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SOLUBILITY ENHANCEMENT OF SIMVASTATIN: A REVIEW

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Abstract: Fairly soluble drugs in gastrointestinal (GI) media exhibit complete oral absorption, and thus good bioavailability. About 40% of drugs are not soluble in water in practice and therefore are slowly absorbed, which results in insufficient and uneven bioavailability and GI toxicity. Thus, most exigent phase of drug development practice particularly for oral dosage forms is the enhancement of drug solubility and thereby its oral bioavailability. Solubility, an important factor to achieve desired plasma level of drug for pharmacological response, is the phenomenon of dissolution of solid in liquid phase resulting in a homogenous system. This review describes various traditional and novel methodologies proposed for solubility enhancement of simvastatin, and ultimately improvement in its bioavailability. For simvastatin, solubility is a crucial rate limiting factor to achieve its desired level in systemic circulation for pharmacological response. Thus, problematic solubility of simvastatin is a main challenge for dosage form developing researchers**.** Various procedures, illustrated in this review, have been successfully employed to improve the simvastatin solubility for its bioavailability enhancement; however, successful improvement essentially depends on the assortment of technique. Among all the solubility enhancement techniques, solid dispersion method, in terms of ease and efficiency is most promising and routinely employed technique to resolve the solubility problems of simvastatin.

Keywords: techniques, solubility, polymers, surfactants, absorption, bioavailability

Fairly soluble drugs in gastrointestinal (GI) media exhibit complete oral absorption, and thus good bioavailability. About 40% of drugs are not soluble in water in practice and therefore are slowly absorbed, which results in insufficient and uneven bioavailability and GI toxicity (1). Thus, most exigent phase of drug development practice particularly for oral dosage forms is the enhancement of drug solubility thereby its oral bioavailability. Bioavailability refers to the limit of therapeutically active drug that approaches the systemic circulation and thus, is available at the site of action (2). There are two reasons proposed for poor aqueous solubility of drugs (3): (i) high lipophilicity and (ii) strong intermolecular forces which cause the insolubilization of drugs (2). Various approaches have been proposed to enhance solubilization of poorly water soluble drugs for the improvement of their bioavailability (4). The methodologies commonly used for drug solubilization includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization and hydrotropy (5). This review is prepared to narrate different traditional and novel methodologies for the increase in solubility of hydrophobic drugs for converting to oral dosage forms.

There are numerous chemical molecules which experience low aqueous solubility troubles. Although these molecules have prospective pharmacodynamic feature, they exhibit low bioavailability attributable to poor aqueous solubility, and therefore, these molecules turn into abortive entities. Therefore, it is a very tough assignment in drug development to improve aqueous solubility of drug (6).

Simvastatin (SV, Fig. 1), an inactive lactone, is cholesterol lowering agent and a lipid lowering agent developed synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin is hydrolyzed to the analogous β-hydroxyacid form. This is a major metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in the biosynthesis of cholesterol (7–9).

SV is a white, crystalline and non-hygroscopic powder having log P = 4.4 and glass transition tem-

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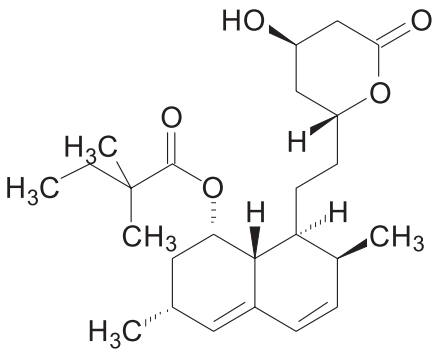

Figure 1. Chemical structure of simvastatin

perature of 25°C. Its formula weight is 418.56. It is practically insoluble in water (30 µg/mL), and 0.1 M HCl (60 µg/mL). It is normally believed that compounds with very low aqueous solubility will exhibit dissolution-controlled absorption and therefore reduced absorption, distribution and target organ delivery. Its biological half life and bioavailability are 3 h and 5% indicating extensive first pass metabolism in liver, respectively. It is well absorbed from GIT (8, 9); therefore, it is vital to augment its aqueous solubility, dissolution rate and bioavailability from its oral solid formulations.

Numerous techniques have been presented for the enhancement of solubility and dissolution of poorly soluble drugs. However, many of these methods have constraints such as particles frequently agglomerate and micronized powder possesses high energetic surface indicating poor flow feature (10). Complexation with cyclodextrin exhibits low drug loading (11). Solid dispersion involves the use of higher quantity of polymer(s) (12) and its scale up procedure is complicated. Several polymers have also been reported for the improvement of simvastatin solubility. Some of them are β-cyclodextrin, arosil 200, PVP K30 and self-microemulsifying agent. In this context, a detailed review of possibly all previous presentations for the enhancement of solubility and dissolution of SV are given in Table 1.

Inclusion complex formation techniques

Inclusion complex formation procedure is one of the most precisely employed techniques for the enhancement of solubility, dissolution rate, and subsequently improved bioavailability of poorly water soluble drugs. Inclusion complexes are prepared by the addition of the non-polar molecule(s) (guest substance) into other molecule(s) (host). Cyclodextrins (CD), degradative products of starch produced by the action of cyclodextrin-glycosyl transferase (CGT), are the cyclic oligosaccharides and are frequently employed as host molecules. Its three natural grades are α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), and γ-cyclodextrin (γ-CD) (13). The CDs have been previously employed in the improvement of solubility and oral bioavailability of glipizide (14), rofecoxib (15), piroxicam (16) and carvedilol (17) by preparing their inclusion complexes. Various techniques such as kneading method, microwave irradiation method, supercritical anti-solvent technique and lyophilization/freeze drying technique have been acclimatized to fabricate the inclusion complexes of poorly water soluble drugs with CDs. Following are the attempts which have been made for the improvement of SV solubility and dissolution by inclusion complexation.

Varshosaz et al. (18) presented this study to enhance the dissolution rate of SV using spherical anti-solvent induced-crystallization method. In this method, SV solution prepared in boiling dichloromethane was added to cold water (5°C), the non-solvent. After sedimentation, bridging solvent (isopropyl acetate) was put in. Finally, the crystals were amassed and dried for 12 h at 50°C in an oven. No alteration in the drug after crystallization process was observed as evident from the FTIR (Fourier transform infrared spectroscopy) and DSC (differential scanning calorimetry) data. The XRPD (powder x-ray diffractometry analysis) exhibited minor reduction in height of the characteristic peaks. The particle size of spherical aggregates was about 37 µm. The dissolution efficiency of SV up to 60 min increased to about 2-fold in phosphate buffer solution having 0.5% sodium dodecyl sulfate (pH 7) using the rotating paddle method. The spherical crystals obtained exhibited improved solubility than that of untreated powder probably by reason of partial change to amorphous form. Their dissolution rate at 60 min was still 4-fold of untreated powder when stored at 25°C and 84% relative humidity for 30 days.

Shiralashetti et al. (19) executed this study with the purpose of observing the influence of preparation techniques on the solubility and dissolution of SV β-CD and hydroxypropyl β-cyclodextrin (HPβ-CD) inclusion complexes. Simple physical mixing, kneading and spray drying techniques were employed to fabricate the complexes. In physical mixture, drug, β-CD and HPβ-CD in the molar ratios of 1:1 were blended independently in a mortar for approximately 1 h with fixed trituration. The mixture was then passed through sieve 100 followed

by storage in the desiccators over fused calcium chloride ($CaCl_2$).

Kneading method involves the soaking of CDs having little quantity of water or hydro-alcoholic solution to transfer into a paste followed by its kneading after the addition of drug. The kneaded product is then dried and sieved if needed (20). In laboratory, kneading can be attained by using a mortar and pestle (21–24). In kneading method, SV with β-CD in the molar ratio of 1:1 was used. First, β-cyclodextrin and a small amount of 50% methanol were mixed in mortar with trituration to obtain slurry like uniformity followed by slow incorporation of drug into the slurry with continuous trituration for 1 h. Slurry was then dried in air at 25°C for 24 h, pulverized, passed through sieve 100 and stored in desiccator over fused $CaCl_2$. The same procedure was repeated for the SV-HPβ-CD complex.. In spray drying method, SV and β-CD were dissolved in isopropyl alcohol (IPA) and distilled water independently using a magnetic stirrer. Then, both the solutions were mixed together with magnetic stirring for 30 min. The consequential solution was sprayed in the chamber from a nozzle with internal diameter of

Table 1. Techniques found in literature for solubility enhancement of simvastatin.

Technique	Methods	Polymer	Reference
Inclusion complex formation techniques	Anti-solvent induced-crystallization method	Polymer not involved	Varshosaz et al. (18)
	Simple physical mixing, kneading and spray drying methods	Hydroxypropyl β-cyclodextrin	Shiralashetti et al. (19)
	Simple physical mixing, kneading and fusion methods	Polyethylene glycol PEG 6000 (PEG) 4000, or hydroxypropyl β-cyclodextrin	Mandal et al. (25)
	Supercritical anti-solvent (SAS) method	Hydroxypropyl β-cyclodextrin	Jun et al. (26)
Solid dispersion techniques	Combination of adsorption equilibrium and solvent evaporation method	Polymer not involved	Zhang et al. (30)
	Solvent evaporation by spray drying and rota-evaporation methods	Hydroxypropyl methylcellulose-K3LV	Pandya et al. (34)
	Physical mixtures and melting method	Polyethylene glycol-4000	Silva et al. (35)
	Ball milling method	Polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA64)	Zhang et al. (36)
	Spray drying method	PVP	Ambike et al. (37)
Solubilization by surfactants techniques	Solvent evaporation from spontaneously formed oil-in-water micro-emulsions method	Polymer not involved	Margulis-Goshen and Magdassi (38)
	Self-microemulsifying method	Polymer not involved	Meng and Zheng (39)
	Microemulsion method	Polymer not involved	Lee et al. (40)
	Emulsification method	Polymer not involved	Ding et al. (41)
	Antisolvent recrystallization method	Polymer not involved	Oh and Lee (42)
Particle size reduction techniques	Milling method	Polymer not involved	Zimper et al. (43)
	Nano-precipitation method		Patil et al. (45)

0.7 mm under the atomization pressure of 1.5 kg/cm^2 with a feed rate of 3 mL/min. The inlet temperature was set at 80^{o}C and outlet temperature at 60 ± 2^{o}C. The vacuum and aspirator in the system were 60 mmWC and 45%, respectively. The same procedure was adopted to prepare inclusion complex of SV-HPβ-CD. The product thus obtained was stored in a desiccator till its analysis.

Then, the inclusion complexes were assessed for phase solubility and *in vitro* release behavior. The physicochemical analysis such as DSC and X-ray diffractometry (XRD) of complexes elaborated that no endothermic and specific diffraction peaks of SV was found in both the inclusion complexes. The results showed the conversion of SV from crystalline to the amorphous form. There was a marked increase in the aqueous solubility and dissolution rates of drug in inclusion complexes as compared with the drug alone and its physical mixture. Besides, spray dried complexes performed better in all the evaluated factors as compared to the complexes fabricated by other methods.

Mandal et al. (25) executed this study with the purpose of observing the influence of preparation techniques on the solubility and dissolution of simvastatin-PEG 4000, PEG 6000 or HPβ-CD inclusion complexes. Simple physical mixing, kneading and fusion techniques were employed to fabricate the complexes. In physical mixture, drug, PEG 4000, PEG 6000 or HPβ-CD in the molar ratios of 1:1, 1:3, 1:5 were blended independently in a mortar for approximately 1 h with fixed trituration. The mixture was then passed through sieve 80 followed by storage in the desiccators over fused calcium chloride ($CaCl_2$). In kneading method, SV with HPβ-CD in the molar ratio of 1:1 was used. First, β-cyclodextrin and a small amount of 50% (v/v) alcohol were mixed for 45 min in mortar with trituration to obtain slurry like uniformity followed by slow incorporation of drug into the slurry with continuous trituration for 1 h. Slurry was then dried in air at 60^{o}C, pulverized, passed through sieve 80 and stored overnight in desiccator and named as KNCD (representing "kneading cyclodextrin"). In melting method, solid dispersions of SV and carrier PEG 4000 or PEG 6000 in the molar ratios of 1:1, 1:3, 1:5 were prepared by the melting method. The carrier was melted in a water bath at 70^{o}C, the solid drug was incorporated with stirring to make a homogenous mixture. In a freezing mixture of ice, the mixture was then cooled swiftly and stored in a desiccator for 24 h. Then, the dispersion was ground in a mortar and passed through sieve 80.

The products were analyzed in liquid state by phase solubility studies and in the solid state by DSC, XRD and FTIR. The type, ratios of drug to carriers and selection of the method of preparations of solid dispersions markedly influenced the dissolution rate. The highest dissolution rate of SV was achieved from the inclusion complex prepared with HPβ-CD by kneading method. Marked increase in dissolution rate was observed from solid dispersions systems, compared with those in physical mixtures and pure drug alone. The highest enhancement in wettability and dissolution rate of SV was achieved from the SV-HPβ-CD solid dispersions (1:1) prepared by the kneading process. This could be due to the amorphous nature formed and dissolved of 100% of drug was achieved within 60 min. Accordingly, this amorphous solid dispersions could be valuable for supplementary formulation as an appropriate competitive formulation.

In another study, Jun et al. (26) prepared simvastatin-inclusion complex with HPβ-CD using supercritical anti-solvent (SAS) procedure to investigate the improvement in aqueous solubility and the dissolution rate of drug, consequently improving its bioavailability. Phase solubility diagram, DSC, XRPD, FT-IR and scanning electron microscopy (SEM) tests were used to evaluate the inclusion complexation in aqueous solution and solid state. The phase solubility diagram with HPβ-CD was categorized as A(L)-type at all temperatures conditions, showing the configuration of 1:1 stoichiometric inclusion complex. The apparent complexation constants (K(1:1)) evaluated from phase solubility diagram were 774, 846 and 924 M^{-1}) at 25, 37 and 45 ± 0.5^{o}C, respectively. No endothermic and typical diffraction peaks related to SV was found for the inclusion complex in DSC and XRPD. FT-IR study elaborated the presence of intermolecular hydrogen bonds between SV and HPβ-CD in inclusion complex, showing the development of amorphous form. The results of aqueous solubility and dissolution tests signified that there was a remarkable increase in the dissolution rates of inclusion complex, compared with the physical mixture and simvastatin alone. In conclusion, the narrated process could be a valuable process for the development of the inclusion complex of SV with HPβ-CD for significant increase in its solubility and dissolution rate.

Solid dispersion

Solid dispersion is an assembly of solid products consisting of no less than two unlike con-

stituents, normally a hydrophilic medium and a hydrophobic drug. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone (PVP), polyethylene glycols (PEG) and Plasdone-S630 (PS630). Surfactants like Tween-80, docusate sodium, myrj-52, pluronic-F68 and sodium lauryl sulfate, are also commonly inserted in the solid dispersion. Solid dispersions using appropriate hydrophilic carriers were used in the solubility improvement of celecoxib (27), halofantrine (28) and ritonavir (29). There are various techniques like hot melt (fusion) method, solvent evaporation method and hot melt extrusion to formulate solid dispersion of hydrophobic drugs to enhance their aqueous solubility. Following are the attempts made for the improvement of SV solubility and dissolution by solid dispersion.

Zhang et al. (30) developed spherical mesocellular foam (MCF) loaded with SV *via* a procedure involving a combination of adsorption equilibrium and solvent evaporation, aimed to be orally administered, capable to enhance the dissolution rate and improve the drug loading aptitude. Spherical MCF having an incessant 3-D pore system was produced using a surfactant (Pluronic 123 triblock polymer) and a co-surfactant (cetyltrimethylammonium bromide). Based on the drug release rate and the drug loading efficiency, the spherical MCF and fibrous SBA-15 were compared. The physicochemical evaluation revealed the successful incorporation of SV into the MCF host. The results indicated that spherical MCF has a high drug loading efficiency up to 37.5%, and higher than that of fibrous SBA-15, with a pore diameter of 6.5 nm. It was concluded that faster release rate of SV was acquired from spherical MCF compared with SBA-15 and pure crystalline SV using enzyme-free simulated intestinal fluid (pH 6.8). In solvent evaporation, both the drug and the carrier are dissolved in a common solvent followed by the evaporation of solvent under vacuum to prepare a solid solution. Many studies have proposed the solid dispersion of meloxicam (31), naproxen (32) and nimesulide (33) using solvent evaporation technique. Major benefit of the solvent evaporation technique is the prevention of thermal decomposition of drugs or carriers because of the low temperature needed for the evaporation of organic solvents. Hovewer, some disadvantages related with this process are the higher expenditure of formulation development, the complexity in entire removal of liquid solvent, the possible unfavorable consequence of the added solvent on the chemical stability of the drug, the assortment of a common volatile solvent, and the obscurity of reproducing crystal forms.

In a study, solubility and dissolution of SV was improved using hydrophilic, low viscosity grade polymer – hydroxypropylmethylcellulose (HPMC-K3LV). The co-solvent evaporation method was employed for successful encapsulation of hydrophobic drug (SV) in polymer micelles of HPMC-K3LV. Solvent evaporation was achieved by spray drying and rota-evaporation techniques. In rota-evaporation, Pandya et al. (34) applied co-solvent evaporation technique for improvement of solubility and dissolution rate of SV. The solvent evaporation of SV-HPMC-K3LV (1:1, w/w) solution was conducted using Buchi rota-evaporator (Buchi Rotavapor, R215, Buchi, Switzerland). Two grams of simvastatin in 100 mL of methanol and 2 g of HPMC-K3LV in 60 mL of distilled water were dissolved and both solutions mixed to get a clear solution followed by its evaporation at 253 torr pressure and 60^{o}C for 0.5 h in rota-evaporator. In spray drying, the solvent evaporation of SIM and HPMC-K3LV (1:1) solution was conducted using spray dryer (LU-222, Advanced, Labultima, India). Two grams of simvastatin in 70 mL of methanol and 2 g of HPMC-K3LV in 30 mL of distilled water were dissolved and mixing both solutions gave a clear solution. The solvent evaporated at inlet 110^{o}C and outlet 60^{o}C, feed pump speed 10 mL/min and aspiration 45%. The spray dried mixture of drug with HPMC-K3LV was achieved in 20–30 min.

The DSC, XRD, SEM, and FTIR tests were also applied to evaluate formulations. Results showed the alteration of crystalline SV into its amorphous form. There was a remarkable increase in the dissolution rate of SV in co-solvent-evaporated mixtures, compared to simvastatin alone. It could be due to the surfactant property of low HPMC-K3LV (viscosity grade HPMC), which improves the wettability of SV and therefore enhances its solubility. Consequently, this technique also showed promising encapsulation efficiency and generated amorphous form of SV, which exhibited better solubility and dissolution than the crystalline SV.

Silva et al. (35) prepared the solid dispersions of SV with polyethylene glycol (PEG 4000) using different drug:carrier ratios by the melting method. Physical mixtures (PM) in the same ratios were also prepared for comparison. The products were investigated by XRPD, DSC and infrared spectroscopy and solubility studies. Solid dispersions samples were evaluated by high performance liquid chromatography (HPLC) to assess stability. The XRPD results demonstrated the presence of SV and PEG crystalline. A possible decrease of crystallite size was also observed. The obtained thermograms and

chromatograms showed no incompatibility between components of solid dispersions and physical mixtures. A great effect on SV solubility and release rate was found in the SV solid dispersions with PEG 4000 in all percentages. Solid dispersions of SV with PEG caused a significant augment of drug solubility with almost 100% increase at 1:5 drug:polymer ratio. The enhancement of drug release in the solid dispersions might be a result of the reduction in the crystallite size, as well as, the surface tension lowering influence of polymer, causing an enhancement in wettability and dispersibility of SV.

Zhang et al. (36) investigated the development of kinetics of a solid dispersion of SV with an amorphous copolymer using ball milling and compared the stability of developed products. They ball milled the physical mixtures of quench-cooled amorphous SV and polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA64) in weight ratios of 1:1 and 1:4 for 3–40 min. With increased milling time, the two Tgs (glass transition temperatures) (29.5°C for the drug and 108.5°C for the polymer) primarily present in the 1:4 samples progressively shifted nearer to each other and ultimately outlined a single Tg at 91°C after 30 min, which agreed to the predicted Tg at 89.2°C using Gordon-Taylor equation, demonstrating the development of a one phase solid dispersion. On the other hand, samples at the 1:1 ratio still demonstrated two Tgs (at 74.4°C and 101.5°C) after 30 min milling, disclosing a two phase system with fractional miscibility. These two separate phases were compiled by drug to polymer ratios of 0.46:0.54 and 0.11:0.89, respectively. Additionally, milling of these samples for another 10 min revealed no supplementary variation in thermal performance. Intermolecular hydrogen bonding happening between the two constituents was noticed by DRIFTS (diffuse reflectance IR Fourier-transform spectroscopy) for all milled samples. Amorphous SV in physical mixtures with PVP/VA64 without milling tended to transfer back to the crystalline form during storage at 45°C. Samples at both weight ratios after milling for 10 min revealed a spectacular enhancement in stability although only a small part of drug had structured a single amorphous phase with polymer. There was no notable increase in stability under the conditions studied by further milling. Both MT (modulated temperature) DSC and DRIFTS could be employed to analyze the kinetics of solid dispersion development during milling. The 1:4 drug polymer mixtures produced a one phase solid dispersion while 1:1 drug-polymer mixtures did not. It materializes a completely miscible system for physical stabilization of amorphous SV.

Ambike et al. (37) obtained free flowing, stable, amorphous solid dispersions of SV, a drug with relatively lower Tg, by spray drying technique. In this method, SV was suspended in dichloromethane either alone or in combination with PVP (1:1 or 1:2, w/w ratio between drug and PVP). This suspension was spray dried with anticipated amount of Aerosil 200 (1:1, 1:1:1, 1:2:2 parts by weight of SV, Aerosil 200 and PVP, respectively). To overcome the constraints of spray drying method for amorphization of low Tg drugs, combination of solid dispersions and surface adsorption techniques has been attempted. Solid dispersions 1:2:2 was choosed as the optimized product on the basis of powder features, drug content, saturation solubility and practicability of processing into tablets. In physicochemical evaluation, scanning electron microscopy (SEM), DSC, and XRPD analyses verified the presence of amorphous form in solid dispersions 1:2:2. The IR spectroscopy exhibited the prospect of hydrogen bonding between SV and PVP in solid dispersions. Also, there was dramatical increase in the rate and extent of *in vitro* drug release of solid dispersions 1:2:2. During accelerated stability studies of solid dispersions 1:2:2, inconsequential decline in dissolution was found with no confirmation of crystallinity. Moreover, comparative *in vivo* study in rats also justified the improvement in therapeutic efficacy of solid dispersions 1:2:2, compared to pure SV. Consequently, this study reveals promising ability of spray drying method for finding stable amorphous solid dispersions of low Tg drugs.

Solubilization by surfactants

Surfactants are molecules having distinctive polar and non-polar parts. A large number of surfactants contain a hydrocarbon part attached to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small polar molecules are inserted, they can mount up in the hydrophobic core of the micelles (5) resulting in a decrease in surface tension, however, in an increase in solubility of drug within an organic solvent (12). Following are the attempts made for the improvement of SV solubility and dissolution involving solubilization by surfactants.

Margulis-Goshen and Magdassi (38) evaluated a method for the preparation of nanoparticles of SV by solvent evaporation from spontaneously formed oil-in-water micro-emulsions. In this study, freeze-drying technique was applied to convert micro-emulsions containing a volatile solvent as an oil phase into nanoparticles in the form of dry non-oily flakes. The loading efficiency of SV in nanoparti-

cles was evaluated by dispersing the flakes in water followed by filtration through a 0.1 μm pore size filter. The filtrate was used to assess the SV concentration. The results indicated that > 95% of the drug was present in amorphous particles (size < 100 nm) after freeze-drying. The dissolution studies showed a remarkable increase in dissolution rate from the tablets containing the flakes of SV nanoparticles, compared with conventional tablets. The X-ray diffraction test exhibited that resulting SV nanoparticulate flakes were originally amorphous, but a slow crystallization process occurred when the formulation was stored at room temperature.

Meng and Zheng (39) stated that self-microemulsifying drug delivery systems are valuable to get better bioavailability of simvastatin by enhancing their apparent solubility through solubilization. To achieve this goal, an empirical experimental model was utilized to simulate the effect of the mixture compositions on SV apparent quantitative solubility. The reduced cubic polynomial equation successfully modeled the development of SV apparent solubility. Response surface diagram was presented to show a scale of possible SV apparent solubility in a range of 0.0024 ~ 29.0 mg/mL. Additionally, this procedure proved that SV apparent solubility was primarily affected by microemulsion quantity and advised that the drug precipitation would occur in GIT by reason of dilution by GI fluids. Moreover, the developed model can be helpful in formulation designing to improve drug's apparent solubility and avoid its precipitation.

Microemulsion based formulation of SV was prepared to enhance its solubility and dissolution (40). SV solubility was evaluated after interacting with different saturated substances like fatty acids, oils, surfactant and co-surfactant at 25°C over 24 h. Drug solubility data were used to construct phase diagrams forming optimal microemulsion regions at room temperature on the basis of electric conductivity and visual stability. The self-microemulsifying drug delivery system (SMEDDS) was formulated by heating at 40°C until a clear solution was formed. The SMEDDS consisted of drug, oil, surfactant and co-surfactant. The USP (XXIII) paddle method in simulated gastric (pH 1.2) and intestinal (pH 6.8) fluid was employed to investigate the dissolution rate of SMEDDS. Laser scattering particle analyzer was used to measure the microemulsion size after exposing SMEDDS to distilled water.

The solubility of SV was over 130 mg/mL in light fatty alcohol and carbonates oils. The improvement in the solubility and stability of the drug was also observed with co-solvent addition without recrystallization. The particles size of microemulsion was approximately 90–300 nm. The dissolution rate (< 5%) of marketed formulation (Zoco®) was very low and almost negligible, compared to that of the SMEDDS formulations, which was much higher and faster, reaching 40–50% and 90–100% in simulated gastric and simulated intestinal media, respectively. The SMEDDS was found very successful for the enhancement of solubility and dissolution of SV by preparing stable isotropic and transparent microemulsion with nano-sized particles.

Polyglycerol diisostearate ethoxylates with two hydrophobic chains were prepared by the reacting polyglycerol diisostearate with ethylene oxide as follows (41): 50 g of polyglycerol diisostearate (PGDIS) and 0.2 g of potassium hydroxide (KOH) were mixed in autoclave and heated to about 70°C under nitrogen atmosphere. Then, ethylene oxide was introduced gradually into the autoclave to maintain temperature at 100–110°C and pressure between 0.15 and 0.20 MPa. Acetic acid was then used for the neutralization of final products followed by filtration through celite. The surface features such as cloud temperature, water solubility, critical micelle concentration, the solubilizing capacity and emulsification of polyglycerol diisostearate ethoxylates for simvastatin were explored as compared to those of Tween-80. The critical micelle concentrations of all polyglycerol diisostearate ethoxylates were < 0.01 mM/L, and it was lower than that of Tween-80. Polyglycerol diisostearate ethoxylates exhibited better emulsification than Tween-80. To enhance the SV solubility in micelles, polyglycerol diisostearate ethoxylates also were better than Tween-80.

The phase behavior of simvastatin and lovastatin in solvent mixtures of dichloromethane (DCM) and supercritical carbon dioxide (CO_2) has been explored to elaborate a principle for ascertaining operating circumstances in the particle configuration of the drugs by a supercritical antisolvent recrystallization procedure using DCM and CO_2 as a solvent and antisolvent, respectively. Oh and Lee (42) determined the solubilities of the statin drugs in DCM + CO_2 at different conditions of temperature and pressure by evaluating the cloud positions of the solutions having dissimilar compositions. A mixture of the drug + DCM + CO_2 was arranged and converted into a homogeneous single-phase solution by compression. When the solution reached a cloud position, it turned into clouds and the drug precipitation occurred. Thus, the cloud position symbolized the phase conversion from the single-phase to the two phase solution and behaved as the margin

between the whole dissolution and precipitation of the drug in DCM + CO_2 mixture. Then, the cloud position was measured by the following process.

Any entrapped air in the cell was removed by purging the cell with sufficient CO_2 gas, and then the cell was loaded with drug. Using a gastight syringe, DCM was injected into the cell followed by the immediate positioning of piston. The amounts of the drug and DCM loaded into the cell were determined using a sensitive balance. Then, high-pressure cylinder was employed to charge CO_2 into the cell. The amount of CO_2 introduced into the cell was found out by weighing the sample cylinder using a balance, before and after loading. A hot, fine and short feed line (0.03 inches internal diameter, 10 cm long) was employed to reduce the quantity of CO_2 lost during charging.

At a desired temperature, the pressure generator was employed to compress the solution in the cell by moving the piston located within the cell. The magnetic stirrer was employed for agitation. As the pressure rose, the drug dissolved in the solvent mixture of DCM + CO_2 becoming a single phase. On thermal equilibrium with a single phase solution, the pressure was then gradually decreased at about 0.5 MPa/min until the solution changed into clouds. At a constant temperature, the cloud position signifying the single-phase to two-phase conversion was characterized as the pressure at which it was no longer promising to visually monitor the stirring bar. Thus, a pressure-temperature (P-T) cloud point curve was created for a solvent mixture of DCM and CO_2 with a definite quantity of the drug dissolved.

In short, the solubilities of the statins in the mixture of DCM + CO_2 were established as functions of solvent composition, temperature and pressure by calculating the cloud positions of the ternary mixtures of SV + DCM + CO_2 and lovastatin + DCM + CO_2 at different situations. High-pressure phase equilibrium apparatus equipped with a variable-volume view cell was employed for this purpose. The solubility facts of SV and lovastatin are described in the DCM + CO_2 mixtures with the DCM mole fractions in a range of 0.18–0.34 at a temperature range of 303.25–333.25 K and at pressures up to approximately 45 MPa. The cloud point phase behavior of a typical lower critical solution temperature phase behavior was observed from ternary mixtures. The results showed that the drug solubility boosted with the augment in the DCM composition in solution and the system pressure at a constant temperature. Moreover, there was a decrease in drug solubility with the increase in temperature.

Particle size reduction

The techniques of size reduction involve the increase in surface area of particles with the decrease in particle size, resulting in the increase in drug solubility (5). Size reduction involves well established milling procedures, which are typical part of formulation preparation and can be accomplished generally by micronization and nanosuspension (6). Sometimes, sonocrystallization technique is also used for particle size reduction (43). Following attempts have been made for the improvement of SV solubility and dissolution involving particle size reduction.

The dissolution rate of poorly water soluble BCS-class II and IV drugs can be enhanced by reducing their particle size. On the other hand, the main disadvantage of this procedure is the possible appearance of process related muddle such as the alteration in the molecular configurations of drugs, which may elaborate changed features like solubility and dissolution rate and consequently, process related solid state alterations require to be observed. Zimper et al. (44) investigated the dissolution rates of milled and un-milled SV, screened the main milling parameters, and optimized the milling process in connection with the opposing reactions, particle size and process related muddle by using a central composite face centered drawing. Weighed drug samples (600 mg) were milled in 25 mL stainless steel jars employing an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH and Co., Germany) at 4°C. Processing times (5–60 min), milling frequency (5–25 Hz) and number of stainless steel balls (3–60 with a diameter of 4 mm) were opted using a central composite face centered design (MODDE software version 7, Umetrics AB, Sweden). Silica gel was used to store the processed samples at 4°C. SEM and image analysis were applied to assess particle size. XRPD and Raman spectra were applied to determine process induced disorder by partial least squares regression modeling. Applicable and significant quadratic models were fabricated. The milling frequency, ball quantity and milling time were the investigated milling parameters at constant drug load, out of which milling frequency appeared as the most significant parameter for particle size as well as the process related muddle. An interacting influence on the responses was exhibited by milling frequency and milling time. The optimum milling settings with the maximum number of milling balls (60 balls with 4 mm diameter) was assessed to be at a milling frequency of 21 Hz and a milling time of 36 min with a resulting primary particle size of 1.4 μm and the

process related muddle of 6.1% (assessed by Raman spectroscopy) and 8.4% (assessed by XRPD), at a set optimization limit of less than 2 μm for particle size and greater than 10% for the process induced muddle. This optimum response was analyzed experimentally and the process related muddle was established to be 6.9% (± 2.2) by Raman spectroscopy and 7.8% (± 2.3) by XRPD. The successive intrinsic dissolution analysis exhibited that the process related muddle was insignificant regarding the dissolution rate. The envisaged crucial particle size (1.4 μm) could be corroborated by experimentation; however, by reason of agglomeration of the primary particles, a dissolution rate improvement was not elaborated, emphasizing the significance of dissolution analysis at an initial stage of drug development.

The particle size reduction can also be achieved by nanosuspension (45). The exposed particulate area increases with the decrease in particle size resulting in the increase in solubility. Nanosuspension can also be achieved by precipitation. In precipitation method, the drug substance is dissolved in a solvent, and the resulting solution is then added to non-solvent for precipitating the crystals. It is a simple and economical technique. Nanoparticles, due to their promising aptitude to carry a wide range of drugs to various areas of the body, have gained excellent importance in the area of drug delivery systems. The nanoparticles exhibit a larger surface-to-volume ratio than the bulk material, and thus the dose and frequency of administration may be decreased, which increases patient compliance. In this context, SV nanoparticles were prepared by nano-precipitation technique by Patil et al. (45). A partially water-miscible solvents and the mutual saturation of the aqueous and organic phases were used prior to form a nano-suspension with the aim of reducing the initial thermodynamic instability of the nanoparticles. Due to the self-emulsifying characteristics of the methacrylic acid co-polymers, it was likely to develop aqueous dispersions of colloidal size having up to 30% w/v of eudragit L100 using methanol as a water-miscible solvent with surfactant. Patil et al. (45) dissolved SV and eudragit L100 in methanol at definite concentration followed by the filtration of obtained solution through 0.45 μm pore size membrane for the removal of likely particulate contaminations. Then, the controlled nano-precipitation technique was employed to prepare SV nanoparticles involving the addition of 5 mL of SV solution into the previously prepared mixture of distilled water and poloxamer with continuous mechanical stirring followed by the immediate precipitation. The stirring rate and polymer concentration were varied to observe their effect on the properties of products. The obtained nanoparticles were filtered and dried using rota-evaportor under vacuum at 50^{o}C for 3–4 h.

CONCLUSION

For SV, solubility is a crucial rate limiting factor to achieve its desired level in systemic circulation for pharmacological response. Thus, problematic solubility of SV is a main challenge for dosage form developing researchers**.** Various procedures, illustrated in this review, have been successfully employed to improve the SV solubility for its bioavailability enhancement; however, successful improvement essentially depends on the assortment of technique. Among all the solubility enhancement techniques, solid dispersion method, in terms of ease and efficiency, is the most promising technique to tenacity the solubility problems of SV. However, there are many other methodologies that can also be employed to enhance the solubility of SV.

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