



## Lovastatin: history, physicochemistry, pharmacokinetics and enhanced solubility

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### ABSTRACT

Lovastatin is a statin drug that blocks the body's synthesis of cholesterol and is administered especially to individuals at risk of heart disease. Categorized as a Biopharmaceutics Classification System (BCS) Class II drugs, lovastatin demonstrates low solubility and bioavailability. This review focuses on the importance of lovastatin and the obstacles during its administration. The history of statins from the discovery until they become one of the successful cholesterol-lowering agents to prevent complications and fatality especially related to coronary heart disease has been outlined along with their recent applicability in neurodegenerative diseases. Due to the respective physicochemical characters of the statins, they pose several challenges related to their effective administration to the patients. The aqueous solubility is the main issue related to their poor bioavailability. Besides that, other solubility and bioavailability enhancement approaches were discussed systemically. Finally, this review suggests current advanced technologies employed in order to provide effective and competent utilization of the drug.

**Keywords:** Arginine; Lovastatin; Pharmacokinetic; Physicochemistry; Solubility enhancement.

### INTRODUCTION

Low aqueous solubility of Active Pharmaceutical Ingredients (APIs) in drugs is a major problem in the pharmaceutical industry (Savjani *et al.* 2012). This may limit their efficacy and utility where low solubility would result in inadequate and varying bioavailability after oral administration (Meor Mohd Affandi *et al.* 2016). Thus it is crucial for researchers to overcome this phenomenon by developing suitable and viable method of solubilisation to be used during product development since almost 70% of new drug candidates have poor water solubility (Kawabata *et al.* 2011).

Lovastatin (LVS), a natural statin, is a specific and potent competitive inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA), hence a powerful cholesterol-lowering drug. It has revolutionized the alleviation and treatment of hypercholesterolemia. It has been proven that LVS is also effective as a therapeutic and prophylactic agent in the management of major morbidities such as atherosclerosis, sepsis, peripheral arterial disease, cerebro-vascular disease, ischemic

disease and bone fracture (Seraman *et al.* 2010). LVS, however, has very low bioavailability; only a small fraction of the administered dose will reach the systemic circulation. Numerous studies have been conducted to overcome this inconvenience.

The main objectives of this review are to explore the history of LVS, assess its physicochemistry and pharmacokinetic properties, and analyse various techniques and procedures that have been used by researchers to improve its solubility. Journal finders such as Science Direct, Scopus, Springer, Google Scholar and Directory of Open Access Journals (DOAJ) were used with keywords: solubility issue of statins, statins history, lovastatin pharmacokinetics, chemical properties and dissolution improvement techniques. This review is based on journals published between September 2000 to May 2016. Currently available techniques to improve dissolution are also discussed in the later part of the review.

### Role of cholesterol in coronary heart disease

Initially, physicians were not convinced of any relation between cholesterol and coronary heart disease (CHD) because most of the patients with CHD disease had plasma cholesterol levels only slightly different as compared to the general population average (Saeedan *et al.* 2015). The link was finally established by the Framingham study led by Dawber in the 1950's (Mahmood *et al.* 2014). This work showed a highly significant correlation between high plasma cholesterol

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and mortality due to CHD. The correlation is further supported by many other within-population studies (Tobert 2003). In addition, the Seven Countries Study led by Keys *circa* 1950's reported that high plasma cholesterol and CHD mortality rates were shown to occur in northern European countries and the United States (Menotti *et al.* 2000). Contrarily, plasma cholesterol and CHD mortality were both considerably less in southern Europe and much lower in Japan (Sekikawa *et al.* 2015). Later investigations established that the relation with CHD mortality was mainly with low density lipoprotein (LDL) cholesterol, which typically makes about 70% of the total cholesterol, when in fact high-density lipoprotein (HDL) cholesterol is inversely correlated with CHD mortality (Ravnskov *et al.* 2016). These findings led to the establishment of the 'Lipid Hypothesis', which proposed that elevated LDL cholesterol caused CHD and reducing it would lower the risk of myocardial infarction and other coronary events Saedan *et al.* 2015; Meor Mohd Affandi *et al.* 2016).

### The synthesis of cholesterol

Cholesterol can be acquired from the diet or it can be synthesized *de novo* (Berg *et al.* 2002). It is produced via a biosynthetic pathway of over 40 cytosolic and membrane-bound enzymes which are subject to feedback regulation by the end-product, cholesterol and its oxygenated form, oxysterols (Orth and Bellosta 2012). To date, the mechanisms of regulation have been elucidated at the molecular level through extensive studies by various chemists, biochemists and cell biologists for over 100 years. The pathway could be simplified as in Figure 1 (figure adapted from Olivier and Krisans, 2000).

### History of statins

HMG-CoA reductase is the rate limiting enzyme in the cholesterol biosynthetic pathway (Sung II *et al.* 2000). Its substrate, hydroxymethylglutarate is water soluble and there are alternative metabolic pathways for its breakdown when HMG-CoA reductase is inhibited so there would be no build-up of potentially toxic precursors if competitive inhibitors were used. Hence, the enzyme became an interesting target to be analysed by scientists in the 1970's (Tobert 2003). In 1976, the first HMG-CoA reductase inhibitor was discovered by Endo named mevastatin which is a fungal product extracted from *Penicillium citrinu*. It has been shown to be an ideal and potent competitive inhibitor to the enzyme reaction and capable of considerably lowering plasma cholesterol in hens, dogs and monkeys. In another study by Endo and Yamamoto, mevastatin also significantly lowered the plasma cholesterol level of patients with serious hypercholesterolemia (Endo 2004). However, in September 1980 Sankyo halted clinical trials of mevastatin due to serious animal toxicity issue (Goswami *et al.* 2012). LVS, a potent HMG-CoA inhibitor extracted from the broth of *Aspergillus terreus* was discovered by a group of scientist from Merck around

the same time. The clinical trial for LVS was done in the mid-1980's and it was proven to be effective in lowering plasma LDL cholesterol level of healthy human volunteers with no unfavourable effect (Tobert 2003). The second phase clinical trial was carried out in 1984 and the results indicated LVS to be effective in patients with CHD, non-familial hypercholesterolemia and heterozygous FH23 (Hajar 2011). The third phase clinical study in 1988 and 1990 reported that LVS produced a large reduction in LDL cholesterol. There were lesser extent in plasma triglyceride and minimal increase in HDL cholesterol with much less adverse effects than that of the controlled agents cholestyramine and probucol. Considering promising clinical trial results, United States Food & Drug Administration (USFDA) approved the usage of LVS in August 1987 and the drug became available for prescribing at the end of 1980's. It showed a mean reduction of 40% LDL cholesterol through daily dosing of 80 mg (Saeedan *et al.* 2015). Physicians and patients rapidly accepted the drug due to its few adverse effects and easy adherence by patients (Rashid 2007). The fourth phase clinical trial which concerned a larger number of patients (more than 8000) was done in 1991 which further proved its efficacy and tolerability. The accomplishment of LVS catalysed the discovery of other groups of statin such as simvastatin (1988), pravastatin (1991), fluvastatin (1994), atorvastatin (1997), cerivastatin (1988), pitavastatin (2002) and rosuvastatin (2004; Saeedan *et al.* 2015).

### Lovastatin molecules

#### Chemistry and functional properties

LVS is a naturally occurring compound that is biosynthesized as a secondary metabolite of several filamentous fungi and acts as competitive inhibitors of HMG-CoA reductase (Manzoni and Rollini 2002). It prevents the enzyme from binding to its substrate, HMG-CoA by literally getting 'stuck' in the substrate since it is bulky (Bizukojc and Ledakowicz 2007). LVS, [(1S,3R,7R,8As)-8-[2-[(2R,4R)-4-hydroxy-6-oxo-oxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-2-yl];(2S)-2methylbutanoate (IUPAC name) has the empirical formula  $C_{24}H_{36}O_5$  with molecular weight of 404.55 g/mol. The 3D structure of LVS is presented in Figure 2 (Lulla 2014). Formerly it was known as mevinolin; monacolin K, and Mevacor® (Goswami *et al.* 2012). LVS appears as a white, non-hygroscopic crystalline powder which is insoluble in water and sparingly soluble in ethanol, methanol and acetonitrile (Subazini and Kumar 2011).

#### Mechanisms of action of lovastatin

LVS interferes with the production of mevalonate, a required building block for cholesterol biosynthesis by acting as a reversible competitive inhibitor for HMG-CoA which is a substituent of the substrate of HMG-CoA reductase (Jahromi *et al.* 2013). The inhibition occurs due to the structural similarity between the  $\beta$ -

hydroxyacid form of the statins and the HMG-CoA intermediate formed. LVS is inactive in the native form in which it is administered. Thus it is first hydrolysed to the  $\beta$ -hydroxyacid form in the body to assume activity (Ryska and Merckx 2003). Reduced intracellular cholesterol synthesized induces the hepatic LDL-receptor, which results in increased extraction of LDL cholesterol from the blood and decreased circulating LDL cholesterol (Lagor and Millar 2010).

#### Pharmacokinetics of lovastatin

LVS has distinguished pharmacokinetic characteristics (Chong *et al.* 2001). As previously stated, it is administered in an inactive lactone form and converted to the active  $\beta$ -hydroxyacid in the body. The main excretory mechanism for the less hydrophilic statins is oxidative biotransformation. LVS is metabolized mainly through CYP3A4 (Kebamo *et al.* 2015). These characteristic excretory mechanisms are factors that decide the drug-drug interactions affecting LVS pharmacokinetics (Niemi 2009).

After being administered orally, LVS is absorbed rapidly from the small intestine, reaching maximum plasma concentration  $T_{max}$  within 4 hours (Nirogi *et al.* 2007). LVS is best taken with meal in the morning and evening as its bioavailability increases with food. It has a short half-life of 3 hours. Additionally, in the evening the rate of endogenous cholesterol synthesis is the highest (Gazzerro *et al.* 2012). Elaborate metabolism in the liver and guts combined with the fact that LVS is poorly soluble in water causes low bioavailability of the drug which is at a mere 5%. Table 1 summarises the pharmacokinetics of LVS (adapted from McFarland *et al.* 2014).

#### Safety and effectiveness of lovastatin

The efficiency of LVS is evaluated by monitoring the level of low density lipoprotein (LDL) cholesterol as it is a good predictor of coronary heart disease risk status. In a previous study by Davidson (1997), for a period of 52 weeks, among the low risk CHD patients who underwent LVS-induced reduction in LDL cholesterol, 82% of them attained the target LDL cholesterol which was less than medium risk CHD patients (85%). It is found that doubling dose of LVS does not improve responsiveness to treatment as observed in the study (Ward *et al.* 2005)

LVS is found to cause some side effects on the liver and muscular tissue. Other than these, it also causes hepatic dysfunction, hypothyroidism, advanced age and serious infections (Stasi *et al.* 2010). LVS is reported to cause myotoxicology. Even though this case is a rare occurrence, it can still lead to fatal rhabdomyolysis. Researchers have begun to seriously emphasize on the adverse effect of LVS (Golomb and Evans 2008). Most importantly, high incidents of myopathy can be triggered if an inhibitor of cytochrome P450 or other inhibitors of LVS metabolism are administered together,

as this will increase their concentration in blood (Hu *et al.* 2010).

#### Pleitropic benefits of lovastatin

Other than treatment for hypercholesterolemia, statins in general exert cholesterol-independent or 'pleiotropic' effects through direct inhibition of HMG-CoA reductase which consequently impedes the synthesis of isoprenoids (Chao-Yung *et al.* 2008). These pleiotropic effects include improvement of endothelial dysfunction, antioxidant and anti-inflammatory effects, increased nitric oxide bioavailability and stabilization of atherosclerotic plaques (Davignon 2004). Other outcomes of interest include the ability to recruit endothelial progenitor cells (EPCs), inhibition of cardiac hypertrophy and putative immunosuppressive activity. Be as they may, pleiotropic effects other than being beneficial or neutral, may also be undesirable such as side effects or toxicity (Davignon 2004). Hence, understanding of benefits associated with statin therapy allows better therapeutic application and leads to the early use of statins in acute coronary syndromes (ACS), neurological disorders, infectious diseases and renal insufficiencies (Ostadal 2012).

Emerging data show the additional benefit of statins to induce apoptosis in prostate cancer cells (Jang *et al.* 2016), lymphocytes (Gullu *et al.* 2005), hepatocytes (Zhao *et al.* 2013), leukemic cells (Burke and Kukoly 2008) and colon cancer cell lines (Davies *et al.* 2016) in culture. LVS is also widely used as an agent of combination therapies in neurodegenerative diseases like multiple sclerosis (MS) (Paintlia *et al.* 2013), Parkinson's disease (Schuster *et al.* 2008) and Alzheimer's disease (Robles 2009).

LVS in particular, or statins in general, are bone anabolic agents that have relatively low toxicity in humans. They could be used for treatment of osteoporosis especially when significant amounts of trabecular bone have been lost (Schachter 2005). A study where a significant increase in bone mineral density in postmenopausal women associated with taking statins has been published. Moreover, among older women, statins have shown a protective effect against non-pathological fracture (Garrett and Mundy 2002).

#### Solubility issue on lovastatin

Solubility can be defined as the maximum quantity of a solute that can dissolve in a certain quantity of solution or solvent at a certain temperature (Kadam *et al.* 2013). For a drug to have an active effect, it is important to achieve the desired proportion of it entering the body's circulation when administered (Sakai 2008). The efficiency of a drug can be limited by poor aqueous solubility. Some drugs also demonstrate adverse effects due to their poor solubility (Chaudhary *et al.* 2012). Hence, it is very important for researchers to overcome this phenomenon by developing suitable and viable methods of solubilisation to be used during

product development since almost 70% of new drug candidates show poor water solubility (Kakran *et al.* 2012). An increase in aqueous solubility of our target drug, LVS which is a class II BCS (low solubility, high permeability) drug, could be very useful to help increase the efficiency of the drug by having it dissolved in the gastrointestinal fluid, and releasing its content to achieve optimum absorption into the systemic circulation (Savjani *et al.* 2012).

Hitherto, there have been various techniques and methods reported on the enhancement of drug solubility. They are grouped into physical and chemical modification of the drug substance, and other techniques. For physical modifications there are techniques such as particle size reduction (e.g. micronization and nano-suspension), modification of the crystal habit (e.g. polymorphs, amorphous form and co-crystallization) and drug dispersion in carriers (e.g. eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques). Meanwhile, chemical modifications include change of pH, use of buffer derivation, complexation and salt formation. Finally, for other methods there are supercritical fluid processes, use of adjuvants like surfactants, solubilizers, cosolvency, hydrotrophy and novel excipients (Chaudhary *et al.* 2012). However, we only focus on four main categories of solubility enhancement techniques in this review namely; particle size reduction, solubilisation of surfactant, inclusion complex and solid dispersion, since these are abundantly studied by researchers (Gupta and Sehrawat 2011; Kadam *et al.* 2013).

### Solubility enhancement of lovastatin

#### Particle size reduction

Drug particle size is often related to bioavailability of poorly soluble drugs due to the fact that surface area to volume ratio increases with the decrease in particle size (Sun and Zhai 2012). Increased surface area allows greater interaction with the solvent and improves the solubility properties of the drug (Patel *et al.* 2012). Size reduction may be achieved by conventional methods such as comminution and spray drying. These methods depend on mechanical stress to break apart the active compound. On the other hand, comminution such as milling and grinding often imposes high physical stress upon drugs due to its mechanical forces. This may induce degradation of the drug. There is also micronization technique that increases the solubility rate of a drug by increasing the surface area. Micronization is carried out by milling techniques using jet mill and rotor stator colloid mills.

Based on the literature review, particle size reduction was applied to LVS in three research projects. In the first study reported by Nanjwade (2011), particle size reduction was performed by the preparation of rapid expansion supercritical solution nanocrystal. The particle size is reduced by the precipitation process, with acetone as the excipient. This method produced a tre-

mendous increase in solubility by 18-folds as compared to pure LVS. In another study by Al-Nimry and Khanfar (2016), particle size reduction involved coacervation phase separation. This was done by dissolving or dispersing the LVS with continuous agitation in a polymer solution, depositing the coating polymer on the drugs and finally rigidising the coating by thermal technique to form microparticles. Two types of excipient were used in the study which are ethanol+Eudragit® L100 and SDS Polaxomer 188. Increment in solubility by four times was reported when using both types of excipient, however Eudragit® L100 provided an additional mechanism for size stabilization and resulted in higher enhancement in the release as compared to SDS Polaxomer 188 (Al-Nimry and Khanfar 2016). Moreover, a study involving high pressure homogenization milling to prepare nanostructured lipid carriers (NLC) was also attempted. In this research, LVS (LVS)-loaded NLCs (LVS-NLC) were prepared by hot high-pressure homogenization method. It was reported that via this method, LVS's solubility was enhanced 3 folds as compared to pure LVS (Zhou and Zhou 2015). A summary of solubility enhancement by particle size reduction is listed in Table 2.

#### Solubilisation of surfactant method

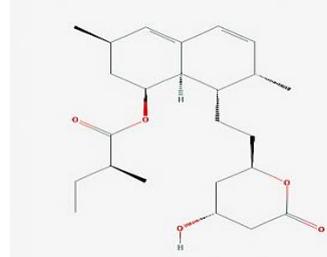
Surfactants are molecules that are made up of polar and non-polar parts. Much of surfactants contains a hydrocarbon part attached to a polar group. The polar group can be anionic, cationic, zwitterionic or non-ionic. When small polar molecules are introduced, they can attach to the hydrophobic core of the micelles (Murtaza 2012) causing a decrease in surface tension which makes the drug more soluble in an aqueous solution. Mandal (2011) reported the usage Capmul® MCM-based LVS microemulsion (ME) formulation with Cremophor® EL as the surfactant and Transcutol® P as the co-surfactants. The optimised ME formulation showed a 4.7 times increase in the bioavailability as compared with the commercially available LVS (Mandal 2011).

Additionally, three attempts were carried out by researchers on self-microemulsifying drug delivery system (SMEDDS). The usage of peanut oil, labrasol and span 80 as an excipient exhibited nearly a 1.42 fold increase in LVS solubility as compared to raw LVS (Yadava *et al.* 2015). Moreover, another study by Goyal *et al.* (2012) exhibited more than 1.9 times solubility improvement as compared to pure LVS solution. In another attempt, the usage of caprylic acid (10%), Cremophor RH40 (30%), and methanol (60%) by simple mixing resulted in an increase in its dissolution compared with the conventional tablet by 1.44 fold (Vinod *et al.* 2014). A summary of solubility enhancement by surfactant method is listed in Table 3.

#### Inclusion complex

Among several techniques that can be used to solubilize drugs, one approach to overcome low solubility,

**Table 1: Lovastatin's pharmacokinetic (PK) characteristics**

PK Parameter	Lovastatin
Molecular structure	
Statin Type	I
Dosing Time	With food morning & night
Prodrug	Yes
Bioavailability	5%
Half-life	3h
Lipophilicity	Lipophilic
Active metabolites	Yes
CYP substrates	3A4
OATP Transporters	1B1
Protein binding	Very high (95%)
Excretion (Renal)	10%
Excretion (Faecal)	83%

**Table 2: Summary of particle size reduction techniques; SDS, sodium dodecylsulphate**

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)
Particle size reduction	Rapid expansion of supercritical solution nanocrystal	Acetone	3mM drug in organic solution Drug:polymer	18
	Coacervation phase separation	Ethanol, Eudragit® L100	SDS 1:2:0.25%	4
		SDS Polaxomer 188		
Nanostructured lipid carriers (Hot high-pressure homogenization method)	Solid lipid (Prericrol® ATO5 4.65% and soybean lechitin 1.25%), liquid lipid (Labrasol® 0.82%) and surfactant (Cremophor® ELP 3.2%)	0.1:0.9	3	

**Table 3: Summary of solubilisation of surfactant methods: LVS, lovastatin; Capmul® MCM, Glycerol Monocaprylate; Cremophor® EL, Polyoxyl castor oil; Transcutol® P, Highly purified diethylene glycol monoethyl ether EP/NF; Cremophore® RH40, PEG-40 Hydrogenated Castor Oil**

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)
Solubilisation of surfactant	Microemulsion	Capmul® MCM	20 mg LVS with 7% Capmul® MCM	1.3 times (approx.) more than commercial tablet
		Cremophor® EL	24% Cremophor® EL	
		Transcutol® P	8% Transcutol® P and water	
	Self-micro emulsifying drug delivery system (SMEDDS)	Peanut oil, Labrasol®, span 80	Labrasol®, span 80, peanut oil (40:20:40)	2.27 times more than raw LVS
		Capryol™ 90, Cremophore® RH40, Transcutol® P	Capryol® 90, Cremophore® RH40, Transcutol® P (20:40:40)	1.9 times more than pure drug solution
		Caprylic acid, Cremophor® RH40, methanol	Caprylic acid, Cremophor® RH40, methanol (10:30:60)	1.44

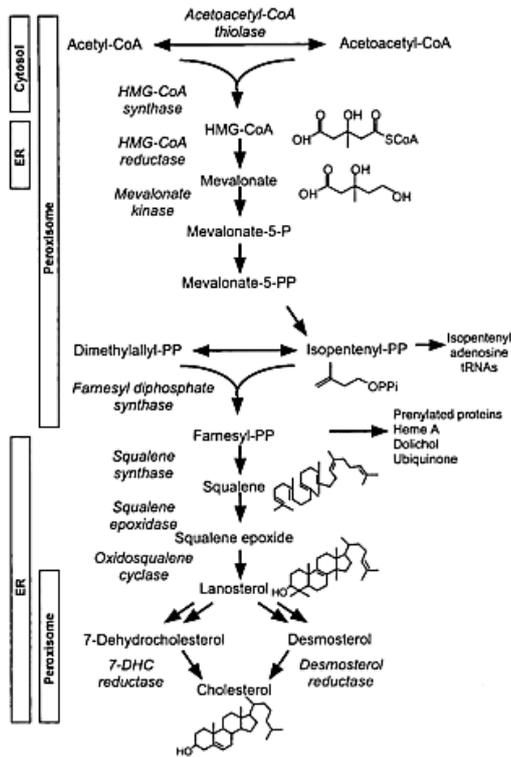
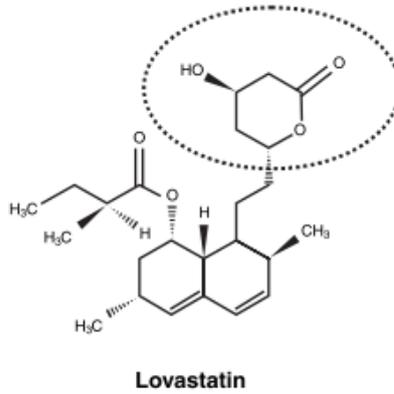


Figure 1: Synthesis of Cholesterol

HMG-CoA analogue



Lovastatin

Figure 2: Lovastatin (from PubChem, 2016)

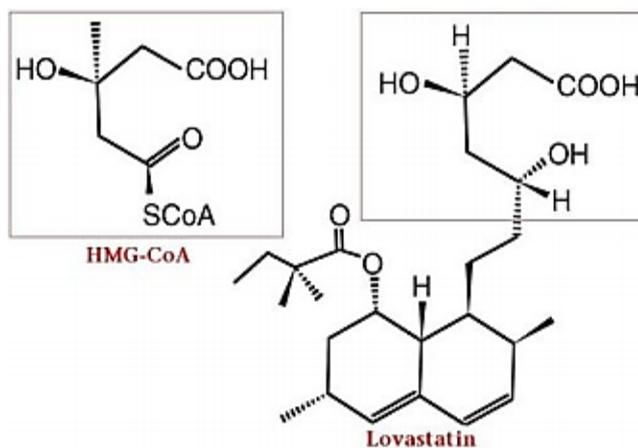
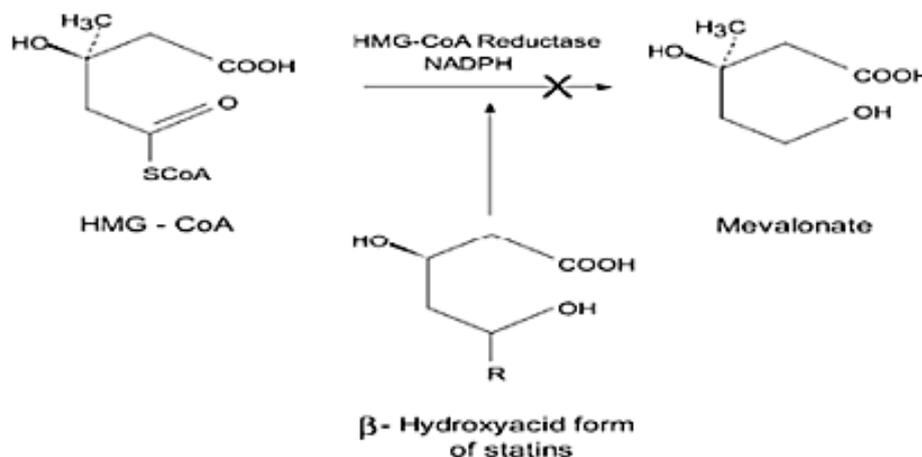


Figure 3: Structural similarity between HMG-CoA and Lovastatin



**Figure 4: Structural analogy between HMG-CoA and the β-hydroxyacid form of statins and mechanism of inhibition**

**Table 4: Summary of inclusion complex techniques; LVS, lovastatin**

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)
Inclusion complex	Kneading	B-cyclodextrin	1:01	3.4 times more than pure LVS (in phosphate buffer pH 6.8)
		Hydroxypropyl-β-cyclodextrin + methanol + water	LVS+ hydroxypropyl-β-cyclodextrin: methanol +water (1:1)	2.4 times higher than regular drug formulation
	Not mentioned	Randomly methylated B-cyclodextrin	Not mentioned	3
				Not mentioned

**Table 5: Manufacturing Methods of Solid Dispersions**

1	Solvent evaporation	Spray drying Freeze drying Spin drying Fluid drying Hot plate drying Vacuum drying Slow evaporation at low temperature Rotary evaporation
2	Melt/cool method	Hot stage extrusion Melting solvent method
3	Co-precipitation	Addition of an anti-solvent
4	Dropping method	

issue is complexation. Cyclodextrin-Drug Complexation (CDC) has been in the spotlight of the pharmaceutical field in recent years (Rasheed *et al.* 2008). In formulations of less water soluble drugs, CDC has played an important role by improving drug solubility and/or drug dissolution through inclusion complexation or solid dispersion by acting as a hydrophilic solid carrier (Mehramizi *et al.* 2007). In terms of inclusion complex, a CDC is capable to form inclusion complexes with poorly water-soluble compounds by taking up a hydrophobic part of the guest molecule into its cavity with-

out forming any covalent bonds (Shiralashetti *et al.* 2010).

There are a few examples of LVS inclusion complex formulated by various researches reported recently. A complexation of LVS β-cyclodextrin prepared by the kneading method shows a faster and higher dissolution rate as compared to the pure LVS (at 3.4 times fold) (Patel and Patel 2007). Another attempt by Mehramizi *et al.* (2007) also reported an increase in LVS dissolution by complexation with β-cyclodextrin by 2.4 times (Mehramizi *et al.* 2007). Emőke *et al.* (2012) recorded

**Table 6: A summary of solid dispersion methods; PEG, polyethylene glycol; LVS, lovastatin; SIF, simulated intestinal fluid; SGF, simulated gastric fluid**

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Solid dispersion	Solvent evaporation	Modified locust bean gum	1:5	2.9	(Patel et al. 2008)
		Sodium starch glycolate, crospovidone	1:2	2 (in SIF) 1.5(in SGF)	(Maji et al. 2013)
		Poloxamer F68	1:5	1.3	(Katare et al. 2011)
	Fusion	Soluplus & PEG-1500	1:0.5	2	(Sambath et al. 2013)
		PEG-600	1:2	1.5	(Vidyadhara 2011)
	Physical Mixture		1:1.5	1.55	
	Kneading		1:2	1.55	
	Freeze drying	Mannitol	7:5	1.43	(Verma et al. 2014)
	Carrier	Soluplus	N/A	1.2	(Rajeswari et al. 2012)
	Grinding	Acetylsalicylic acid (aspirin)	1:4	1.8	(Górniak et al. 2016)
Hot melt extrusion	Soluplus	1:2	2	(Sambath et al. 2013)	

**Table 7: A summary of liquid-solid system techniques**

Technique	Methods	Excipient	Drug-carrier-coating ratio	Increase in solubility (times)	Reference
Liquisolid compaction	Not mentioned	Microcrystalline cellulose (MCC), aerosil	1.4:2.3:1	2.54	(Viswanath and Somasekhar 2014)
		Starch, aerosil	1:20:1	3.42	(Neduri and Vemula 2014)

**Table 8: A summary of mesoporous carrier method; LVS, lovastatin; SDS, sodium dodecylsulphate**

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Mesoporous carrier	Solvent immersion/evaporation	Uniform mesoporous silica spheres (UMCS)	6% (w/v) drug with UCMS	3.3 times greater than pure LVS powder (in enzyme-free buffer with 0.10% SDS (pH 6.8))	(Zhao et al. 2012)
		Porous silica monolith (PSM)	1:3	1.8 times greater than pure LVS powder (phosphate buffer with 0.2% SDS (pH7))	(Wu et al. 2012)

an approximately 3-fold increase in LVS-hydroxypropyl- $\beta$ -cyclodextrin complex dissolution rate as compared to pure LVS. A summary of solubility enhancement by inclusion complex method is listed in Table 4.

#### Solid dispersion technique

The utilization of solid dispersions to improve the dissolution and oral absorption of poorly water-soluble drugs was first proposed by Sekiguchi and Obi in 1961. Solid dispersion can be defined as “the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), sol-

vent or melting-solvent method” (Bhusnure et al. 2014).

Physicochemical interactions occur between a hydrophobic drug and the carrier which then deposits the drug on the surface of an inert carrier. This system offers a variety of preparation methods and carrier options that allows flexibility when formulating poorly water soluble drugs (Dhirendra et al. 2009). Table 5 listed a number of manufacturing methods of solid dispersion.

Based on the literature compilation, there are at least nine studies for the application on LVS that have been

reported (Górniak *et al.* 2016; Katare *et al.* 2011; Maji *et al.* 2013; Patel *et al.* 2008; Rajeswari *et al.* 2012; Sambath *et al.* 2013; Vidyadhara 2011; Vinod *et al.* 2014). Patel *et al.* (2008) reported modified locust bean gum (MLBG) as a carrier using modified solvent evaporation shows the highest increase of solubility at 2.9 fold as compared to pure LVS (Patel *et al.* 2008). Another attempt by Vinodh *et al.* (2015) using sodium tripolyphosphate and Pluronic F68 as surfactants has resulted in the improvement of solubility at 2 folds as compared to pure LVS solution. Meanwhile, an attempt using Poloxamer F-68 as an excipient resulted in a 1.3 times increase in solubility of LVS as compared to raw LVS (Katare *et al.*, 2011). Additionally, Verma *et al.* (2014) used freeze drying method which resulted in solubility enhancement at 5-6 folds as compared to pure LVS (Verma *et al.* 2014). A summary of solubility enhancement by solid dispersion method is listed in Table 6.

### Novel techniques

Some novel approaches are discussed in this part to highlight other possible methods available to improve drug solubility which may be further applied to LVS.

### Liquid-solid system

In a liquid-solid system, formulations are derived from the conversion of drugs in liquid form, or as a suspension or solution in non-volatile solvents, into dry non-adherent, free flowing and compressible powder mixture by blending the suspension or solution with the selected carrier and coating material (Viswanath and Somasekhar 2014). For the carrier, essentially various grades of starch, cellulose and lactose may be used while for the coating material very fine silica powder is available. Usually, a liquid-solid compact in a fine particulate form will enhance the dissolution rate, and increase oral bioavailability (Balaji *et al.* 2014). A study on LVS in microcrystalline cellulose (MCC) with aerosol as the excipient improved drug solubility by 2.54 times (Viswanath *et al.* 2014). Meanwhile, using starch with aerosol as the excipient further improved the dissolution rate by 3.42 times. In another study by Neduri *et al.* (2014) LVS had the highest solubility in propylene glycol with the value of 12.84% w/w—as compared to other liquid vehicles (PEG-200, PEG-400, distilled water & 0.1N HCl) (Neduri *et al.* 2014). A summary of solubility enhancement by the liquid-solid system method is listed in Table 7.

### Mesoporous carrier method

Porous materials are known to possess ordered or irregular arrangement of pore size ranging from millimetre to nanometre. These porous materials provide surfaces that are hydrophilic and have large effective area which is advantageous since it would engage the effects of surface interactions of the drug molecules and the pore wall. Some attempts on this technique were done on LVS via solvent immersion/evaporation meth-

od using uniform mesoporous silica spheres (UMCS) and porous silica monolith (PSM) (Wu *et al.* 2012; Zhao *et al.* 2012). In the first study, the results showed that the dissolution rate of LVS prepared by UMCS was remarkably increased (3.3 times fold) compared with pure crystalline LVS (Zhao *et al.* 2012). Another study using PSM allowed rapid drug dissolution, increasing the solubility by 1.8 times (Wu *et al.* 2012). A summary of solubility enhancement by mesoporous carrier method is listed in Table 8.

### CONCLUSION

The effectiveness of oral administration of poorly-water soluble drugs, such as LVS is determined by their solubility. The importance of LVS as cholesterol-lowering drug demands the best method to improve its solubility which consequently will maximize its bioavailability and therapeutic efficacy. Due to its physico-chemical characteristics, LVS poses several challenges before it can be effectively administered to the patient. Numerous solubility enhancement methods of LVS have been explored by researchers, both orthodox and unorthodox techniques. The former include particle size reduction, use of surfactant, inclusion complex and solid dispersion. For the latter, there are liquid solid compaction and mesoporous carrier methods. These methods have all been discussed in this review. In the final analysis, the jury is still out on the best technique to apply to improve the solubility of the cholesterol buster, LVS.

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