

Critical Appraisal of Physicochemical Characteristics of Statins and Drug Delivery Systems for Improving Their Bioavailability

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Abstract

Statins have cholesterol and non-cholesterol (pleiotropic) action. They play a crucial role in preventing cardiac disease brought on by elevated blood cholesterol levels and atherosclerotic plaques, which decrease cholesterol levels by restricting the enzyme HMG-CoA reductase. In recent decades, several kinds of research have been published to discuss several physicochemical properties of statins. They have low solubility and bioavailability for several of their members. They have a similar chemical structure and molecular weight. Meanwhile, lipid-soluble or lipophilic statins (atorvastatin, simvastatin, fluvastatin, lovastatin, cerivastatin) undergo hepatic and enteric metabolism via cytochrome P450. Nowadays Statins have a proven decrease in heart disease death rates and a very favorable safety record. Long-term statin therapy for at-risk individuals significantly reduces illness and death from cardiac disease. The neurological system, kidney, and liver have all been impacted negatively by statin use. Long-term use of statins causes rhabdomyolysis, which is among the most commonly reported side effects of it. Simvastatin is a weakly water-soluble medication (liquid solubility of 0.03 g/L) with a low half-life of around two hours plus a low bioavailability of 5%. Due to its sluggish dissolving rate in the digestive system and substantial first-pass impact. This review focused on different techniques used to improve the solubility and bioavailability of the statins group.

Keywords

statins, physicochemical properties, solid lipid nanoparticles, pleiotropic effect

Introduction

One of the medications that is most frequently administered worldwide is statins. Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors used to reduce cholesterol levels by inhibiting the enzyme HMG-CoA reductase. The generation of cholesterol in the liver is mostly regulated by this enzyme [1, 2]. There are seven different types of statins. They have some physical-chemical properties. One of the statins family members (cerivastatin) was recently removed from the market owing to 52 fatalities linked to drug-related rhabdomyolysis, resulting in renal failure [3]. The statins will be briefly discussed in the following article. Firstly, the mechanism of this group will be illustrated. The advantages and disadvantages of statins will be discussed. Finally, it remains to study how to improve the solubility of statins, especially simvastatin.

Statins group Mechanism and properties

The mechanism of statins to reduce cholesterol is as follows: The HMG-CoA reductase (HMGCR) catalyzes the transformation of HMG-CoA to mevalonate, the rate-limiting step in the production of cholesterol (shown in Figure 1) [4, 5]. It's linked to decreased intracellular cholesterol levels that induce LDL-receptor expression on the hepatocyte cell surface. This causes a greater amount of LDL-C to be removed from the blood and a lower level of circulating LDL-C [6]. The additional useful effects of the

statins' elevations in elevated-density lipoprotein cholesterol percentage (HDL-C) and reduction in triglyceride percentage were seen on other lipid parameters [6, 7].

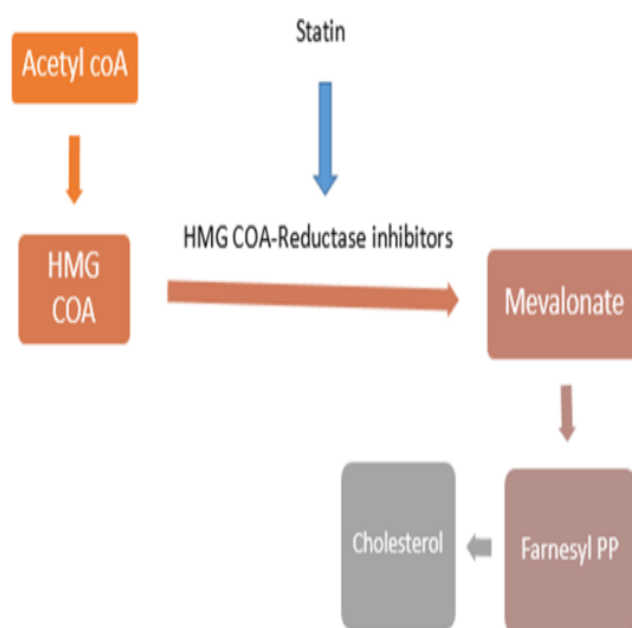


Figure 1. The inhibitory effects of statins on cholesterol production [5]

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Mevalonic acid produces nonsteroidal isoprenoid compounds which, upon inhibition, produce the abovementioned pleiotropic properties. In addition to their ability to change cholesterol levels, statins have positive cardiovascular effects as well. They also have hepatoselectivity properties, which are in connection with their lipophilicity [4]. Statins with greater lipophilicity have a tendency to be more exposed to non-hepatic tissues, whereas statins with higher hydrophilicity have a tendency to be highly hepatoselective. The varying levels of choices come from lipid-soluble statins that diffuse passively and non-selectively beyond hepatocytes and non-hepatocyte tissue, respectively [4, 8].

Rosuvastatin and pravastatin (statin groups having hydrophilic properties) depend greatly upon active transfer (utilizing the organic anion transporting polypeptide, OATP) into hepatic tissue to have an impact. The hydrophilic statins with great hepatoselectivity are anticipated to lower the likelihood of negative complications such as myositis and myopathy, plus the tendency for rhabdomyolysis (the abnormal degradation of skeletal muscle) to cause abrupt kidney failure [2]. Meanwhile, lipid soluble statins (atorvastatin, simvastatin, fluvastatin, lovastatin, cerivastatin) undergo hepatic, moreover enteric metabolism, which is carried out by cytochrome P450 (CYP450 group of enzymes) according to Table 1.

As a result, its involvement in any therapeutic significant drug-drug interactions with CYP450 agents has not been proven [1]. Lipophilic statins may have undesirable metabolic effects, like as decreased insulin secretion and a rise in insulin resistance [9]. Statins with a high lipophilicity are known to pass through the blood-brain barrier (BBB), whereas statins that are hydrophilic are not thought to. Scientific proof suggests that extremely fat-soluble statins for example simvastatin and atorvastatin penetrate the blood-brain barrier (BBB) and degrade cognitive function by affecting the physiology of the central nervous system [10]. On the other hand, updated population-based research concludes that patients who frequently take lipophilic statins may develop Parkinson's disease more frequently than those who continue to consume the statins. Clinical research suggests that dosage can cause permeability to decrease or increase [11]. After that, we've discussed some of the statin group's advantages and side effects.

Advantages of Statins Group

Impacts on low-density lipoprotein (LDL), endothelium, and C-reactive protein (CRP):

Since the statins are structurally similar to (3-HMG-CoA) and competitively restrain the HMG-CoA reductase enzyme, this enzyme carries out the first committed step in sterol biosynthesis. By lowering intracellular cholesterol levels, the expression of LDL receptors in liver cells is increased, resulting in improved LDL clearance from the circulation. Thus, their major function is to lower LDL cholesterol levels [2, 12]. Statins have numerous additional actions aside from lowering LDL, which are referred to as "pleiotropic" and consist of lowering oxidative stress, vascular inflammation, and improving the stability of atherosclerotic plaques. The majority of established hazard factors for atherosclerosis are linked to endothelial dysfunction, particularly in individuals with heart disease and hyperlipidemia. Statins improve endothelial function by reducing tumor necrosis factor (TNF) levels in the blood as well as disease and death [2, 13]. Statins lower the cholesterol level of platelet membranes, hence reducing their capacity to clot. They also decrease platelet function by lowering thromboxane A2 synthesis, which is a cholesterol-independent impact. C-reactive protein (CRP) levels are known to be reduced by statins and have a direct role in

atherosclerosis. Specifically, CRP, in particular, causes oxidized low-density lipoprotein (LDL) to be more sensitive to absorption by macrophages, enhances cellular adhesion molecule expression, enhances tissue factor synthesis, and inhibits nitric oxide generation [14, 15].

Atherosclerosis is a familiar illness in whose fatty aggregates are known as atheromatous lesions develop in the inner layers of arteries, causing hyperlipidemia and lipid oxidation. It is considered one of the major causes of mortality in most countries today [16]. Atherosclerosis is classified into two types: *arthrosis*, which is a buildup of fat accompanied by many macrophages; moreover *sclerosis*, which is characterized by fibrous tissue proliferation, results in a fibrosis layer composed of smooth muscle cells (SMC), and protrusion inside the artery, results in decreased blood flow, leukocytes, and connective tissue (CT). All of these lead to hardening of the arteries, the formation of clots, and thrombosis, leading to obstruction of blood flow inside the arteries (show in Figure 2) [17, 18]. Both hyperlipidemia and hyperglycemia are related to induce oxidative destruction, which affects the antioxidant status and lipoprotein values. However, statins' medicinal group can reduce the blood cholesterol level; they have the ability to inhibit atherosclerosis and vascular endothelial deterioration [6, 16, 19].

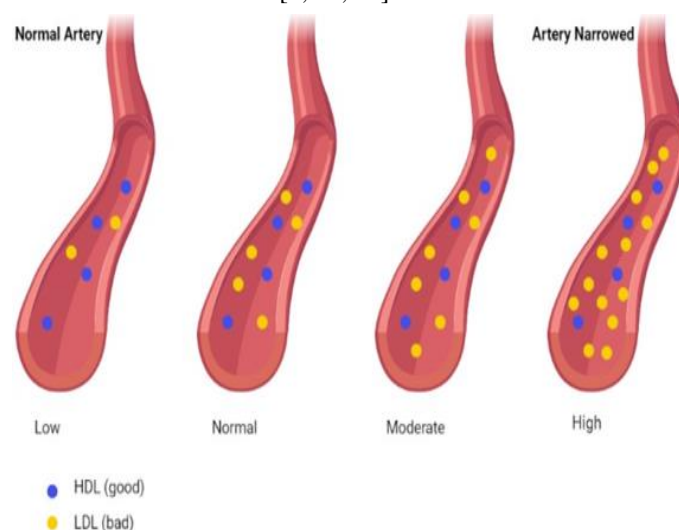


Figure 2. Different stages of deposition of cholesterol plaque on blood vessels [18]

The hypercholesterolemia family is a heritable disease that happens by gene defect for low-density lipoprotein (LDL) receptors' development on the cell surface. The liver is unable to absorb LDL in the lacking of these receptors. Hypercholesterolemia also elevates superoxide-free radical development in the vessels and falls off the production as well as release of endothelium-derived vasodilators. It also induces nitric oxide (NO) deactivation after its release from endothelial cells [20].

Clinical Advantages

Aggressive statin therapy can reduce severe coronary episodes within two to six months. This is assumed to be related to macrophages reducing their inflammatory activity, not the reduction in cholesterol levels. LDL and inflammatory markers, including CRP and interleukin-6, are reduced more effectively with intensive statin therapy (IL-6), implying a link between these indicators and the course of the disease. Treatment that is

too vigorous might result in a sluggish recovery. Plaques regressed a little. In the meantime, one study discovered a 6.3 percent decrease in atheroma thickness after one year [2, 14]. Additionally, active macrophages within the lesion are prevented from releasing matrix metalloproteinases (MMPs), which aids in the stability of atherosclerotic lesions. This reduces the chance of thrombosis, severe coronary syndrome progression, and plaque burst by preventing the collagen in the fibrous cap from breaking down (shown in Figure 3) [8, 12, 21-23]

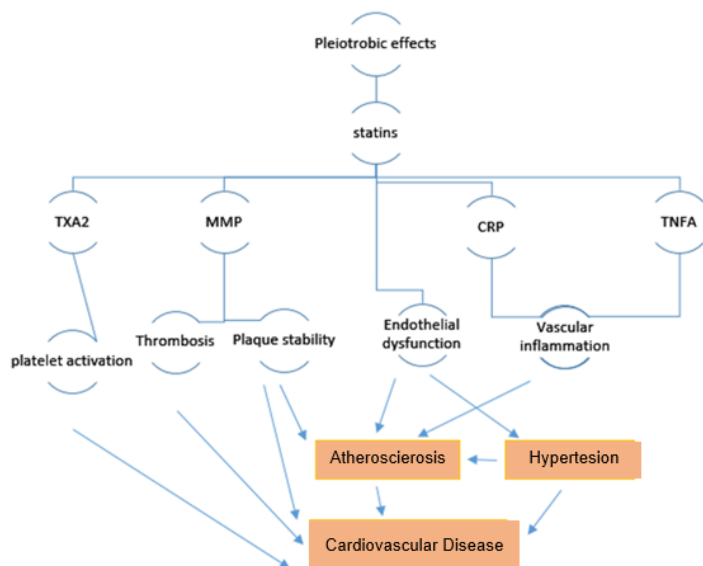


Figure 3. Diagram illustrating the Pleiotropic Effects of Statins [23]

Adverse Effects of Statins Group

Statins have a wide range of side effects, ranging from minor gastrointestinal problems to life-threatening diseases like rhabdomyolysis. When weighing the danger profile of statin drugs, it's better to think of adverse effects in terms of incidents per patient per year of care. Today's statins have a very strong safety record and have been shown to reduce the mortality rate from cardiovascular disease. The following is a list of the most serious side effects that have been recorded.

1. **Effects on Muscle:** Nausea, diarrhea, constipation, and myotoxicity, which can range from moderate myalgia to the uncommon occurrence of rhabdomyolysis, are among the most commonly reported side effects of statins. Severe muscular discomfort and palpable sensitivity, muscular sluggishness, and dark urine owing to myoglobinuria. The same 9% of fatalities are from rhabdomyolysis, with an expected risk of 0.3 every 100,000 person-years [1]. When any statin is combined with a fibrate, the risk of rhabdomyolysis rises to about 6.0 per 100,000 people per year. In contrast, the ratio of survival advantage is 360 every 100,000 person-years simply as a result of a decrease in fatal cardiovascular disease. Myotoxicity is more common when statin frequency and dosage rise. The CYP3A4 isozyme metabolises lovastatin, simvastatin, and atorvastatin, however CYP2C9 does so for rosuvastatin and fluvastatin. Therefore, medications that inhibit these enzymes (such as verapamil, azole antifungals, macrolides, diltiazem, and grapefruit juice) reduce the degradation of their substrates, increasing the danger of toxic effects. On August 1, 2010, this entry was published [12].

2. **The result for the liver:** Increases in liver enzymes, notably aspartate transaminase (AST) plus Alanine transaminase (ALT),

to more than 3-times the maximum tolerated range are a dose-related effect of statins that occur in fewer than 1% of individuals receiving first therapy and in 1-3 percent of individuals taking greater dosages (e.g., 80 mg of atorvastatin). According to estimates, statin-treated individuals experience liver problems at a rate of 0.5 to 1 in every 100,000 people, which is comparable to the background risk of liver failure in the general population. This shows that there is either no link between statin therapy and liver failure or that there is one [24].

3. **Result for the nervous system:** Statins are lipophilic, which means they have a higher likelihood of influencing the central nervous system after passing through the blood-brain barrier (BBB). Law and Rudnicka estimated that peripheral neuropathy because of statins has an occurrence of 12 every 100,000 person-years. Conversely, the new research explains that statins may have a favorable reflect on CNS illnesses, such as Alzheimer's disease, according to neurological evidence [2, 25].

In at least one nation, seven statins have now been licensed for clinical use. Despite the removal of cerivastatin in 2001, statins are generally thought to be a very safe and well-tolerated family of medications [26].

4. **The physicochemical qualities, durability, and bioavailability of pharmaceutical compounds, as well as their pharmacological action, are all affected by polymorphism.** Physical qualities for examples, chemical reaction, solubility, dissolving rate, stability, melting and sublimation temperature, density, hardness, adsorption, hygroscopicity, and refractive index may vary amongst polymorphic forms of the same medicinal ingredient. Amorphous variations, which are great energy systems with a great free enthalpy, are thermodynamically more stable than crystalline forms. Crystalline forms have lower solubility and dissolving rates than amorphous materials. In addition, the crystallites are less hygroscopic. Because amorphous forms have a greater solubility, they have a higher bioavailability, which is the percentage of a drug's supplied dosage that enters systemic circulation at a certain rate and is a determinant in identifying the drug's pharmacological activity. In the creation of medicine in the form of tablets in industrial settings, the polymorphism of medicinal ingredients can be significant. Because of the diversity in the pharmacokinetics of this class of medications, the efficacy of statin treatment varies from compound to compound and may be reduced. This variation may be due to statins' differing lipophilic characteristics and solubility. Statins are classified as grade II biopharmaceuticals in the categorization scheme for biopharmaceuticals (BCS), which indicates they are weakly soluble yet have a high permeation rate through biological membranes. Several oral formula techniques, such as salt production, decrease of particle size, the application of lipid carriers and co-solvents as liquid-filled capsules, complexation, amorphous solid diffusion, are used to induce the existence of the active pharmaceutical ingredient (API) in the gastrointestinal tract for poor-solubility BCS II drugs. Statins are an example of a medicine that comes in amorphous and crystalline forms, each with its own set of physical features and pharmacological effects. As a result, the polymorphic form of specific statins may have a major effect on their bioavailability and, as a result, their cholesterol-reducing actions. The current paper provides a complete overview of the available research on the impact of the polymorphic form on statin solubility and bioavailability, as well as potential therapeutic consequences [27]. Compounds that inhibit HMG-CoA Reductase have been shown to directly

reduced cholesterol production. We demonstrate the statin group's physical and chemical characteristics.

Physicochemical Properties of Statins Group

Since pharmacological compounds come in both crystalline and amorphous forms, the selection of the proper form is crucial to ensuring safe and effective pharmacotherapy. It affects not only a drug's solubility and dissolution rates but also how stable it is in storage. Due to their limited solubility and low absorption, statins require it especially. Statins' limited overall bioavailability necessitates the development of novel polymorphic forms that will improve therapeutic impact and lower patient dosage according to Table 1.

Based on the scientific studies that are currently available, it can be said that statins in amorphous form have the potential to raise the dissolution and bioavailability of this class of medications, which, then presents a chance to maximize their efficacy in the therapy for cardiovascular condition. In the following section, we will illustrate biopharmaceutical issues [28].

Table 1 illustrates the chemical composition of statins, which consists of three main components: an equivalent of HMG-CoA, a complex ring structure linking the statin molecule to the HMG-CoA reductase enzyme, and, finally, a branch chain ring structure that regulates the structure's solubility. By inhibiting HMG-CoA reductase, an enzyme that controls the rate of cholesterol manufacture, they lower LDL cholesterol levels. Due to the availability or lack of polar moieties on the mostly hydrophobic networks, statins exhibit significantly different solubility. Moreover, since lipid soluble drugs (e.g. atorvastatin, lovastatin, fluvastatin, cerivastatin and simvastatin) are carried out by cytochrome P450, there is a highly decreased bioavailability. Adversely, water-soluble medications (such as pravastatin and, to a minor extent, rosuvastatin) are primarily excreted unchanged [9]. Log P indicates the lipophilicity of the medications. An increase in Log P leads to increased lipid solubility and a decrease in water solubility. For example, atorvastatin log P = 6.3 indicates poor solubility in water. Another pKa is the pH at which the molecule is 50% protonated. This fact is important because most biologically active compounds are ionizable and also to raise their value of ionization, which can help to improve the bioavailability of medications [29]

Owing to metabolism in the gut wall and following "first-pass" metabolism, oral statin medication bioavailability is quite poor. Additionally, drug permeability, inadequate water solubility, as well as drug proportionate partition all contribute to the oral bioavailability being constrained [30]

Simvastatin and its properties

It is a cholesterol-reducing drug that belongs to the statins family. It is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Simvastatin is more successful than other lipid-regulating medicines at lowering LDL cholesterol levels, although they are less effective than fibrates at lowering triglyceride levels. Simvastatin reduces cardiovascular disease events and overall mortality regardless of cholesterol levels at the start [32]. It is an inactive prodrug that is converted to the hydroxyl acid form of the drug through enzymatic and chemical transformation in the gut, plasma, and liver. The majority of statins, including simvastatin, are available in immediate-release forms. SVA, on the other hand, is a weakly water soluble

medication (aqueous solubility of 0.03 mg/L) with a short half-life of around 2 hours and is removed by substantial cytochrome P 3A metabolism in the intestinal tract and liver. The oral bioavailability of SV in humans is as low as 5% due to its sluggish dissolving rate in the digestive system and substantial first-pass impact [33]. Because the medication is almost completely immiscible in water, it is weakly absorbed by the gut after oral administration, leading to limited bioavailability and ineffective clinical results. Micronization, solid dispersion, cyclodextrin complexation, microemulsion, liposomes, nanoparticles, phospholipid complexes, self-micro emulsifying drug delivery systems (SMEDDS), and other procedures or techniques are used. These techniques have been used to try and increase the drug's dispersion, dissolving rate, and increased bioavailability [34]. The poor bioavailability of SVA necessitates the development of an efficient delivery system that can improve the oral bioavailability of SVA. Transdermal, buccal, rectal, and parenteral modes of delivery are all options for avoiding first-pass metabolism.

Techniques Used to Enhance the Physicochemical Properties of Statins

1. Solid Dispersion: Since statins do not dissolve well in water, solid dispersion is one of the most practical and effective ways to boost solubility and dissolving rate, which raises bioavailability. A "solid dispersion" is a set of solid goods made up of minimum double separate ingredients. A hydrophilic lattice and a hydrophobic medication are usually used together. The combination can be crystalline or amorphous [35, 36]. Solid dispersion can take numerous forms, containing straightforward eutectic mixtures, solid solutions, glass solutions, and amorphous precipitations in crystalline carriers, and so on. There are several ways for preparing solid dispersions, including melting, solvent approaches [37], melt evaporation, melt extrusion lyophilization, melt agglomeration, surfactant usage, electrospinning, and extreme fluid technologies. Statins have also been studied for potential solubility increase using the solid dispersion approach. Simvastatin (SVA) solid dispersions containing either polyvinylpyrrolidone (PVP K15) or polyethylene glycol (PEG 6000) were created, and their consistency and dissolving properties were studied. The solubilization profiles of tablets containing solid dispersion of SVA: PEG 6000 demonstrated a progressive release of SVA, with a maximum dissolution amount of more than 80 percent within 60 minutes [38]. A solid dispersion formulation of atorvastatin was created by M. Shaker *et al.* using Pluronic F127® or Pluronic F68® in order to increase atorvastatin's solubility, speed up its dissolution, and increase its oral bioavailability. Atorvastatin's oral bioavailability was increased by 4.04 times when it was contained in rigid gelatin capsules with Pluronic F127® as opposed to when it wasn't [39].

2. Cyclodextrin inclusion system: The starch substitutes cyclodextrins (CD) have been identified as an important type of pharmaceutical formulation for enhancing the solubility and dissolving rate of poorly water-soluble medicines [40]. They are cyclic oligosaccharides with a hydrophobic inner cavity and a hydrophilic outside surface made up of (α-1, 4)-α-D-glucopyranose units. CD molecules are water-soluble due to their hydrophilic outer surface. Also providing a microenvironment for the integration of well-suited non-polar molecules is the hydrophobic cavity. CDs can form inclusion complexes with a variety of medications by encasing the entire or medication molecules in the cavity in portion. The complexes dissolve

readily in an aqueous medium, plus unbound drug molecules are in fast dynamic equilibrium with drug molecules bound within the CD cavity [1, 41, 42]. The advantages of CDs exhibit novel physicochemical properties such as improved stability, enhanced water solubility, improve bioavailability, and less harmful effects [43]. If statins-CD inclusion complexes can be formed and their solubility can be controlled their drug-release qualities should be able to be controlled. Controlling the hydrophobicity of the substituent is critical because CD and statin hydrophobic reactions are the primary mechanism for creating statins-CD inclusion complexes. Two aspects determine the release character: the degree of CD substitution and the crystallinity of the inclusion complexes. The ability of CD to dissolve in water and create complexes are both influenced by the degree of substitution.

These findings show a 5 to 8-fold increase in the statins' solubility at higher CD concentrations. It is reasonable to assume that the development of inclusion complexes between the statins (lovastatin and simvastatin) and the CD molecules is what caused the observed improvement in drug solubility as well as enhanced bioavailability [44].

3. Solutions: Statins' poor water solubility is one of its major drawbacks. The outcome, the drug's solubility rate in the GI tract is low, resulting in limited bioavailability. Statins' water solubility has nothing to do with their physical composition, whether crystalline or amorphous. Numerous strategies have been tried to boost solubility's, such as medication encapsulation and nano- suspension, however, the active constituent remains solid in these treatments, resulting in a poor dissolving rate. Water - insoluble active compounds in conventional solid dosage forms, such as tablets or multi particulates in capsules, Because of their delayed and imperfect disintegration and absorption, are linked to the risk of drug-food interactions. Solubilization is the procedure which weakly water-soluble solute molecules passing spontaneously into an aqueous system of cleansers, forming a thermodynamically stable solution [36]. An agent that inhibits HMG-CoA reductase and contains atorvastatin, N-methyl pyrrolidone as a solubilizer, and a variety of carriers (PEG 400, PEG 1540, PEG 4000, etc.) has been reported to increase bioavailability in one invention. The composition can be administered as a solution or suspension using traditional dispensing methods, such as gelatin capsules, and it can also be delivered as a tablet or suppository. The researchers created atorvastatin calcium, N-methyl pyrrolidone, and PEG 400 solution that may poured straight into a harsh gelatin capsule. It can also be made as a solid dispersion and then packed into a harsh gelatin capsule or a buccal tablet. In contrast to Lipitor®, a bioavailability analysis of the one dose oral bioavailability of the produced atorvastatin oral tablet revealed a relative bioavailability of 49.77 percent [36].

4. Self-emulsifying drug-delivery system: When put into the aqueous phase under mild agitation, SEDDS are mixtures of oils and surfactants that automatically emulsify to produce fine oil-in-water emulsions. They are typically isotropic and occasionally contain co-solvents. SEDDS has developed in recent years by utilizing medium-sequence triglyceride oils and non-ionic surfactants, which are fewer hazardous. improved oral bioavailability, allowing for dose reduction greater consistency in the periodic patterns of medication uptake, careful selection of the drug(s) and application to specific GIT absorption windows Preservation of the medication(s) from the harsh environment in the gut, management of the transportation profile, decreased

variability, and consideration of the impacts of meals, preservation of essential drug ingredients, higher drugs in packages, and a choice between liquid and solid dosage are all factors. Self-emulsification is a difficult process that still requires more research. SMEDDS differ from SEDDS in that they form significantly tinier emulsion beads with dilution, leading to a clear or transparent solution. SMEDDS commonly contain hydrophilic co-solvents (propylene glycol, polyethylene glycols) and have relatively high surfactant concentrations (typically 40–60% w/w). Due to it avoiding the rate-limiting dissolving phase for example BCS class II pharmaceuticals, including a drug into SMEDDS/SEDDS boosts its solubility (decrease solubility and rise permeability). Statins in BCS class II can be formulated as SMEDDS or SEDDS to improve bioavailability. In comparison to Lipitor® tablets, SEDDS formulations of statins had a 1.5-fold improvement in the bioavailability of SVA and atorvastatin [45]. The potential of a SEDDS to both minimize degradation and boost absorption may be particularly advantageous for medicines with low oral bioavailability due to both decreased solubility and GIT degradation. Many medications deteriorate in physiological systems, which might be due to the stomach's acidic pH, enzymatic breakdown, or hydrolytic destruction.

When provided in the type of SEDDS, such medications can be shielded from these deterioration procedures because the SEDDS aqueous crystalline phase can function as a partition between the medication and the degrading environment. Because SVA has minimum dissolves in the stomach owing to its acidic surroundings, SEDDS has been investigated as a potential medication delivery device [46].

5. Liposomes: Liposomes have proven to be effective carriers for badly soluble medications for example ibuprofen, amphotericin B, griseofulvin, and statins. Micelle liposome exchange is a unique and very effective liposomal encapsulation technology used in statin liposomal formulations. The solubility of statins is considerably improved by liposomal encapsulation, with one study showing a 1000-fold increase in solubility. This formulation was created primarily to treat rheumatoid arthritis. In preliminary experiments, Plasma from people and joint fluid have mentioned great stability [47]. A technique for the distribution of lovastatin, for instance, was created by Romana *et al.* In comparison to individual micelles and liposomes, the liposome exhibits better lovastatin loading and water solubility, prolonged lovastatin release, greater permeability, and superior transport through an epithelial cell. Because of this, lovastatin's oral bioavailability can be improved by this method [48].

6. Niosomes: they are lipid vesicles made from synthetic non-ionic surfactants, are seen as a synthetic substitute for the more well-known phospholipid vesicles (liposomes) as discussed by Abdelkader *et al.* [49, 50]. The stability and solubility of pharmaceuticals can be improved by using niosomes (non-ionic surfactant cavities), a novel nano-vesicular drug delivery technology. They were developed to keep medications from degrading and to get medications to the desired organs [51]. Niosomes are a superior to liposomes in several important respects. They cost less to produce and are more chemically stable. Additionally, they may be biodegradable and biocompatible. By extending the precorneal drug residence time and reducing drug loss through ineffective absorption of the medication through the conjunctiva, nasolacrimal duct, and finally the GI tract [52]. Niosomes dramatically increase the ocular bioavailability. So-used topical statins can lessen the causes and symptoms of dry eye and blepharitis, perhaps by

reducing MMP-9 and pro-inflammatory cytokines, in addition to inhibiting LFA-1 and its effects on HMG-CoA reductase in the sebaceous cells of the meibomian glands [53].

As well as niosomal technique improvements in stability and physicochemical properties of statin drugs, the biological properties of entrapped drugs could also be improved *in vitro* and *in vivo*. The niosomal preparation appears to have an effect on cancer cells when used with cancer drugs and enhances the therapeutic efficiency [54].

7. Lipid nanoparticles: Since the 1990s, solid lipid nanoparticles (SLN) have been claimed to be a superior alternative to nano-systems, liposomes, and their polymeric equivalents for a variety of development methods. SLNs are a new colloidal delivery system with a size range of 100–300 nm. They're a variant to polymers since they're equivalent to oil-in-water emulsions for oral nutrition, even though with the watery lipid substituted with SLNs [55]. They have several benefits, including high biocompatibility, minimal toxicity, and adequate physical stability. Plus SLNs are superior at delivering lipophilic medicines [33]. A lovastatin-solid lipid nanoparticle formulation, for instance, was created by Sarangi *et al.* with a drug loading of 17.7 percent on average and an entrapment efficiency of 71%. When given orally to a rabbit model, the lovastatin-SLN preparation showed a 1.72-fold increment in C_{max} and a 269 percent on average enhance in bioavailability contrasted to a lovastatin suspension [56].

In comparison to other particulate systems, lipid nanoparticles provide several benefits, such as

1. Large-scale manufacturing is simple.
2. There is a minimal possibility of toxicity.
3. The materials' biocompatibility and biodegradability.
4. Possibility of medication release that is regulated and adjusted.
5. Improvement of drug solubility and inclusion of both hydrophilic and lipophilic drugs.

Solid lipid nanoparticles (SLNs):

SLNs are one of the types of lipid nanoparticles. SLN is particles composed of solid lipids (lipids that are solid at both room and body temperatures) and stabilized by a surfactant (s). The lipids can be highly purified triglycerides, complicated glyceride combinations, or even waxes [57]. The size of SLNs is submicron (less than 1000 nm) [58, 59]

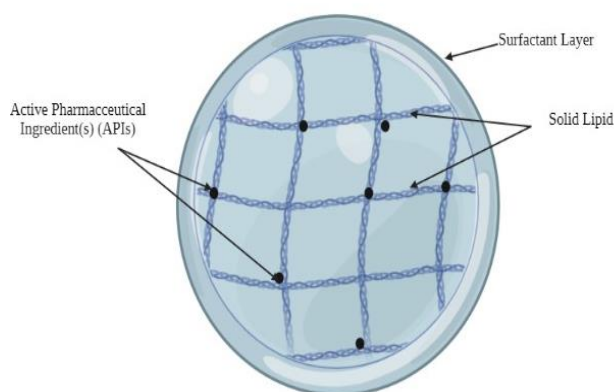


Figure 4. Schematic of SLN [60]

The advantages of solid lipid nanoparticles (SLN):

1. They are physicochemical stable.
2. The cost of raw materials and production is inexpensive.
3. Controlled release kinetics
4. Increase drug bioavailability
5. Large-scale generation and purification are feasible [61].

The disadvantages of SLN [62]:

1. Expulsion of drugs during storage.
2. The SLN delivery system arose as a result of their convoluted production. The procedure has poor percentage entrapment efficiency and is problematic for large-scale fabrication.
3. Another disadvantage is the first burst release. This is common with these formulations.

Formulation of SLN and its characterization

SLN consists of a lipid phase and an aqueous phase. The lipid phase contains certain lipophilic polymers, e.g., Precirol® ATO5 and Compritol® 888 ATO, that have a long hydrocarbon chain length, and on the other hand, the aqueous phase contains, e.g., tween 80 and/or chitosan as a surfactant. Both the lipid phase and the aqueous phase are heated at the same temperature above the melting point of the polymers that are used. High shear homogenization for 5 min is enough to get nanoparticles emulsion. This method, called the "hot homogenization technique," is the most popular technique being used to form SLN on Figure 4 [60].

Particle size, polydispersity index (PDI), and zeta potential were chosen as the properties for characterization of nanoparticles because they are significant features that have a significant impact on the stability, release rate, and biological efficiency of the SLN systems [63, 64].

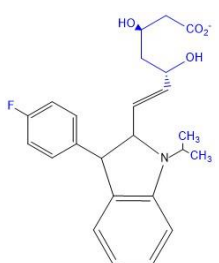
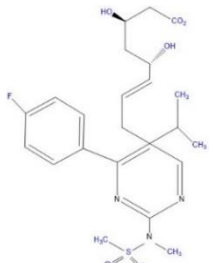
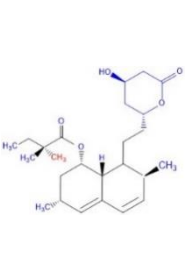
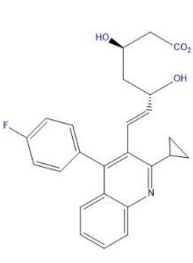
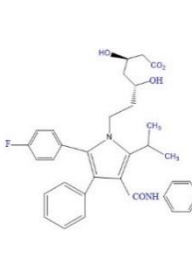


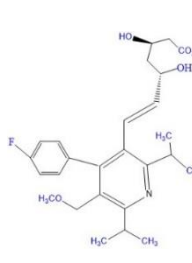
When a decrease in particle size is indicated for more stability, nanosystem and maintain are stable in storage with time. Small particle size enhances solubility and bioavailability, which improves cellular uptake.

When PDI is reduced, it indicates a homogeneous system (PDI < 0.3). Finally, zeta potential indicates the stability of SLN, which is a result of a combination of electrostatic and steric stabilization under storage [65].

Conclusion

Statins have been demonstrated to decrease cholesterol and to lower cardiovascular morbidity and death. As a result, statins are now the preferred medication for the management of numerous dyslipidemias. There are now seven statins that have received clinical approval in at least one nation. Despite having similar mechanisms of action, they contrast in terms of how well they may alter the lipid profile as well as in terms of chemistry and pharmacokinetics. It should be possible to utilize the existing and upcoming statins in clinical practice safely and effectively by taking into account these variations. In this article, we illustrate a drug delivery method to enhance solubility and dyslipidemia. In this article, we describe a drug delivery method to enhance solubility and bioavailability, but most science practices nowadays use nano-techniques to enhance physicochemical properties. The statins group, a medication with low water solubility, was made into nanoparticles using the nanoprecipitation approach to increase solubility and speed of dissolution. By modifying the operating parameters, such as the stabilizer concentration and the organic to aqueous solvent ratio,

Table 1. Physicochemical properties of the statins group [31]

	Atorvastatin	Rosuvastatin	Simvastatin	Pitavastatin	Fluvastatin	Pravastatin	Lovastatin	Cerivastatin
Bioavailability (%)	14	20	5	~60	20-30	18	5	60
Solubility	Insoluble in water	Sparingly soluble in water	Insoluble in water	Very slightly soluble.	Poor water-soluble	Water-Soluble	Insoluble in water	Very slightly soluble.
Log P	6.36	0.13	4.68	4.82	4.85	0.59	4.08	3.4.
M.Wt	558.6	481.5	418.6	421.5	411.5	424.5	404.5	459.5
pka	4.46	4.76	14.91	4.3	4.5	4.2	13.49	3.9
Chemical Structure								

stable particle sizes in this method may be achieved in nano-size ranges. The best stanine nanosuspension can be made in the laboratory using the solvent evaporation or homogenization methods. If nanotechnology is applied as an example, simvastatin in nanosized form dissolves much more readily than pure simvastatin suspension. Thus, nanoprecipitation can be a quick and efficient method to create submicron-sized drug particles that are weakly water-soluble.

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