with LOV suspension. Following intraduodenal administration in rats, the relative bioavailability of LOV was increased 173% and the hydroxyacid form of LOV contained in the SLN formulation was increased 324% compared with the reference LOV suspension [37].

SIM-loaded SLNs demonstrated high encapsulation efficiency (>95%). Absorption of SLNs after oral administration was site specific and occurred by clathrin-mediated endocytosis in enterocytes. The bioavailability of SIM increased when incorporated into SLNs, being 3.37-fold and 2.55-fold greater for SLNIs and SLNIIs, respectively, supporting the concept that formulated SLNs deliver drugs (SIM) effectively. SLNIs comprised Solutol (HS-15) to evaluate the impact of this molecule on increasing the oral bioavailability of SV, whereas SLNIIs comprised Tween 20 and oleic acid (OA) to assess the oral delivery of SV, given that previous studies had shown that these molecules are able to inhibit the activity of the CYP3A enzyme [38].

Nanostructured lipid carriers

'Second-generation' nanostructured lipid carriers (NCLs), a combination of solid and liquid lipids, showed improved bioavailability over traditional SLNs that utilize only solid lipids [39]. A SIM NLC suspension attained sustained and higher release as well as bioavailability of SIM. This NLC was a suspension of nanosized particles with extreme entrapment efficacy and downward recrystallization properties.

Oral administration of SIM-loaded NCLs in mice demonstrated a 4.8-fold increase in bioavailability compared with a SIM suspension and a 2.3-fold increase compared with SIM-loaded SLNs. Biodistribution studies showed enhanced accumulation of NLCs in liver [40].

NLCs and lipid emulsions (LEs) have also been used to deliver LOV. More than 70% LOV was incorporated into NLCs and LEs, a significantly greater loading capacity versus SLNs. *In vitro* release kinetics proved that LOV release could be decreased by 60% using lipid NPs incorporating Myverol as the lipophilic emulsifier. LOV release could be further reduced by also incorporating soybean phosphatidylcholine (SPC), with NLCs and SLNs exhibiting the

most protracted release of LOV. Rank order for LOV release from these formulations was NLCs > LEs > SLNs [41].

Lipid nanocapsules

Lipid nanocapsules (LNCs) show promise as a drug delivery system, their structure sharing features of both polymeric NPs and liposomes [42]. They comprise less toxic biomimetic substances and have a size range allowing absorption across fenestrated endothelium.

Incorporation of a PEGylated surfactant (solutol) into the LNC structure imparts special properties to these NPs, such as targeting tumor cells, with fewer adverse reactions and bypassing uptake by the mononuclear-phagocytic system. Nanocapsules formulated by the phase-inversion process have a spherical and homogenous morphology and showed improved stability, particle size, polydispersity, and drug release profiles. Passive targeting of breast cancer cells was accomplished using SIM-loaded lipid LNCs [43].

Chitosan nanoparticles

Chitosan (CTS) is a naturally occurring aminopolysaccharide that is widely used to improve the biodegradability of pharmaceutical formulations [44]. CTS NPs (CSNPs) are promising drug delivery vehicles or platforms, because of their low immunogenicity, low toxicity, biodegradability, and favorable biocompatibility. There is great interest in utilizing CSNPs to deliver anticancer agents. The anticancer properties of CSNPs loaded with anticancer compounds appear to be related to their interference in cancer cell metabolism, thereby curtailing tumor growth [45], disrupting tumor cell membranes, and stimulating apoptosis [46]. Pravastatin (PRV) was packed onto CSNPs (PRV/CSNPs) that were formulated by an ionic gelation process and assayed by FTIR and XRD. This revealed the spherical shape of the NPs, with an average size of 129.8 ± 10.5–270.4 ± 23.3 nm. These NPs used PRV in CSNPs, because PRV promoted anti-tumorgenicity against hepatocellular carcinoma (HCC) cell lines more effectively than did other statins [47].

Glycyrrheytinic acid (GA)–CSNPs have been produced to target liver cells, where they provide controlled release of incorporated atorvastatin upon reaching the liver, demonstrating significant reduction in hepatotoxicity compared with unformulated atorvastatin. The GA–CTS conjugate has great affinity for hepatocytes, which it specifically targets, providing continued release of the drug and decreasing hepatotoxicity compared with CSNPs [44].

In one study, CSNPs and PR-loaded CSNPs (PR-CSNPs) were prepared by ionic gelation. The prepared PR-CSNPs had acceptable NP size dimensions, excellent entrapment efficiency, and excellent temporal release kinetics of PR *in vitro*. CSNPs and PR-CSNPs are spherical with dimensions ~90 nm, a positive zeta potential, and sustained PR release *in vitro*. Additionally, the erythrocyte incorporates more PR when delivered from PR-CSNPs than from PR in solution. The impact of CSNPs and PR-CSNPs on the redox status of erythrocytes was more evident than with free drugs; consequently, PR-CSNPs are favorable drug carriers for delivery of PR into erythrocytes and, furthermore, have favorable characteristics for treatment of hypercholesterolemia [48].

Poly(D,L-lactide-co-glycolide) acid nanoparticles

Poly(D,L-lactide-co-glycolide) acid (PLGA) poly(esters), which contain poly(lactic acid), poly(glycolic acid), and their co-polymers, are the most studied polymers used in drug delivery because of their biocompatibility and biodegradability [49]. The physicochemical features, morphological properties, and *in vitro* release kinetics of drug-loaded PLGA-based NPs have also been extensively investigated.

PLGA is frequently used for the delivery of anticancer drugs [50]. Linear PLGA had several obstacles associated with, for example its biomedical application, hydrophobicity, and poor entrapment efficiency of drugs [51]. Therefore, to enhance the biological, chemical, and physical properties of linear PGLAs, formulation scientists introduced branched, dendritic, and star-shaped versions of PGLAs [52]. Wu and coworkers used cholic acid (CA) as the steroidal nucleus to develop star-shaped CA-PLGA polymers. SIM-loaded, star-shaped CA-PLGA NPs significantly decreased the viability of triple-negative breast cancer MDA-MB-231 cells (a human epithelial breast cancer cell line) and MDA-MB-468 cells (a triple-negative human breast cancer (TNBC) cell line) after 24 h by 65.35% compared with SIM solution (58.99% decrease) or SIM-loaded, linear PLGA NPs (52.66% decrease). After 48 h, cell viability was significantly reduced (particularly for SIM-loaded, star-shaped CA-PLGA NPs), and a constant (zero-order) rate of SIM release was achieved [53].

Chen *et al.* prepared a formulation of pitavastatin NPs using a PLGA with a MW of 20 000 and a copolymer fraction ratio of lactide to glycolide of 75:25 for the NP. PLGA-NPs including pitavastatin was formulated by using an emulsion solvent diffusion method in filtered water. Briefly, 15,16 PLGA was dissolved in a mixture of acetone and methanol, and pitavastatin was added. The subsequent PLGA-statin solution was emulsified in a polyvinyl alcohol (PVA) solution. Pitavastatin-loaded PLGA-NPs included 13% (wt/vol) pitavastatin. The pitavastatin-NP formulation was superior to both oral pitavastatin alone (oral administration) or pitavastatin administered systemically for the treatment of pulmonary artery hypertension (PAH) [54].

Chitosan nanogels

Nanogels are modified NPs that comprise hydrogels. They have a hydrophilic polymer structure formed by crosslinking of their components [19]. Nanogels represent intelligent drug delivery systems that are biologically compatible, degradable, and enhance absorption. However, their almost immediate removal from blood by the reticuloendothelial system (RES) impacts their function [55]. Thus, the combination of CTS nanogels and erythrocytes enhances biocompatibility, biodegradation, and extends the circulating half-life. Currently, numerous formulation techniques for improved drug loading into erythrocyte (ER) exist.

Harisa *et al.* examined the antitumor properties of PR in hepatocellular carcinoma cell lines. CTS nanogels were prepared by an ionic gelation process. The CTS nanogel system comprised CTS (3% w/w) and sodium tripolyphosphate (1% w/w). An improved hypotonic preswelling was used for loading of PR–CTS nanogels and free PR into human ER. ER-loaded, PR-containing CTS nanogels (PR-CNG-ER) exhibited suitable entrapment efficacy, drug loading capacity, and a constant release profile of PR over 48 h *in vitro* with antitumor effects against HepG2 cells; cell viability was reduced by 28%, whereas PR-ER and CNG-ER decreased cell viability by 18% and 13%, respectively [56].

Nanoliposomes

Liposomes are closed phospholipid bilayer vesicles that incorporate an aqueous phase. During the 1960s, Bangham prepared liposomes as an analytical device to examine the dynamics of

biomembranes. Different types of molecule can be loaded into the liposomal aqueous space or injected into their membranes. Given their chemical structure, liposomes are efficient delivery systems for pharmacologically active substances, including water- and lipid-soluble drugs. Depending on the composition and dimensions of the phospholipid bilayer, liposomes are categorized as either unilamellar (UV) or multilamellar vesicles (MLV) [42].

Intravenous injection of SIM liposomes suppressed neointima formation and inhibited the growth of monocytes/macrophages cell lines. Nano liposomes were prepared by a thin film and freeze-thaw method. Cerivastatin was incorporated into liposomes with a mean diameter of 98 ± 27 nm. The encapsulated cerivastatin demonstrated prolonged release, which reduced the proliferation of pulmonary artery smooth muscle cells *in vitro* with less cellular cytotoxicity compared with free cerivastatin. Liposomal cerivastatin was shown to be highly effective in the recovery of cardiac and lung function in PAH models. Metabolic and pharmacokinetic studies suggest that inhaled delivery of the cerivastatin nanoliposome for patients with PAH could be therapeutically advantageous compared with oral administration [57].

Beretta *et al.* administered both lipophilic SIM lactone and hydrophilic SIM acid by intravascular infusion for ischemia in guinea pig brains; SIM lactone delayed ischemia onset and improved the antioxidant capacity of the brain compared with SIM acid. The effect of intravascularly delivered SIM was associated with SIM lipophilicity during the initial stage of cerebral ischemia [58].

Nanocrystals

Nanocrystallization was the first process utilized to decrease drug particle size to a nanoscale, with a particle dimension of 1–1000 nm. Nanocrystals, as pure solid drug particles, enhance the solubility of a drug in three ways: (i) increasing surface area; (ii) increasing solubility; and (iii) producing high-energy solid-state particles, most of which exist in the amorphous state [59] Statins in the form of nanocrystals have been investigated with the goal of increasing both their water solubility and rate and extent of dissolution.

Athul *et al.* prepared a promising SIM nanosuspension using a high-pressure homogenization strategy. The SIM formulation prepared by this method appeared to exhibit increased stability, dissolution, solubility, and permeability compared with unformulated SIM. The enhancement in these properties resulted in an increase in the rate and extent of SIM absorption *in vivo*, with a significant increase in oral bioavailability. *In vitro* drug release data demonstrated a maximum cumulative percentage of dissolved drug of 98.7% within 1 h, compared with 45.9% for unformulated SIM [60]. Nanocrystals of atorvastatin were developed using the same method and complete drug dissolution occurred within 30 min [61].

SIM nanocrystals (300 nm) have also been prepared by nanoprecipitation in the presence of surface stabilizers, such as polyvinylpyrrolidone K-30 and sodium lauryl sulfate. The SIM nanocrystals produced by nanoprecipitation exhibited a similar enhancement in the dissolution rate *in vitro* compared with commercially available crystalline SIM [62].

Recently, SIM nanocrystals were synthesized using a sonoprecipitation technique in the presence of Pluronic F-68, the resulting formulation showing a fourfold increase in the dissolution rate, faster absorption (t_{max} reduced from 2.88 h to 1.99 h), and a 1.5-fold increase in bioavailability following oral administration in rats compared with unformulated SIM [63].

Nanosuspensions

Nanosuspensions comprise nanocrystal drug particles, liquid dispersion in the liquid state, and stabilizers (surfactants and polymer stabilizers). They normally include the poorly water-soluble drug (active) suspended without matrix and exhibit improved solubility for drugs with low water and lipid solubility [64]. This improved solubility results in faster C_{max} attainment following oral administration. This method is suitable for substances with low solubility and/or low permeability. Nanosuspension particles are <1 μm, allowing intravenous administration of poorly water-soluble drugs without the need to cross a biological membrane, such as the gastrointestinal tract or capillary wall following intramuscular injection. Nanosuspensions are formulated as liquids but can be lyophilized into a solid matrix [64].

Arunkumar and coworkers prepared atorvastatin calcium NPs using nanosuspension technology (high-pressure homogenization) and assessed the solid-state properties of the formulation. Crystalline atorvastatin was converted to the amorphous form and showed increased dissolution and greater solubility, suggesting that enhanced drug dissolution plus increased solubility increases the oral bioavailability of atorvastatin, although this was not tested *in vivo*. Their study demonstrated the effectiveness of high-pressure homogenization for improving the dissolution rate of poorly water-soluble drugs such as atorvastatin calcium [61].

Concluding remarks

Nanotechnology provides advantages for the delivery of statins, most importantly in oral bioavailability. At least two mechanisms should be considered to enhance the oral bioavailability of statins: (i) increasing their dissolution in the gastrointestinal tract; and (ii) reducing and/or eliminating first-pass metabolism following oral absorption, which can prevent some statins from attaining desired systemic concentrations.

Given that oral administration of statins is preferable, improving dissolution and bioavailability is key to enabling lower effective doses. Micelles, nanocrystals, and lipid-based NPs (NLCs and SLNs) are drug delivery systems and/or formulations that have positive impacts on drug solubilization in the gastrointestinal tract because of the decreased particle size of the entrapped statin. Liposomes, as polymeric NPs, could be considered for other-than-oral administration routes, especially when the goal involves site-specific drug delivery and sustained release. When selecting among polymeric NPs and liposomes, biocompatibility, formulation stability, and temporal release properties become crucial. Given that sustained and/or controlled drug release at the site of action is paramount for the success of an injected nanocarrier formulation, polymeric NPs could serve as the 'gold standard' to achieve a depot effect. Additionally, because statins might be therapeutically beneficial for the treatment of neurological diseases, such as Alzheimer's disease, SLNs are the most attractive nanocarrier to date for achieving suitable central nervous system penetration.

In conclusion, nanocarriers, for the safe and effective delivery of statins or any other drug, can meet the biopharmaceutical challenges that oftentimes limit the full therapeutic potential of a drug. By judicious selection of a nanocarrier system, challenges such as poor solubility, inadequate dissolution, chemical instability, limited oral bioavailability, compromised site-specific drug delivery, and inadequate sustained and/or controlled release of the active, can be overcome. This makes nanocarriers a diverse set of drug carriers or platforms with which to target diseases, such as diabetes, neurodegenerative diseases, and atherosclerosis.

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