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Review Article

THE PROSPECT, PROMISES AND HINDRANCES OF STATIN BASE MOLECULES: LOOK BACK TO LOOK FORWARD

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ABSTRACT

This review narrates the importance of the statin-based molecules and their inherent challenges during their administration. The chronological appearance of the statin, their source and the journey with time so to evolve as one of the successful cholesterol-lowering agents to prevent the morbidity and mortality especially related to coronary heart disease have been illustrated along with their recent utilities in neurodegenerative diseases. The statins, because of their respective physicochemical characters pose several challenges in regards to their effective administration to the patients. One of the major issues related their poor bioavailability is their aqueous solubility. The different approaches for the enhancement of solubility and hence bioavailability have been discussed systematically. This review finally suggests the importance of more related research in regards to their successful administration so to have greater realization of therapeutics efficiency.

Keywords: Statin-based molecules, Poor solubility, Solubility enhancement

INTRODUCTION

The solubility enhancement of the Active Pharmaceutical Ingredients (APIs) is one of the important tasks in the field of pharmaceutical technology that needs to be addressed by the researchers as it may limit their efficacy and utility [1]. Poor aqueous solubility of APIs results in a low drug absorption hence inadequate and variable bioavailability [2]. Hence the phenomenon of solubility is an area of particular important. The development of suitable and viable method of solubilisation is very important during product development [3]. The discovery of new unknown molecules with potent pharmacological activities is costly and difficult. More and more researchers either from industries or academia are focusing on the molecules which are established as a drug, but suffering with some drawback such as low aqueous solubility [4].

Since the introduction of the Biopharmaceutical Classification System (BCS) by Amidon in 1995 [5], it has become an important research tools in classifying drug molecules based on their bioavailability. This system is classified on the basis of their aqueous solubility and intestinal permeability. Solubility and permeability are two key parameters responsible for effective bioavailability and good *in vitro* and *in vivo* correlation [6]. In general drug can be classified into 4 classes as per table 1.

Table 1: Biopharmaceutical drug classification system [5]

Class	Permeability	Solubility
I-Well absorbed and their absorption rate is higher than excretion	High	High
II-The bioavailability is limited by the solvation rate. A correlation between *in vivo* bioavailability and *in vitro* solvation can be found.	High	Low
III-The absorption is limited by the permeation rate with fast solvation rate.	Low	High
IV-The bioavailability is poor. Usually not well absorbed over the intestinal mucosa and a high variability is expected.	Low	Low

As illustrated in table 1, class II drugs which have low aqueous solubility and high permeability become the main target for the improvement of their solubility. By improving the aqueous solubility of these molecules will lead to the improvement of their oral bioavailability [7]. In this context, statin molecules the well-known hypolipidemic drugs are classified as class II drug as per BCS [8].

The main objective of this article is to review the various techniques and procedures that have been in use by researchers to enhance the solubility of statin molecules. We searched Google scholar, MEDLINE, EMBASE, Web of Science, ISI Proceedings and BIOSIS Previews bibliographic databases using search terms such as statin history, characteristics, solubility and solubility enhancement techniques. The review is based on the scientific articles published in between January 2000–December 2015. In the later part of the article the potential current techniques choose need to be considered in order to improve the solubility shall also be discussed.

Cholesterol and coronary heart disease relationship

The link between cholesterol and Coronary Heart Disease (CHD) was not established until it was reported by Dawber in 1950 [9]. Prior to that, the physicians were skeptical of any link between cholesterol and CHD. This is due to the fact that most patients diagnosed with CHD are recorded with insignificant difference in plasma cholesterol level than those of the general population [10]. Research led by Dawber in 1950 established significant correlation between high plasma cholesterol and CHD mortality [11]. The outcomes of the study was then supported by another study led by Mariottia [12] which reported that CHD mortality rate were high with the increased of plasma cholesterol in european country and the United States. Contrary to that, southern europe and Japan which reported low plasma cholesterol level had substantially recorded lower CHD mortality. Later studies by various researchers [13-19] established that Low density lipoprotein (LDL) cholesterol which comprises 70% of total cholesterol, together with triglycerides promotes the formation of atherosclerotic plaques. The lipid hypothesis was then born that proposed elevated LDL cholesterol and triglyceride together with the lower High Density Lipoprotein (HDL) to increase the risk of CHD.

Cholesterol biosynthesis

Most mammalian cells can produce cholesterol through cholesterol biosynthesis pathway. This complex process involved more than 30

enzymes and the details pathway was extensively studied in the 1950-1960s [20]. The simplified version of the biosynthesis was reduced in fig. 1. An early attempt to reduce cholesterol biosynthesis was not successfully encouraged when triparanol introduced in mid-1960 for the clinical trial was withdrawn from the market after it developed cataract and tissue accumulation of desmosterol, the substrate for the inhibited enzyme [21].

The discovery and history of statin

Hydroxymethylglutarate, the substrate of HMG-CoA reductase is a water soluble compound which can breakdown with alternative metabolic pathways, as its concentration builds up in the body. This condition reduced the buildup of toxic precursors that might be accumulated if the competitive inhibitors are being used [20]. Based on those factor, a new compound which can act as an inhibitor of HMGA-CoA reductase become an attractive target to be explored by the scientist in the mid 70's. The first HMGA-Co A reductase inhibitor, mevastatin was discovered by Endo in 1976, as a fungal product extracted from *Penicillium citrinu* [22]. Mevastatin was found to be effective in lowering the plasma cholesterol of rabbit [23], monkey [24] and dog [25]. Its prototype trial then began in 1980 and indicated to be highly effective in lowering the total and LDL cholesterol in human plasma [26]. But in September 1980 its clinical trial was terminated due to the serious animal toxicity issue. At the same time, a group of scientist from Merck found a potent HMGA-CoA inhibitor named lovastatin from the fungal product extracted from the fermentation broth of *Aspergillus terries* [27]. The first clinical trial was done in mid 1980's on lovastatin and found to be effective in lowering down plasma LDL cholesterol of healthy human volunteers with no obvious adverse effect [28]. The phase II clinical study was done in 1984 and the results indicated lovastatin to be effective in patients with CHD, non-familial hypercholesterolemia and heterozygous FH23 [29]. The phase III clinical study in 1988 [30] and 1990 [31]reported that lovastatin resulted a large reduction in LDL cholesterol, the lesser extent in plasma triglyceride and minimal increased in HDL cholesterol with minimal adverse effects than that of the controlled agents cholestyramine and probucol. Due to promising clinical trial results, USFDA approved the usage of the drug in August 1987 [20] and lovastatin became available for prescription use at the end of 80's and showed a mean reduction of 40% LDL cholesterol through daily dosing of 80 mg [29]. This drug was rapidly accepted by the physicians and patients due it's few adverse effects and easy patient compliance. The phase IV clinical trial which involved a larger number of patients (more than 8000) was carried out in 1991 which further proved its efficacy and patient tolerability [32]. The success of lovastatin catalyze the discoveries of another group of statin such as simvastatin in 1988, pravastatin in 1991, fluvastatin in 1994, atorvastatin in 1997, cerivastatin in 1998, pitavastatin in 2002 and rosuvastatin in 2003 [20].

Statin molecules

Chemistry and functional properties

Statin molecules can be divided into 3 classes based on their origin. As mentioned previously, lovastatin is derived naturally from the fungal product of A*spergillus terries.* Simvastatin is a semi-synthetic derivative of lovastatin (it has additional side chain methyl group) and pravastatin is derived semi-synthetically from mevastatin by biotransformation process [17]. Fluvastatin, atorvastatin, cerivastatin, pitavastatin and rosuvastatin are synthetically synthesized. Fluvastatin has a very different structure from statin derived from the fungal product. It is a mevalonolactone derivative with fluorophenyl-substituted indole ring. Another synthetic statin has a similar structure with flurophenyl group with open ring acid forms. (fig. 2) [33]. Based on its molecular structure (fig. 2), simvastatin, atorvastatin, fluvastatin and lovastatin are relatively lipophilic in nature, while pravastatin and rosuvastatin are more hydrophilic due to the presence of polar hydroxyl group and methane sulphonamide group respectively on their molecular structure.

Mechanisms for the action of statins

Study by Istvan [34] revealed that statin act by binding to the active side of the enzyme (HMG-CoA reductase) therefore preventing the substrate (HMG-CoA) to binding. Its unique binding affinity towards the enzyme which is in the nanomolar range compared to the micromolar range for the substrate contributes to its specificity and competitive inhibitors characteristics [35]. Different type of statin shows different modes of binding with HMG CoA reductase. In the case of atorvastatin, an additional hydrogen bond was demonstrated in the atorvastatin–enzyme complex which resulted in more binding interaction with the substrate. These characteristics differentiate their pharmacokinetics properties and pharmacological effects [17]. The inhibition of HMG-CoA reductase resulted in the reduction of cholesterol synthesized by the hepatocyte. The reduction in intracellular cholesterol concentration induced hepatic LDL-receptor, which results in increased extraction of LDL-C from the blood and decreased circulating LDL-C concentrations [36].

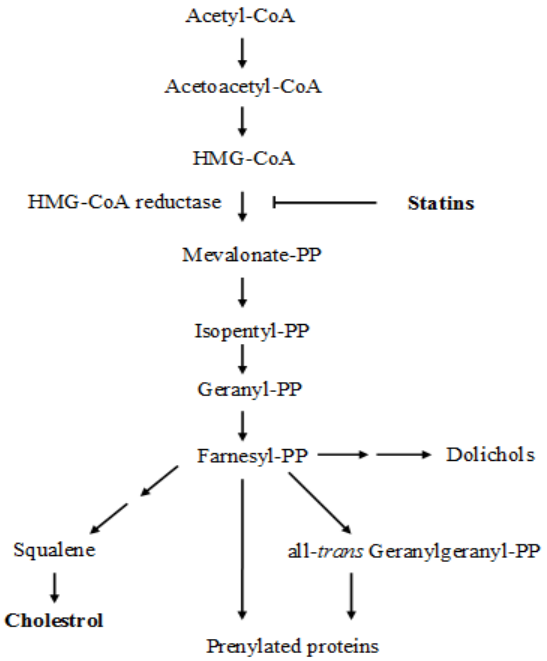

Fig. 1: Cholesterol biosynthesis pathway

Pharmacokinetic properties

Statin molecules exist in two forms ie lactone (prodrug) and open ring hydroxyl acid. The hydroxyl acid forms are the active form of drug which can lower the plasma cholesterol *in vivo*. The lactone form of statin will be transformed into the active form in the liver and non-hepatic tissue [37]. Lovastatin and simvastatin are an inactive lactone prodrug. The lactone is absorbed from GIT Tract and hydrolyzed rapidly by cytochrome P450 3A4 in the liver to form β-hydroxyacid metabolite [30, 38]. Another statin is administered as their hydroxyl acid active form. After oral administration, all statin are absorbed rapidly reaching maximum plasma concentration T_{max} within 4 h [39-41] atorvastatin, pitavastatin and rosuvastatin rate and extent of absorption was not affected by the time of day of its administration. This is contributed by their long half-life characteristic which recorded at 14h, 11h to 19h respectively. Other statins which have a shorter half-life ranging from 1.2h–3h are best administered in the evening, when the rate of endogenous cholesterol synthesis is highest [39-41]. The long half-life characteristics of atorvastatin, pitavastatin and rosuvastatin also contribute to their greater efficacy for lowering LDL-C compared with other statins [42]. With the exception of pitavastatin and cerivastatin, most of the statin possesses low systemic bioavailability ranging from 5%-24% [43, 44]. This is due to the several factors such as low solubility in water [45], transmembrane efflux via P-glycoprotein [46] and extensive metabolism in the liver and guts [47].

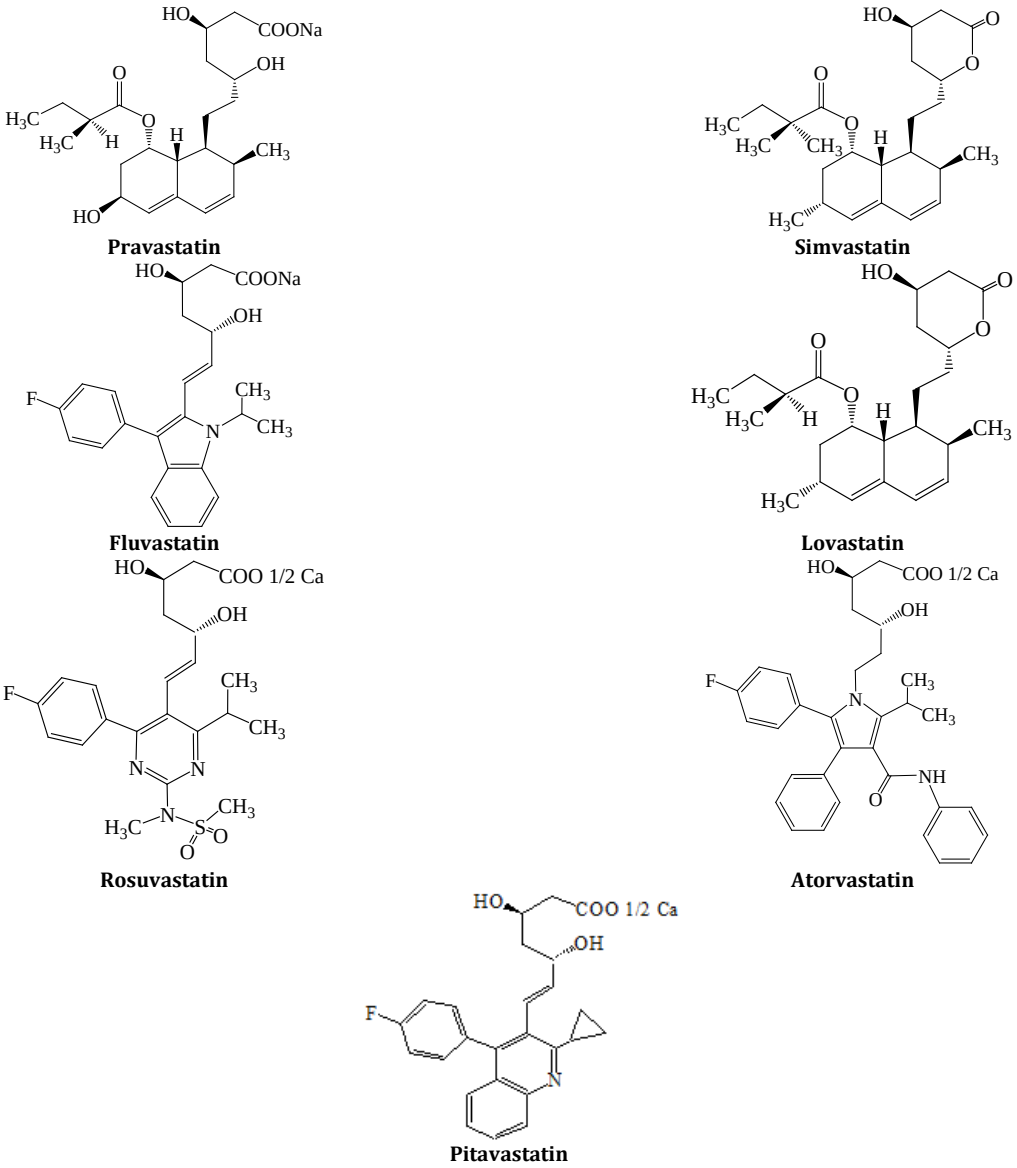

Fig. 2: Commercialized statins molecular structures

With the exception of pravastatin, all statins are extensively bound to plasma proteins (ranging from 95%-98%) [48]. Due to this factor, the concentration of the active drug in the systemic system is relatively low and reduces their pharmacological activities. In the case of pravastatin, although circulating levels of unbound pravastatin in the systemic system is very high, its hydrophilic characteristic limits its tissue distribution [48, 36].

Statins are primarily metabolized by the cytochrome P450 (CYP450) family of enzymes, which consist of more than 30 isoenzymes [49]. Simvastatin, atorvastatin and lovastatin is metabolized by the CYP3A4 isoenzyme whereas fluvastatin is mainly metabolized by the CYP2C9 isoenzyme. Other statins such as pravastatin, pitavastatin and rosuvastatin do not significantly metabolized through CYP450 pathways [50]. Recent studies show that statin molecules which metabolized by the CYP450 system particularly CYP3A4 isozyme are more prone to lead to muscle toxicity issue [51, 52]. Other drug interaction with a statin might increase statin concentration in plasma with a consequent increased risk of toxic effects. Most statin undergoes extensive metabolism in the liver and mainly excreted in the bile [42]. Due to this factor, the incident of statin-induced myopathy was high for hepatic dysfunction patient [53]. Pravastatin and rosuvastatin, on the other hand, are eliminated as an unchanged drug by kidney and liver [54, 55].

Efficacy and safety of statins

As the most commonly prescribe lipid modifying drugs, statins are highly effective at lowering LDL-C. However, different types of statin show a different degree of LDL-C reduction at therapeutic doses [56]. Of the clinically approved statins, rosuvastatin is the most effective at lowering LDL-C, with reductions of up to 63% followed by atorvastatin, pitavastatin, and simvastatin with the LDL-C reduction of 50%, 48% and 41% respectively [57]. The ability of statins to increase HDL-C levels is also shown at varying degrees. Results by comparative trials confirmed that at 10-40 mg doses, rosuvastatin increased HDL-C level by 7.7–9.6% as compared to that of 2.1–5.7%, 5.2–6.8% and 3.2–5.6% as in the case of atorvastatin, simvastatin and pravastatin respectively [58].

In general, statins are well tolerated and their safety is well established. However, statin has been reported to effect liver and muscular tissue adversely. Although the incident of myotoxicity is low (approximately one in 1000 patients treated) it can lead to a fatal rhabdomyolysis [59]. The incident of fatal rhabdomyolysis in a number of patients treated with cerivastatin in 2001 has become an eye opener for the researchers to emphasize seriously the adverse reaction of other statin molecules. On the other hand, it must be stressed here that, high incidents of myopathy can be triggered if an inhibitor of cytochrome P450 or other inhibitors of statin

metabolism are administered together with a statin that increases their concentration in blood. Other risk factor includes hepatic dysfunction, hypothyroidism, renal insufficiency, advanced age and serious infections [53].

Beneficial effects of statin

Besides being used extensively for the treatment of hypercholesterolemia, comprehensive research on statin molecules has led to the discovery of its therapeutics pleiotropic effects. These include anti-inflammatory [60] and antioxidative properties [61] neuroprotective activities [62], improvement of endothelial function and increased nitric oxide bioavailability [63]. These discoveries have increased the beneficial effects of statin therapy in the treatment of Acute Coronary Syndromes (ACS), renal failure, neurologic disorder and infectious disease [64].

Recent studies on statin revealed that statin might be the suitable candidate for new chemotherapy for cancer disease. Its selective inhibition of HMGA-CoA reductase activities which resulted in the reduction of mevalonate and inhibit malignant cell proliferation [64]. Additionally, the administration of statin will increase the mineral density of the bones and decrease of bone fracture risk of the 50 y old patient [65].

Though the statins are highly recognized universally for their beneficial effects in reducing serum cholesterol and thereby preventing the morbidity and mortality associated with coronary heart disease, a lot of interest is getting surfaced for their potential benefits in the area of neurodegeneration disease such as cerebrovascular disease [66], Parkinson's disease [67], Alzheimer's disease [68] and multiple sclerosis [69]. Statins unique characteristics such as high potential blood-brain barrier penetration and cholesterol lowering effects on neuron fully explained their role in neuroprotective activities.

Solubility issue

Solubility which can be determined by the thermodynamic and kinetic method can be defined as the amount of a solute that can be dissolved in a fixed volume of solvent at a given temperature. Solubility is affected by various factors such as time, saturation degree of the solution, particle size, temperature and pH of the medium [4]. Solubility issue is one of the major technical problems among the pharmaceutical researchers involved in the pharmaceutical formulation development. The issue becomes more prominent when 40% of new chemical entities are poorly soluble or insoluble in water. Around 50% of orally administrated drugs are reported to have formulation problems related to low bioavailability, hence, become a core issue, and need to be addressed by the researchers [70]. The level of drug concentration in the systemic circulation of poorly soluble drugs is being affected mainly by the time required for the dosage form to release its contents and for the drug to dissolve. Therefore, improving the saturation solubility and dissolution rate of the poorly soluble drug is very crucial in order to achieve complete absorption. As mentioned previously, statin molecules are classified under class II drug (low solubility, high permeability) in BCS. Hence, in order for the drugs of this class to achieve complete absorption in the systemic circulation, they must be dissolved in the gastrointestinal fluid and release its content [71]. Numerous techniques and methods have been presented by previous scientific articles on the enhancement of statin molecules solubility. In this review, all technique reported will be divided into 4 main categories ie solid dispersion technique, inclusion complex formation technique, solubilization of surfactant technique and particle size reduction technique. The detailed review of all techniques are illustrated in table 3-9.

Solubility enhancement strategies

Solid dispersion

Solid dispersion can be defined as the dispersion of one or more active ingredients in an inert carrier matrix at solid state [72]. Since its introduction in 1960s by Sekiguchi and Obi, the system has been widely used to improve the solubility, the dissolution rate and bioavailability of poorly water soluble drugs [73]. In solid dispersion systems, the physicochemical interactions occur between hydrophobic drug and the carrier which involved the deposition of the drug on the surface of an inert carrier. This will lead into the alteration of the dissolution and solubility characteristics of the drug. Various explanation and theories have been proposed by the researchers on this phenomenon. These include the reduction of the particle size, the increased in the surface area, the increased in wettability due to the presence of hydrophilic carriers, the high porosity of the particles, the reduction of aggregation and the possible presence of the drug in its amorphous form [74]. Solid dispersion approach also offers numerous advantages such as simple and economical process, flexibility in formulation, provide great stability, allow dose combination and no use of toxic constituents [4]. Based on those advantages it is no doubt that this approach is preferred by most researchers in order to improve the solubility of poorly water soluble drugs. Basically, solid dispersion system can be prepared by 4 main methods ie melt/cool (fusion) method, solvent evaporation, co-precipitation and dropping method. The list of technique categorized under those methods can be seen in table 2.

Table 2: Solid dispersion techniques

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

Based on our scientific articles compilation, solid dispersion became the main approach used by the researchers in their attempt to enhance the solubility of statin molecules. It has been used for four statin molecules namely simvastatin, lovastatin, atorvastatin and rosuvastatin. Simvastatin and atorvastatin are the most studied statin molecules for solubility enhancement (table 3a and 3b). This might be due to the fact that both molecules are the most commonly used lipid-lowering agents being prescribed by the medical practitioners [75]. Solvent evaporation method was the commonly method used to produce a solid dispersion. In solvent evaporation, both the drug and the carrier are dissolved in a common solvent followed by the evaporation of the solvent to form a solid solution. Major advantage of this method is the usage of low temperature during organic solvent evaporation which can prevent thermal degradation of drug or carrier. The used of HPMC K3LV as a polymer at a proposition of 1:1 to the amount of simvastatin followed by evaporation by spray dryer resulted 18.6 fold increase in simvastatin solubility [76]. Other studies derived the same trend of simvastatin solubility enhancement ie 2.6 and 4.46 fold [77], 8.5 fold [78] and 4.1 fold [79]. The same trend of solubility enhancement was reported for other statin molecules ie 1.5-2.9 fold for lovastatin [80, 81], 2-33 folds for atorvastatin [82-84, 134] and 4.7 fold for rosuvastatin [85]. The results of other solid dispersion approaches used are summarized in table 3a and b. In conclusion, solid dispersion becomes a key focus emphasized by the researchers due to the facts that the method can be easily scaled up, provide great stability, lower manufacturing cost and allow dose combination.

Inclusion complex

Inclusion complex formation is one of the most studied techniques used to enhance the solubility, dissolution rate and successively improved the bioavailability of poorly soluble drug [86]. It can be defined as the formation of a complex by addition of the non-polar molecules or guest substance, into other molecules or host. Cyclodextrins, (CD) which are cyclic oligosaccharides obtained by the enzymatic degradation of starch are the most widely used host. It can be divided into 3 main types namely α, β and γ base on the

number of monomers in the macrocycle (6, 7 and 8 glucopyranose units respectively) [87]. It god a unique molecular structure where its cylinder shape consists of a hydrophobic inner cavity and a large number of the hydroxyl group on the outer surface, that explain its water soluble characteristic [88]. Due to this distinctive feature, CD are capable of forming inclusion complexes with poorly water-soluble compound by taking up a lipophilic part of the guest molecules into its cavity without forming any covalent bonds [89]. Numerous scientific research has been reported on the capability of CD inclusion to improve poorly water soluble molecules solubility and stability such as piroxicam [90], glipizide [91], ibuprofen [92], and itraconazole [93]. Basically, there are 5 techniques usually employed in producing CD inclusion complexes. These include kneading, co-evaporation, lyophilization, spray drying and extraction in the supercritical fluid. The details of each method employed are summarized in table 4a-b.

Based on our compilation, kneading became the main approach used by the researchers in their attempt to enhance the solubility of statin molecules. In kneading statin molecules and CD are mixed with a small amount of water or hydroalcoholic mixture and the complex formed was dried in air or oven. This approach has been reported for three statin molecules namely simvastatin, lovastatin, and rosuvastatin. The ternary inclusion complexation of simvastatin with βCD and Soluplus ® (polymeric solubilizer with an amphiphilic chemical structure) resulted 55 fold increase in simvastatin solubility [94]. An increase of 3.4 fold on simvastatin solubility was also reported by Mandal *et al.* in 2010 [95]. The same trend of solubility enhancement was also reported for other statin molecules such as 3.4 and 1.54 fold for lovastatin [96] and rosuvastatin [97] respectively. Another inclusion complex formation involving other approaches has shown the same trend on statin molecules solubility. Jun *et al.*, 2006 [98] reported 8 fold increase in simvastatin solubility from the βCD-Simvastatin complex prepared with the supercritical anti-solvent method. Palanisamy *et al.*, 2016 [135] reported 35.8 fold increase in atorvastatin solubility from the binary systems with HPβCD using freeze drying method at drug: carrier ratio of 1:5. An interesting attempt was performed on βCD inclusion complexes, where simvastatin and lovastatin were dissolved in a liposomal dispersion of L-α-dipalmitoyl phosphatidylcholine (DPPC). The solubility enhancement of both molecules was reported at 9 times as compared to the complexes which was derived from βCD alone [87]. The results of other inclusion complex studies are summarized in table 4. In conclusion, complex inclusion approach has also been employed for improving the solubility of statin molecules. However, low drug loading is one of the drawbacks this method suffers with.

Table 3a: Solubility enhancement of statin molecules by solid dispersion approach (1)

Statin molecules	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Simvastatin	Cosolvent-evaporation method	Sodium starch glycolateCroscarmellose sodium	1:31:3	2.64.46	Rao *et al.*, (2010) [77]
		Hydroxypropyl methyl cellulose (HPMC K3LV)	1:1 (Rotaevaporation)1:1 (Spray Dryer)	12.718.6	Pandya *et al.*, (2008) [76]
	Solvent evaporation	PEG 6000, sorbitol, Gelucire 44/14	1:1:1 (Fusion)	8.5	Jatwani *et al.,* (2011) [78]
	Fusion method	PEO-PPO block copolymers	1;4	4.7 times greater than pure drug (dissolution medium phosphate buffer	Singh *et al.*, (2012) [125]
	Physical mixture	Oat powder	1:3	3.1 times greater than pure drug (dissolution medium–phosphate buffer	Bolla *et al.*, (2013)[126]
	Spray drying*Hot melt**(extrusion temp 78-80 °C)	*Methocel E3 LV (HPMC)**Methocel E3 LV (HPMC) and propylene glycol	1:41:8.3:0.7	4.1 3.6	Javeer *et al.*, (2013) [79]

Table 3b: Solubility enhancement of statin molecules by solid dispersion approach (2)

Statin molecules	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Lovastatin	Solvent evaporation method	Sodium starch glycolate, Crospovidone	1:2:2	2 (in SIF)1.5 (in SGF)	Shaik *et al.*, (2011) [80]
		Modified locust bean gum	1:5	2.9	Patel *et al.*, (2008) [81]
Atorvastatin	Solvent evaporation	Skimmed milk	1:9	33	Choudharya *et al.*, (2012) [84]
		HPMC	2:1	2	Uddin *et al.*, (2010) [82]
		Nicotinamide	1:1	2	Shayanfar *et al.*, (2013) [83]
	Hot melt extrusion	PEG 4000	1:5	2	Bobe *et al.*, (2011)[127]
	Dropping method	PEG 6000	1:3	2.2	Lakshmi *et al.*, (2011)[128]
	Fusion method	PEG 4000	1:3	1.7	Shamsudin *et al.,* (2016) [134]
	Supercritical anti-solvent (SAS) method	Supercritical CO2, methanol, PVPVA64	5% (w/v) in methanol1(Drug):1(PVP VA64)	1.4 in bioavailability than the amorphous atorvastatin nanoparticle	Kim *et al.*, (2008)[129]
Rosuvastatin	Spray drying	PVP K30	1:6	4.7 times greater than pure drug (dissolution medium–pH 6.8 of phosphate buffer)	Swathi *et al.*, (2013) [85]

Table 4a: Solubility enhancement of statin molecules by complex inclusion approach (1)

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Simvastatin	Simple physical mixing, kneading and spray drying	Hydroxypropyl-β-cyclodextrin and Soluplus®	1:1:0.005	55	Taupitz *et al.*, (2013) [94]
	Supercritical anti-solvent (SAS) method	Hydroxypropyl-β-cyclodextrin	1:1	12.2	*Jun et al.*, (2006) [98]
	Cyclodextrin complex in liposomal dispersion	Randomly methylated β cyclodextrin	Not mentioned	Drug solubility was proportional to the quantity of methylated β cyclodextrin in liposomal dispersion around 9 times	Csempesz *et al.*, (2010) [87]
	Kneading	Hydroxypropyl-β-Cyclodextrin	1:1	3.4 times greater than pure drug (dissolution medium–phosphate buffer	Mandal *et al.*, (2010) [107]
Lovastatin	Not mentioned specifically	Randomly methylated β Cyclodextrin	Not mentioned	79	Csempesz *et al.*, (2010) [87]
	Kneading	β Cyclodextrin	1:1	3.4 times greater than pure powder of lovastatin (dissolution medium–phosphate buffer pH 6.8)	Patel and Patel (2007) [96]

Table 4b: Solubility enhancement of statin molecules by complex inclusion approach (2)

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Atorvastatin	Freeze dry	Substituted derivative (HP β-Cd)	1:5	35.8	Palanisamy *et al.*, (2016) [135]
Rosuvastatin	Freeze dry	randomly methylated-β-CD (RM-β-Cd)	1:1	9.2	Vyas, A (2013)[130]
	hydrotropic solubilization	Sodium salicylate	Excess rosuvastatin in 0.2N sodium salicylate	55	Nainwal *et al.*, (2011)[131]
	Kneading method	B-cyclodextrin	1:1	1.54 times greater than pure drug (dissolution medium–pH 6.8 of phosphate buffer)	Akbari *et al.* (2011) [97]

Surfactant based approach

Surfactant are usually organic compounds that are amphiphilic. Most of the surfactant consist of a hydrocarbon part that is attached to a polar group. This polar group can be anionic, cationic, zwitterionic or non-ionic. When hydrophobic molecules are introduced, it can be attached to the hydrophobic core of the micelles [99] resulted in a decrease in surface tension. The decrease in the surface tension will increase the solubility of the drug in aqueous solution. An attempt to enhanced statin molecules solubility with this method was reported for simvastatin, lovastatin and rosuvastatin. Margulis and Magdassi successfully obtained simvastatin nanoparticles form by solvent evaporation from spontaneously formed oil-in-water microemulsions. The nanoparticles formed showed a tremendous enhancement in dissolution profile ie 50 times greater compared to the conventional tablet [100]. Another attempt by Mandal reported for an increased in *in vitro* micro-emulsion lovastatin (LVS) release as compared to conventional suspension and commercially available lovastatin. This study also revealed for an increase of 4.7 times in bioavailability after oral administration of LVS formulation as compared with the commercially available lovastatin [95].

Self micro emulsifying drug delivery system (SMEDDS) and self nano emulsifying drug delivery system (SNEDDS) is another approached that commonly used to enhance the solubility of poorly soluble drugs. In SMEDDS and SNEDDS, the isotropic mixture of oil, surfactant and co-surfactant will form oil-in-water micro or nanoemulsion upon mild agitation, followed by administration into aqueous media such as GI fluid [101]. Based on our literature search, both methods has been used to enhance the bioavailability of simvastatin, lovastatin, and rosuvastatin. An increased in bioavailability has been reported for simvastatin-SMEDDS, lovastatin-SMEDDS and rosuvastatin-SNEDDS for about 1.5 [102], 2.27 [136] and 2.45 fold [103] respectively as compared to the commercially available drug. Lipid nanoparticle (LN) is another approach that has been reported to increase the bioavailability of statin molecules. Simvastatin-LN obtained from the emulsification solvent evaporation mixture of Solutol® HS-15 (surfactant), oil and lecithin reported for a bioavailability increased in about 3.37 fold as compared to simvastatin suspension. The details of all approaches are summarized in table 5a-b.

Particle size reduction

Particle size reduction technique involved physical modification of the particle with the aim to increase particle surface area, solubility and wettability with the decrease in particle size. This technique focused on the particle size reduction or generation of amorphous state [104]. In typical part of formulation preparation, size reduction involved well-established media milling procedure such as high-pressure homogenizer. In media milling, the drug particles are subjected to milling in the high energy shear forces generated from the impaction between the drug and the milling media [105]. This action will provide energy to reduce the drug from micro to nano sized particle. The implementation of supercritical antisolvent (SAS) approach in particle size reduction currently gained significant attention among the researches. This technique offer process efficiency, selectivity and accommodating the principles of green chemistry [108]. Sometimes nanonization technique is also used for particle size reduction [109]. Based on our literature search, the size reduction technique has being used to enhance the solubility and bioavailability for 3 statin molecules namely simvastatin, atorvastatin and lovastatin. Two studies are reported for atorvastatin solubility enhancement by media milling. The first attempt involved the formation of the nanosize chitosan-atorvastatin (CH-AT) conjugate by high-pressure homogenizer milling. Nanoconjugate CH-AT shows a tremendous enhancement in atorvastatin solubility. It was reported that nanoconjugate of CH-AT showed solubility enhancement of nearly 4 fold and 100 fold compared to CH-AT conjugate and pure atorvastatin respectively [110]. Similar media milling approach was reported by Arunkumar [111] In this study, atorvastatin nanosuspension was formed by high speed homogenizer followed by high pressure homogenizer. An average size of 200 nm particle size of suspension was formed. This suspension managed to increase atorvastatin solubility for up to 3.4 fold as compared to pure atorvastatin [111].

Table 5a: Solubility enhancement of statin molecules by surfactant based approach (1)

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Simvastatin	Solvent evaporation from spontaneously formed oil-in-water micro-emulsion	Soy lecithin, tween 80, n-butylacetate, Ethanol	Produced microemulsions, incorporated simvastatin and lyophilized (100 nm nanoparticles, 10.8and Simvastatin). Tablets then made with 24% of freeze dried material	50 times greater than conventional tablet (dissolution medium–simulating gastric medium	Margulis, Magdassi (2009) [100]
	Solid lipid nanoparticle-emulsification solvent evaporation	Solutol ® HS-15, Miglyol 812, lecithin S-75	(5:20:14:20) for SV: HS-15:M812:S-57	3.37 increased in bioavailability compared to Simvastatin suspension	Zhang *et al.*, (2010) [106]
	Self micro emulsifying drug delivery system (SMEDDS)	Capryol 90, carbitol, CremophorL	(7:37:28:28) for simvastatin: Capryol 90,: Carbitol,: CremophorL	1.5 increased in bioavailability compared to conventional tablet	Kang *et al.*, (2004) [102]

Table 5b: Solubility enhancement of statin molecules by surfactant based approach (2)

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Lovastatin	Microemulsion	Capmul® MCM Cremophor® EL Transcutol® P	20 mg lovastatin with 7% Capmul® MCM 24%Cremophor® EL 8%Transcutol® P and water	Approximately 1.3 times greater than the commercially tablet	Mandal S (2011) [107]
	Self micro emulsifying drug delivery system (SMEDDS)	peanut oil, labrasol, span 80	labrasol, span 80, peanut oil (40:20:40)	2.27 times increased in bioavailability compared to raw lovastatin	Yadava *et al.*, (2015) [136]
Rosuvastatin	Self nanoemulsifying drug delivery system (SNEDDS)	Cinnamon oil, labrasol, capmul MCM C8	10 mg drug: 30% cinnamon oil: 60% labrasol: 10% capmul MCM C8	1.72 times greater than marketed formulation (dissolution medium–pH 6.6 of 0.05M Citrate buffer)	Balakumar *et al.*, (2013) [103]

Table 6: Solubility enhancement of statin molecules by size reduction

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Simvastatin	Nanonization	Tween 80	0.5 (drug):1 (tween)	2.6 times increased in bioavailability compared to conventional drug	Chavhan *et al.*, 2013 [105]
	Supercritical anti-solvent (SAS) method	Supercritical CO2, Methanol	4% (w/v) in methanol	1.8 times increased in bioavailability compared to conventional drug	Chavhan *et al.*, 2013 [105]
	Rapid expansion of supercritical solution	NA	NA	4 fold increased in dissolution rate	Fattahi *et al.,* 2016 [132]
Lovastatin	nanocrystal	Acetone	3 mM Drug in organic solution	18	Nanjwade *et al.*, (2011) [109]
	Coacervation phase separation	Ethanol, Eudragit® L 100, SDS	drug: polymer: SDS 1:2: 0.25%	4 fold increased in dissolution rate	Al-Nimry *et al.*, 2016 [133]
Atorvastatin	High pressure homogenization and spray drying	Polaxomer 188	10 (Drug): 1 (Surfactant)	3.4	Arunkumar *et al.*, (2009) [111]
	Supercritical anti-solvent (SAS) method	Supercritical CO_2, Acetone	10 % (w/v) in acetone	3.4	Kim *et al.*, (2008) [112]
		Supercritical CO2, Methanol	5 % (w/v) in methanol	3.2	Kim *et al.*, (2008) [113]
	Antisolvent precipitation method	Methanol HPMC, water	40 (Drug):1 (HPMC)	Approx 1.2 times greater than atorvastatin powder (dissolution medium–phosphate buffer	Zhang *et al.*, (2009) [114]
	Chitosan–atorvastatin conjugate and High Pressure Homogeniser	Chitosan	10:1	100 fold than pure atorvastatin	Anwar *et al.*, (2011) [110]

Table 7: Solubility enhancement of statin molecules by drug-dentrimer conjugates approach

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Simvastatin		PEG-PAMAM dentrimer	Not mentioned	33	Kulhari *et al.*, (2011) [116]
		NH2–PAMAM dentrimer		23	
		OH-PAMAM dentrimer		17.5	

As been mentioned in the early part of this section, SAS approach is a promising technique that has been given significant attention among the researches recently. In SAS, the drug will be dissolved in the solvent and will be introduced into the temperature and pressure equilibrated particle precipitation vessel which has being filled with the constant rate of Supercritical CO2(Sc-Co2) [112]. In this vessel, precipitation will forms instantaneously by a rapid desolvation of the drug. At washing step, the SC-CO2 will wash out the residual content of solvent solubilized in the supercritical anti-solvent [112]. This technique has been successfully used for simvastatin and atorvastatin solubility and bioavailability enhancement. Simvastatin prepared with SAS technique showed bioavailability increment (1.8 times) compared to the plain drug [105]. The same trend has been reported by another 3 scientific publications on atorvastatin. All researchers concluded that this process has increased either the solubility or dissolution of the pure drug [112-114]. Another approach that has been explored by the researcher is nanonization, This approach was not using any surfactant and claimed to produce more soluble, biologically available and safer dosage form of the poorly soluble drug. Researchers reported, a nanocrystal of lovastatin obtained through nanonization showed an increased solubility for up to 18 folds as compared to the pure lovastatin [109]. Rapid expansion of supercritical solution (RESS) and coacervation phase separation are another approaches that have been reported to increase the dissolution rate of simvastatin and lovastatin by 4 and 5 fold respectively [132-133]. The details of all approaches mentioned are summarized in table 6.

Novel formulation approaches

In this section some novel approaches are discussed so to highlight some possible methods of solubility enhancement, which may further be explored for the statins.

Table 8: Solubility enhancement of statin molecules by mesoporous carrier approaches

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Simvastatin	Solvent immersion/evaporation	Highly ordered mesoporous carbon (HMC)	1: 0.2	4.5	Zhang *et al.*, (2013) [118]
	Media milling	Tween 80	0.5:1	3.3	Chavhan *et al.*, (2013) [105]
Lovastatin	Solvent immersion/evaporation	Uniform mesoporous silica spheres(UMCS)	6% (w/v) drug with UMCS	3.3 times greater than pure powder of lovastatin (dissolution medium–enzyme-free buffer with 0.10% SDS (pH 6.8)	Zhao *et al.*, (2012) [119]
		Porous silica monolith (PSM)	1:3	1.8 times greater than pure powder of lovastatin (dissolution medium–phosphate buffer with 0.20% SDS (pH 7)	Chao Wu *et al.*, (2012) [117]

Table 9: Solubility enhancement of statin molecules by liquid-solid system approach

Technique	Methods	Excipient	Drug-carrier ratio	Increase in solubility (times)	Reference
Atorvastatin	Liquid-solid compact	Propylene glycol Avicel PH 102, Aerosil 200, Sodium starch glycolate	10% w/w drug in PG, 20: 1 ratio of Avicel, and Aerosil, 10% explotab	Approx 2 times greater than conventional formulation (dissolution medium–distilled water)	Gubbi, Jarag (2010) [120]
Rosuvastatin		Propylene glycol Microcrystalline cellulose, Aerosil 200, Sodium starch glycolate	10% w/w drug in PG, 166.6 mg Avicel, 8.33 mg Aerosil, 5% Sodium starch glycolate	Approx 2 times greater than marketed formulation (dissolution medium–300 ml distilled water)	Kapure *et al.*, (2013) [124]
		PEG200, Avicel PH,Aerosil 200, Sodium starch glycolate	15% w/w drug in PEG 200, 305.77 mg Avicel, 10.19 mg Aerosil,17.46 Sodium starch glycolate	Approx 2 times greater than marketed formulation (dissolution medium–phosphate buffer PH 6.8)	Kamble *et al.* (2014) [121]

Drug-dentrimer conjugate

Dendrimers are large and highly branched complex molecules with very well defined 3D chemical structure. It's having a nanoscale structure with very low polydispersity and high functionality [115]. A dendrimer is inert and small enough to pass through the cell and can be used to deliver the drug to the targeted cell. There are three basic family of dendrimer namely poly (amidoamine) (PAMAM), diamino butane (DAB) and polypropylene imine (PPI). As the first synthesis dentrime, PAMAM has been extensively used as a drug carrier in drug delivery. PAMAM unique characteristics such as allowing the precise control of the size, shape and placement of the functional group, provide minimum toxicity and widely available make it the right candidate for an ideal drug carrier. PAMAM has been reported to form a conjugate with simvastatin in order to improve simvastatin aqueous solubility [116]. The effect of PAMAM concentration, pH and the type of functional group attached to the dendrimer was also assessed in this study. This study showed a significant enhancement on simvastatin solubility among Simvastatin-PAMAM conjugates. A 33 fold increment on simvastatin solubility is reported for PEGlated dendrimer simvastatin followed by amine (23 times) and hydroxyl (17.5 times) dendrimer [116]. The positive finding of this study can become the catalyst for more studies on other statin molecules-dendrimer conjugates. The details of the study reported by Kulhari are summarized in table 7.

Mesopourous carrier

The porous material can be defined as the material with an ordered or irregular arrangement of different pore size ranging from nanometer to millimeter. These highly pourous materials provide a large effective surface area and hydrophilic surface. Its unique characteristic such as biocompatible, not toxic, stronger adsorbability and structural versatility has attracted the attention of recent studies on their capability to enhance the solubility of poorly soluble drug [117]. Two studies are reported on the solubility enhancement of lovastatin by this approach. Wu, investigating the feasibility of 2 novel starch-derived porous material namely porous silica monolith (PSM) and Porous Starch Foam(PSF) in improving the dissolution of lovastatin. In this study lovastatin was loaded into PSM (LV-PSM) and PSF (LV-PSF) by solvent exchange method. This study showed a significant increase in dissolution rate of LV-PSM

and LV-PSF. Both complex exhibit more than 80% release of lovastatin at 45 min in comparison with 50% release for the pure lovastatin [117]. The same trend of results was reported by Zhao *et al.* lovastatin loaded in uniform mesopourous silica spheres (LV-UMCS) showed an increased in lovastatin accumulated released. More than 90% of lovastatin in LV-UMCS was released at 45 min in comparison with 20% release for the pure lovastatin [119]. Another study on simvastatin loaded in highly ordered mesoporous carbon (SIM-HMC) also reported an increased 4.5 fold release as compared to the pure powder of simvastatin [118]. The details of the study reported regarding this approach are summarized in table 8.

Liquid-solid system

Liquid-solid system are acceptably flowing and compressible powder form of liquid medication [120]. In this system, poorly water soluble drug get dissolve in non-volatile solvent to form a liquid medication. Further, the system shall be blended with the carrier and coating material to form dry looking, non-adherent, free-flowing and readily compressible powder [121]. Basically various grades of lactose, starch and cellulose may be used as carrier and very fine particle size silica powders may be used as the coating material [122]. Liquid-solid compact normally form in a fine particle form. This characteristic will increase it molecules surface area that will enhanced dissolution characteristics and subsequently, oral bioavailability [123]. An attempt to improve statin molecules solubility with this approach reported by Gubbi and Jarag in 2010 for atorvastatin. An increase in atorvastatin accumulated released of 94.08 % is achieved at 60 min as compared to 46.61% release in case of the pure atorvastatin. The A-LS compact also showed an improvement in bioavailability compared to their directly compressed counterparts [120]. The same trend of enhancement of drug release rate and bioavailability has been reported for rosuvastatin. [124, 121]. The details of the study reported on this approach are summarized in table 9.

CONCLUSION

In this review, an attempt has been made to highlight systematically the emergence of statin-based molecules as the lipid-lowering medicament with due consideration to their therapeutics benefits, possible side effects and poor solubility characteristics. In this context, statin molecules which are categorized under class II BCS and play an important role in a lipid lowering activities demand better solution for its solubility and bioavailability problem. Various methods have been employed by the researchers to overcome this problem. Typical methods such as solid dispersion, inclusion complex, solubilization with surfactant and particle size reduction have been reported. Some innovative approaches such as drug-dendrimer conjugate, mesopourous carrier and liquid-solid have also been discussed in this review articles. It is very difficult to conclude which approach is better than the others since there are several factors that can influence the success of the given method. The assumption cannot be made just on the solubility and dissolution studies alone that are mentioned in some of the articles since it is really necessary to relate it with *in vivo* experiment. Another aspect that need to be addressed by the researchers is on the stability of the product formed through the implementation of the approaches. This is due to the facts that statin molecules show very high stability in crystalline form. Any attempt to change its structure from crystalline to amorphous derivatives demand a thorough investigation on its stability. Lastly, the effects of physical and chemical changes of statin on its pharmacokinetics need to be addressed adequately, which the author notice are lacking in most of the articles collected in this review.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Tripathy S, Kar PR. Albendazole solubilization in aqueous solutions of nicotinamide: thermodynamics and solute-solvent interaction. Orien J Chem 2013;29:1-5.
2. Tripathy S, Kar PR, Majeed ABA. Albendazole solid dispersions in nicotinamide: solid state characterization and *in vitro* dissolution study. Int J Pharma Bio Sci 2013;4:306-19.
3. Solanki CS, Tripathy S, Tripathy M, Dash UN. Studies on the solute, solvent interaction of nimesulide in aqueous solutions of hydrotropic agents at different temperatures E J Chem 2010;7:S223-S30.
4. Rúbia M, Vargas WD, Raffin FN, Flávio T, Lima AD. Strategies used for to improve aqueous solubility of simvastatin systematic review. J Basic Appl Sci 2012;33:497–507.
5. Gordon LA, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 1995;12:413–20.
6. Solanki CS, Mishra P, Talari MK, Tripathy M, Dash UN. Conductometric study of nimesulide in aqueous solutions of hydrotropic agents at different temperatures. E J Chem 2012;9:21-6.
7. Arakaw T, Kita Y, Koyama H. Solubility enhancement of gluten and organic compounds by arginine. Int J Pharm 2008;355:220–3.
8. Kasim N, Whitehouse M, Ramachandran C, Bermejo M, Lennernäs H, Hussain AS, *et al*. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm 2004;1:85–96.
9. William BK. Clinical misconceptions dispelled by epidemiological research. Circulation 1995;92:3350–60.
10. Daniel S, Antonio M, Gotto J. Preventing coronary artery disease by lowering cholesterol levels : Fifty years from bench to bedside. JAMA 1999;282:2043–50.
11. Kannel B. Range of serum cholesterol values in the population developing coronary artery disease. Am J Cardiol 1995;76:69C–77C.
12. Mariottia S, Capocacciaa R, Farchia G, Menottia A, Verdecchiaa AK. Age, period, cohort and geographical area effects on the relationship between risk factors and coronary heart disease mortality: 15-year follow-up of the European cohorts of the seven countries study. J Chronic Dis 1986;39:229–42.
13. Bhatnagar D, Soran H, Durrington PN. Hypercholesterolaemia and its management. Br Med J 2008;337:503–8.
14. Lazar HL. Role of statin therapy in the coronary bypass is patient. Ann Thorac Surg 2004;78:730–40.
15. Otokozawa S, Ai M, Asztalos BF, White CC, Demissie-Banjaw S, Cupples LA, *et al*. Direct assessment of plasma low-density lipoprotein and high-density lipoprotein cholesterol levels and coronary heart disease: results from the Framingham offspring study. Atherosclerosis 2010;213:251–5.
16. Després JP, Lemieux I, Dagenais GR, Cantin B, Lamarche B. Hdl-cholesterol as a marker of coronary heart disease risk: the Québec cardiovascular study. Atherosclerosis 2000;153:263–72.
17. Shitara Y, Sugiyama Y. Pharmacokinetic and pharmacodynamic alterations of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: drug-drug interactions and interindividual differences in transporter and metabolic enzyme functions. Pharmacol Ther 2006;112:71–105.
18. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. Am J Cardiol 2006;98:1363–8.
19. Williams KJ, Tabas I. The response-to-retention hypothesis of early atherogenesis. Arterioscler Thromb Vasc Biol 1995;15:551–61.
20. Jonathan AT. Lovastatin and beyond the history of the HMG-CoA reductase inhibitors. Nat Rev Drug Discovery 2003;2:517–26.
21. Kirby T. Cataracts produced by triparanol (MER/29). Trans Am Ophthal Soc 1967;65:494–543.
22. Endo A. A historical perspective on the discovery of statins. Proc Jpn Acad Ser B 2010;86:484–93.
23. Watanabe Y, Ito T, Saeki M, Kuroda M, Tanzawa K, Mochizuki M, *et al*. Hypolipidemic effects of CS-500 (ML-236B) in WHHL-rabbit, a heritable animal model for hyperlipidemia. Atherosclerosis 1981;38:27–31.
24. Kuroda M, Tsujita Y, Tanzawa K, Endo A. Hypolipidemic effects in monkeys of ML-236B, a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Lipids 1979;14:585–9.
25. Tsujita Y, Kuroda M, Tanzawa K, Kitano N, Endo A. Hypolipidemic effects in dogs of ML-236B, a competitive

inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Atherosclerosis 1979;32:307-13.
26. Hiroshi M, Takeshi S, Yasuyuki S, Akira Y, Akira W, Takanobu W, *et al*. Reduction of serum cholesterol in heterozygous patients with familial hypercholesterolemia-additive effects of compactin and cholestyramine. N Engl J Med 1983;308:609–13.
27. Alberts W, Chen J, Kuron G, Hunt V, Huff J, Hoffman C. Mevinolin: a highly potent competitive inhibitor of hydroxymethyl-glutaryl-coenzyme A reductase and a cholesterol-lowering agent. Proc Natl Acad Sci U S A 1980;77:3957–61.
28. Tobert JA, Hitzenberger G, Kukovetz WR, Holmes IB, Jones KH. Rapid and substantial lowering of human serum cholesterol by mevinolin (MK-803), an inhibitor of hydroxymethyl-glutaryl-coenzyme A reductase. Atherosclerosis 1982;41:61–5.
29. Richard JH, Donald BH, Illingworth DR, Lees RS, Stein EA, Tobert JA, *et al*. Lovastatin (Mevinolin) in the treatment of heterozygous familial hypercholesterolemia: A multicenter study. Ann Intern Med 1987;10:609–15.
30. Tobert JA. A Multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. JAMA 1988;260:359–66.
31. Doty JD, Xhignesse M, Frohlich J, Hayden ML, Vanetta H, Mishkel MA, *et al*. A multicenter comparison of lovastatin and probucol for the treatment of severe primary hypercholesterolemia. Am J Cardiol 1990;66:22b–30b.
32. Bradford RH, Charles LS, Athanassios NC, Carlos D, Maria D, Frank A, *et al*. Medicine expanded clinical evaluation of lovastatin (EXCEL) study results in I_ efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. JAMA Int Med 1991;151:43–9.
33. Khan S, Teitz DS, Jemal M. Kinetic analysis by HPLC-Electrospray mass spectrometry of the pH-dependent acyl migration and solvolysis as the decomposition pathways of Ifetroban 1-O-acyl glucuronide. Anal Chem 1998;70:1622–8.
34. Istvan E. Statin inhibition of HMG-CoA reductase: a 3-dimensional view. Atheroscler Suppl 2003;4:3–8.
35. Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. J Pharmacol Exp Ther 1999;84:413–28.
36. Hobbs HH, Brown MS, Joseph LG. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Hum Mutat 1992;1:445–66.
37. Yang DJ, Hwang LS. Study on the conversion of three natural statins from lactone forms to their corresponding hydroxy acid forms and their determination in Pu-Erh tea. J Chromatogr A 2006;1119:277–84.
38. Alberts AW. Discovery, biochemistry and biology of lovastatin. Am J Cardiol 1988;62:J10–J5.
39. Donald DCJ, Whitfield LR, Gibson DM, Sedman AJ, Posvar EL. Multiple-dose pharmacokinetics, pharmacodynamics, and safety of atorvastatin, an inhibitor of HMG-CoA reductase, in healthy subjects. Clin Pharmacol Ther 1996;60:687–95.
40. Tse FL, Jaffe JM, Troendle A. Pharmacokinetics of fluvastatin after single and multiple doses in normal volunteers. J Clin Pharmacol 1992;32:630–8.
41. Pan HY, Devault AR, Wang-Iverson D, Ivashkiv E, Swanson BN, Ugerman AA. Comparative pharmacokinetics and pharmacodynamics of pravastatin and lovastatin. J Clin Pharmacol 1990;30:1128–35.
42. Warwick MJ, Dane AL, Raza A, Schneck DW. Single and multiple-dose pharmacokinetics and safety of the new HMG-CoA reductase inhibitor ZD4522. Atherosclerosis 1999;151:39-41.
43. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitor. Clin Pharmacokinet 1997;32:403–25.
44. Martin PD, Warwick MJ, Dane AL, Brindley C, Short T. Absolute oral bioavailability of rosuvastatin in healthy white adult male volunteers. Clin Ther 2003;25:2553–63.
45. Serajuddin AT, Ranadive SA, Mahoney EM. Relative lipophilicities, solubilities, and structure-pharmacological considerations of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors pravastatin, lovastatin, mevastatin, and simvastatin. J Pharm Sci 1991;80:830–4.
46. Chen C, Mireles RJ, Campbell SD, Lin J, Mills JB, Xu JJ, *et al.* Differential interaction of 3-hydroxy-3-methylglutaryl-coa reductase inhibitors with ABCB1, ABCC2, and OATP1B1. Drug Metab Dispos 2005;33:537–46.
47. Benet LZ, Wu CY, Hebert MF, Wacher VJ. Intestinal drug metabolism and anti transport processes: a potential paradigm shift in oral drug delivery. J Controlled Release 1996;39:139–43.
48. Hamelin BA, Tergeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. Trends Pharmacol Sci 1998;19:26–37.
49. Bottorff M. Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. Am J Cardiol 2000;85:1846–7.
50. Jacobsen W, Kuhn B, Soldner A, Kirchner G, Sewing K, Kollman PA, *et al*. Lactonization is the critical first step in the disposition of the 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitor atorvastatin. Drug Metab Dispos 2000;28:1369–78.
51. Sica DA, Gehrt T. Rhabdomyolysis, and statin therapy: relevance to the elderly. Am J Geriatr Cardiol 2002;11:48–55.
52. Muscari A, Puddu GM, Puddu P. Lipid-lowering drugs: are adverse effects predictable and reversible? Cardiology 2002;97:115–21.
53. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. Circulation 2000;101:207–13.
54. Singhvi SM, Pan HY, Morrison RA, Willard DA. Disposition of pravastatin sodium, a tissue-selective HMG-CoA reductase inhibitor, in healthy subjects. Br J Clin Pharmacol 1990;29:239–43.
55. Schachter M. Statins, rug interactions and cytochrome P450. Br J Cardiol 2001;8:311–7.
56. Punitha S, Kumar KLS. Statin therapy and their formulation approches: A review. Int J Pharm Sci 2011;3:23–6.
57. Olsson G, Pears J, Mckellar J, Mizan J, Raza A. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. Am J Cardiol 2001;88:504–8.
58. Jones PH, Davidson MH, Stein E, Bays HE, Mckenne JM, Miller E, *et al*. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol 2003;92:152–60.
59. Donald MB. A general assessment of the safety of HMG CoA reductase inhibitors (statins). Curr Atheroscler Rep 2002;4:34–41.
60. Hristov M, Fach C, Becker C, Heussen N, Liehn E, Blindt R, *et al*. Reduced numbers of circulating endothelial progenitor cells in patients with coronary artery disease associated with long-term statin treatment. Atherosclerosis 2007;192:413–20.
61. Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Mol Med 2001;5:378–87.
62. Wood WG, Eckert GP, Igbavboa U, Muller WE. Statins and neuroprotection: a prescription to move the field forward. Ann N Y Acad Sci 2010;1199:69–76.
63. Wang CY, Liu PY, Liao JK. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. Trends Mol Med 2008;14:37–44.
64. Merx MW, Weber C. Benefits of statins beyond lipid lowering. Drug Discovery Today: Dis Mech 2008;5:e325–e31.
65. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H. HMG-CoA reductase inhibitors and the risk of fractures. JAMA 2000;283:3205–10.
66. Nassief A, Marsh J. Statin therapy for stroke prevention. Stroke 2008;39:1042–48.
67. Wahner AD, Bronstein JM, Bordelon YM, Ritz B. Statin use and the risk of Parkinson disease. Neurology 2008;70:1418–22.
68. Eckert GP, Wood WG, Muller W. Statins: drugs for Alzheimer's disease? J Neural Transm 2005;112:1057–71.
69. Neuhaus O, Hartung H. Evaluation of atorvastatin and simvastatin for treatment of multiple sclerosis. Expert Rev Neurother 2007;7:547–56.
70. Naseem A, Olliff CJ, Martini LG. Effects of plasma irradiation on the wettability and dissolution of compacts of griseofulvin. Int J Pharm 2004;269:443–50.
71. Hörter D, Dressman J. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv Drug Delivery Rev 2001;46:75–87.
72. Sekiguchi K, Obi N. Studies on the absorption of eutectic mixture. 1. A comparison of the behavior of a eutectic mixture

of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull 1961;9:866–72.
73. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci 1971;60:1281–302.
74. Patel R, Patel M. Preparation, characterization, and dissolution behavior of a solid dispersion of simvastatin with polyethylene glycol 4000 and polyvinylpyrrolidone K30. J Dispersion Sci Technol 2008;29:193-204.
75. Nováková L, Vlcková H, Satínský D, Sadílek P, Solichová D, Bláha M, *et al*. Ultra high-performance liquid chromatography tandem mass spectrometric detection in clinical analysis of simvastatin and atorvastatin. J Chromatogr B: Anal Technol Biomed Life Sci 2009;877:2093–103.
76. Pandya P, Gattani S, Jain P, Khirwal L, Surana S. Co-solvent evaporation method for enhancement of solubility and dissolution rate of poorly aqueous soluble drug simvastatin: *in vitro-in vivo* evaluation. AAPS PharmSciTech 2008;9:1247–52.
77. Rao M, Mandage Y, Thanki K, Bhise S. Dissolution improvement of simvastatin by surface solid dispersion technology. Dissolution Technol 2010;27–34. Doi.org/10.14227/DT170210P27. [Article in Press]
78. Jatwani S, Rana AC, Singh G, Aggarwal G. Solubility and dissolution enhancement of simvastatin using the synergistic effect of hydrophilic carriers. Der Pharm Lett 2011;3:280–93.
79. Javeer SD, Patole R, Amin P. Enhanced solubility and dissolution of simvastatin by HPMC-based solid dispersions prepared by hot melt extrusion and spray-drying method. J Pharm Invest 2013;43:471–80.
80. Shaikh K, Patwekar S, Payghan S, D'souza J. Dissolution and stability enhancement of poorly water soluble drug–lovastatin by preparing solid dispersions. Asian J Biomed Pharm Sci 2011;1:24–31.
81. Patel M, Tekade A, Gattani S, Surana S. Solubility enhancement of lovastatin by modified locust bean gum using solid dispersion techniques. AAPS PharmSciTech 2008;9:1262–9.
82. Uddin R, Ali F, Biswas SK. Water solubility enhancement of atorvastatin by solid dispersion method. Stam J Pharm Sci 2010;3:43–6.
83. Shayanfar A, Ghavimi H, Hamishekar H, Jouyban A. Coamorphous atorvastatin calcium to improve its physicochemical and pharmacokinetic properties. J Pharm Pharm Sci 2013;16:577–87.
84. Choudharya A, Ranaa AC, Aggarwalb G, Kumara V, Zakir F. Development and characterization of an atorvastatin solid dispersion formulation using skimmed milk for improved oral bioavailability. Acta Pharm Sin B 2012;2:421–8.
85. Swathi T, Vamshi KM, Sudheer KD, Krishnaveni J. Enhancement of solubility and dissolution rate of rosuvastatin by using solid dispersion technique. J Pharm Sci Innovation 2013;2:36–40.
86. Patel RP, Patel M. Preparation, and evaluation of inclusion complex of the lipid-lowering drug lovastatin with B-cyclodextrin. Dhaka Univ J Pharm Sci 2007;6:25–36.
87. Csempesz F, Süle A, Puskás I. Induced surface activity of supramolecular cyclodextrin–statin complexes: relevance in drug delivery. Colloids Surf 2010;354:308–13.
88. Valentine JS, Rajewski RA. Cyclodextrins: their future in drug formulation and delivery. Pharm Res 1997;14:556–67.
89. Frömming KH, Szejtli J. Cyclodextrins in: cyclodextrins in pharmacy. 1ed. Dordrecht, The Netherland: Kluwer Academic Publishers; 1994. p. 1-10.
90. Doijad RC, Kanakal MM, Manvi F. Studies on piroxicam β-cyclodextrin inclusion complexes. Indian Pharm 2007;6:94–8.
91. Aly AM, Qato MK, Ahmad MO. Enhancement of the dissolution rate and bioavailability of glipizide through cyclodextrin inclusion complex. Pharm Technol 2003;27:54–62.
92. Ghorab MK, Adeyeye M. Elucidation of solution state complexation in wet-granulated oven-dried Ibuprofen and β-cyclodextrin: FT-IR and 1H-NMR studies. Pharm Dev Technol 2001;6:315–24.
93. Al-Marzouqi AH, Shehatta I, Jobe B. Phase solubility and inclusion complex of itraconazole with beta-cyclodextrin using supercritical carbon dioxide. J Pharm Sci 2006;95:292–304.
94. Taupitz T, Dressman JB, Klein S. New formulation approaches to improve solubility and drug release from fixed dose combinations: case examples pioglitazone/glimepiride and ezetimibe/simvastatin. Eur J Pharm Biopharm 2013;84:208–18.
95. Mandal D, Ojha PK, Nandy BC, Kanta L. Effect of carriers on solid dispersions of simvastatin (Sim): Physico-chemical characterizations and dissolution studies. Lett Der Pharm 2010;2:47–56.
96. Patel RP, Patel MM. Solid-state characterization and dissolution properties of lovastatin hydroxypropyl-β-cyclodextrin inclusion complex. Pharm Technol 2007. Available from: http://www.pharmtech.com/pharmtech/Analytics/Solid-State-Characterization-and-Dissolution-Prope/ArticleStandard/Article/detail/400647. [Last accessed on 16 Jun 2014].
97. Akbari BV, Valaki BP, Maradiya VH, Akbari AK, Vidyasagar G. Enhancement of solubility and dissolution rate of rosuvastatin calcium by complexation with B-cyclodextrin. Int J Pharm Biol Arch 2011;2:511–20.
98. Jun SW, Kim MS, Kim JS, Park HJ, Lee S, Woo JS, *et al*. Preparation and characterization of simvastatin hydroxypropyl-β-cyclodextrin inclusion complex using supercritical antisolvent (SAS) process. Eur J Pharm Biopharm 2006;66:413-7.
99. Swarbrick J. Encyclopedia of pharmaceutical technology. 3ed. London: Informa Healthcare; 2006. p. 4370-80.
100. Margulis-Goshen K, Magdassi S. Formation of simvastatin nanoparticles from microemulsion. Nanomed Nanotech Biol Med 2009;5:274–81.
101. Wang L, Dong J, Chen J, Eastoe J, Li X. Design and optimization of a new self-nanoemulsifying drug delivery system. J Colloid Interface Sci 2009;330:443–8.
102. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, *et al*. Development ofself-micro emulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int J Pharm 2004;274:65–73.
103. Balakumar K, Raghavan CV, Selvan NT, Prasad RH, Abdu S. Self nanoemulsifying drug delivery system (SNEDDS) of rosuvastatin calcium: design, formulation, bioavailability and pharmacokinetic evaluation. Colloids Surf B 2013;112:337–43.
104. Grau MJ, Kayser O, Müller RH. Nanosuspensions of poorly soluble drugs-reproducibility of small scale production. Int J Pharm 2000;196:155–9.
105. Chavhan S, Joshi G, Petkar K, Sawant K. Enhanced bioavailability and hypolipidemic activity of simvastatin formulations by particle size engineering: Physicochemical aspects and *in vivo* investigations. Biochem Eng J 2013;79:221–9.
106. Zhang Z, Huihui B, Zhiwei G, Yan H, Fang G, Yaping L. The characteristics and mechanism of simvastatin loaded lipid nanoparticles to increase oral bioavailability in rats. Int J Pharm 2010;394:147-53.
107. Mandal S. Microemulsion drug delivery system: design and development for oral bioavailability enhancement of lovastatin. SA Pharm J 2011;78:44–50.
108. Hojjati M, Yamini Y, Khajeh M, Vatanara A. Solubility of some statin drugs in supercritical carbon dioxide and representing the solute solubility data with several density-based correlations. J Supercrit Fluids 2007;41:187–94.
109. Nanjwade K, Derkar BK, Bechra GM, Nanjwade HK, Manvi FV. Design and characterization of nanocrystals of lovastatin for solubility and dissolution enhancement. J Nanomed 2011;2:1-7.
110. Anwar M, Warsi MH, Mallick N, Akhter S, Gahoi S, Jain GK, *et al*. Enhanced bioavailability of nano-sized chitosan-atorvastatin conjugate after oral administration to rats. Eur J Pharm Sci 2011;44:241–9.
111. Arunkumar N, Deecaraman M, Rani C, Mohanraj K, Kumar KV. Preparation and solid state characterization of atorvastatin nanosuspensions for enhanced. Int J PharmTech Res 2009;1:1725–30.
112. Kim JS, Kim MS, Park HJ, Jin SJ, Lee S, Hwang SJ. Physicochemical properties and oral bioavailability of amorphous atorvastatin hemi-calcium using spray-drying and SAS process. Int J Pharm 2008;359:211–9.
113. Kim MS, Jin SJ, Kim JS, Park HJ, Song HS, Neubert RHH, *et al*. Preparation, characterization and *in vivo* evaluation of amorphous atorvastatin calcium nanoparticles using

supercritical antisolvent (SAS) process. Eur J Pharm Biopharm 2008;69:454–65.

114. Zhang HX, Wang JX, Zhang ZB, Le Y, Shen ZG, Chen JF. Micronization of atorvastatin calcium by antisolvent precipitation process. Int J Pharm 2009;374**:**106–13.
115. Svenson S, Tomalia D. Dendrimers in biomedical applications-reflections on the field. Adv Drug Delivery Rev 2012;64:102–15.
116. Kulhari H, Pooja D, Prajapati SK, Chauhan AS. Performance evaluation of PAMAM dendrimer based simvastatin formulations. Int J Pharm 2011;405:203–9.
117. Wu C, Wang J, Hu Y, Zhi Z, Jiang T, Zhang J, *et al*. Development of a novel starch-derived porous silica monolith for enhancing the dissolution rate of poorly water soluble drug. Mater Sci Eng C 2012;32:201–6.
118. Zhang Y, Wang H, Gao C, Li X, Li L. Highly ordered mesoporous carbon nanomatrix as a new approach to improve the oral absorption of the water-insoluble drug, simvastatin. Eur J Pharm Sci 2013;49:864–72.
119. Zhao P, Wang L, Sun C, Jiang T, Zhang J, Zhang Q, et al. Uniform mesoporous carbon as a carrier for poorly water soluble drug and its cytotoxicity study. Eur J Pharm Biopharm 2012;80:535–43.
120. Gubbi SR, Jarag R. Formulation and characterization of atorvastatin calcium liquisolid compacts. Asian J Pharm Sci 2010;5:50–60.
121. Kamble PR, Shaikh KS, Chaudhari PD. Application of liquisolid technology for enhancing solubility and dissolution of rosuvastatin. Adv Pharm Bull 2014;4:197–204.
122. Gavali SM, Pacharane SS, Sankpal SV, Jadhav KR, Kadam VJ. Liquisolid compact : a new technique for enhancement of drug dissolution. Int J Res Pharm Chem 2011;1:705–13.
123. Spiros SS, Charles IJ, Bhagwan DR. Powdered solution technology: principles and mechanism. Pharm Res 1992;9:1351–8.
124. Kapure VJ, Pande VV, Deshmukh PK. Dissolution enhancement of rosuvastatin calcium by liquisolid compact technique. Int J Pharm 2013;274:1–9.
125. Singh H, Philip B, Pathak K. Preparation, characterization and pharmacodynamic evaluation of fused disperions of simvastatin using PEO-PPO Block Co polymer. Iran J Pharm Res 2012;11:443-5.
126. Bolla N, Chandra S, RajanRaju CH, Koteswara Rao, GSN, Uma Devi P. Improvement of simvastatin solubility using natural polymers by solid dispersion technique Int J Pharm Res Biomed Anal 2013;2:1-6.
127. Bobe KR, Subrahmanya CR, Sarasija S, Gaikwad DT. Formulation and evaluation of solid dispersion of atorvatstatin with various carriers. Pharm Globale Int J Comprehen Pharm 2011;11:34-6.
128. Lakshmi NV, Bhaskar J, Venkateswarlu G, Vijaya BK. Enhancement of dissolution rate of atorvastatin calcium using solid dispersions by dropping method. Int J PharmTech Res 2011;3:652-9.
129. Kim MS, Jin SJ, Kim JS, Park HJ, Song HS, Neubert RHH, *et al*. Preparation, characterization and *in vivo* evaluation of amorphous atorvastatin calcium nanoparticles using supercritical antisolvent (SAS) process. Eur J Pharm Biopharm 2008;69:454–65.
130. Vyas A. Preparation, characterization and pharmacodynamic activity of supramolecular and colloidal systems of rosuvastatin–cyclodextrin complexes. J Inclusion Phenom Macrocyclic Chem 2013;76:37–46.
131. Nainwal P, Sinha P, Singh A, Nanda D, Jain DA. A Comparative solubility enhancement study of rosuvastatin using solubilization techniques. Int J Appl Biol Pharm Technol 2011;2:14-8.
132. Fattahia A, Karimi-Sabetb J, Keshavarza A, Golzaryc A, Rafiee-Tehrania M, Dorkoosh FA. Preparation and characterization of simvastatin nanoparticles using rapid expansion of supercritical solution (RESS) with trifluoromethane. J Supercrit Fluids 2016;107:469-78.
133. Al-Nimry SS, Khanfar MS. Preparation and characterization of lovastatin polymeric microparticles by coacervation-phase separation method for dissolution enhancement. J Appl Polym Sci 2016;133:43277-87.
134. Shamsuddin, Fazil M, Ansari SH, Ali J. Atorvastatin solid dispersion for bioavailability enhancement. J Adv Pharm Technol Res 2016;7:22-6.
135. Palanisamya M, James A, Khanam J. Atorvastatin–cyclodextrin systems: Physiochemical and biopharmaceutical evaluation. J Drug Delivery Sci Technol 2016;31:41-52.
136. Yadava SK, Naik JB, Patil JS, Mokale VJ, Singh R. Enhanced solubility and bioavailability of lovastatin using stabilized form of self-emulsifying drug delivery system. Colloids Surf A 2015;481:63-71.