Dissolution Improvement of Simvastatin by Surface Solid Dispersion Technology

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ABSTRACT

The objective of the present study was to formulate surface solid dispersions (SSD) of simvastatin to improve the aqueous solubility and dissolution rate to facilitate faster onset of action. Simvastatin is a BCS Class II drug having low solubility (1.45 μg/mL) and therefore low oral bioavailability (5%). In the present study, SSDs of simvastatin with two different superdisintegrants in three different drug–carrier ratios were prepared by a coevaporation method. Surface solid dispersions were characterized by differential scanning calorimetry (DSC), powder x-ray diffractometry (PXRD), scanning electron microscopy (SEM), and infrared spectroscopy (IR) and evaluated for drug content, saturation solubility, pH-dependent solubility, solubility in biorelevant media (i.e., fasted-state simulated intestinal fluid [FaSSIF] and fed-state simulated intestinal fluid [FeSSIF]), in vitro dissolution, and in vivo studies by a Triton-induced hypercholestermia model in rats. DSC studies revealed that there was no interaction between drug and carrier, whereas the PXRD study demonstrated that there was a significant decrease in crystallinity of pure drug present in surface solid dispersions, which resulted in an increased dissolution rate of simvastatin.

INTRODUCTION

Aqueous solubility of any therapeutically active substance is a key property; it governs dissolution, absorption, and thus the in vivo efficacy (1). To improve the dissolution and bioavailability of poorly water-soluble drugs, researchers have employed various techniques such as micronization (2), solubilization (3), salt formation, complexation with polymers, change in physical form, use of prodrug and drug derivatization, pH alteration, addition of surfactants, and others (4, 5). Chiou (6) and Serajuadin (7) used the solid-dispersion technique for dissolution enhancement of poorly water-soluble drugs. A solid dispersion can be defined as "the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by a melting (fusion), solvent, or melting–solvent method," while Corrigan (8) suggested it is "a product formed by converting a fluid drug–carrier combination to the solid state." Among the various approaches, the solid-dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical, and advantageous.

Preparation of SSDs is a technique that provides deposition of the drug on the surface of certain materials that can alter the dissolution characteristics of the drug. Deposition of drug on the surface of an inert carrier leads to a reduction in the particle size of the drug, thereby providing a faster dissolution rate. Various hydrophilic materials with high surface area can be utilized for deposition of the drug on their surfaces (9). Surface modification and solid-dispersion formulations using hydrophilic excipients can significantly alter the dissolution behavior of hydrophobic drug materials.

Simvastatin (SIM), a crystalline compound, is practically insoluble in water and hence poorly absorbed from the GI tract (10, 11). It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase (12, 13), which catalyzes the reduction of HMG CoA to mevalonate. Thus, simvastatin arrests a key step for cholesterol biosynthesis in the liver and is widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. After oral administration, simvastatin is metabolized to its β-dihydroxy acid form (simvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in cholesterol biosynthesis. This leads to up-regulation of low-density lipoprotein (LDL) receptors and an increase in catabolism of LDL cholesterol. Being a BCS Class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in bioavailability (14).

In the present study, SSDs using two different carriers in three different drug–carrier ratios were prepared by a coevaporation method, evaluated for different parameters, and further evaluated for in vivo performance in albino rats using pharmacodynamic markers such as total cholesterol (CH), triglycerides (TG), low-density lipoproteins (LDL), and very low-density lipoproteins (VLDL).

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MATERIALS AND METHODS
Materials
SIM was obtained as a gift sample from IPCA Laboratories, Athal, India. Sodium starch glycolate (SSG) and croscarmellose sodium (CCS) were obtained as generous gift samples from Colorcon Asia Pvt. Ltd, Mumbai, India. All other reagents used were of AR grade and procured locally.

Preparation of Surface Solid Dispersions
SSDs of SIM with a hydrophilic carrier (i.e., SSG and CCS) were prepared in the ratios of 1:1, 1:2, and 1:3 of drug–carrier. Two techniques can be used for preparation, coevaporation and cogrinding (15). The coevaporation method was used for the preparation of SSD in the present study. In this method, 1 g of simvastatin was accurately weighed and dissolved in a minimum amount of ethanol in which hydrophilic carrier was suspended. The suspension was continuously stirred at 100 rpm using an electronic stirrer at room temperature until all the solvent evaporated. Physical mixtures were formulated by mixing drug and carrier in geometric proportions using a spatula without applying pressure. The SSDs were passed through a No. 60 sieve and stored over anhydrous calcium chloride in a desiccator.

Evaluation of Surface Solid Dispersion
Drug Content
Surface solid dispersions equivalent to 20 mg of SIM were weighed accurately and dissolved in 10 mL of ethanol. The stock solutions were diluted in distilled water and analyzed by UV-vis spectrophotometry (Jasco V-550, Japan) at 238 nm.

Saturation Solubility Studies
Saturation solubility was determined by the shake-flask method (16). Plain SIM and SSDs in excess quantity were placed in separate glass-stoppered flasks containing 10 mL of distilled water. The samples were placed in an orbital shaker (CIS-24 Remi, India) at 37 °C and 100 rpm until equilibrium was achieved (24 h). The aliquots were filtered through Whatman No. 41 filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometrically at 238 nm.

pH-Dependent Solubility Studies
The pH-dependent solubility of SIM and SSDs were determined in pH 1.2 and pH 7.0 buffers using similar procedure as for saturation solubility.

Solubility in Biorelevant Media
Fasted-state simulated intestinal fluid (FaSSIF) and fed-state simulated intestinal fluid (FeSSIF) were used to examine the solubility and dissolution characteristics of several classes of drugs, including lipophilic drugs, to assist

Table 1. Composition of Fasted-State Simulated Intestinal Fluid (FaSSIF)

Component	Amount / Concentration
Sodium taurocholate	3 mM
Lecithin	0.75 mM
NaOH (pellets)	0.174 g
$NaH_2PO_4 \cdot H_2O$	1.977 g
NaCl	3.093 g
Purified water q.s.	500 mL

in predicting in vivo absorption behavior (17). Biorelevant in vitro dissolution testing is useful for qualitative forecasting of formulation and food effects on the dissolution and availability of orally administered drugs. Biorelevant media can provide a more accurate simulation of pharmacokinetic profiles than simulated gastric fluid or simulated intestinal fluid (18). SIM solubility was determined in biorelevant media (i.e., FaSSIF and FeSSIF) because various surfactants and enzymes are present in the gastrointestinal tract. A procedure similar to that of the saturation solubility study was followed. The media were prepared as per the formulas specified in Tables 1 and 2.

In Vitro Dissolution Studies
The in vitro dissolution studies for plain SIM and SSDs were carried out in triplicate in USP Apparatus 2. Samples equivalent to 20 mg of SIM were added to 900 mL of 0.01 M phosphate buffer pH 7.0 with 0.5% sodium lauryl sulfate at 37 ± 0.5°C and stirred at 50 rpm (19). Aliquots of 5 mL were withdrawn at specified time intervals and filtered through Whatman No. 41 filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analyzed spectrophotometrically at 238 nm.

The SSD that showed maximum drug release and saturation solubility was characterized by PXRD, DSC, FTIR, and SEM and compared with pure drug.

Table 2. Composition of Fed-State Simulated Intestinal Fluid (FeSSIF)

Component	Amount / Concentration
Sodium taurocholate	15 mM
Lecithin	3.75 mM
NaOH (pellets)	4.04 g
Glacial Acetic Acid	8.65 g
NaCl	11.874 g
Purified water qs.	1000 mL

Powder X-Ray Diffractometry (PXRD)

The PXRD spectra of samples were recorded using a high-power powder x-ray diffractometer (Ru-200B, Pune, India) with Cu as target filter having a voltage/current of 40 KV/40 mA at a scan speed of 4°/min. The samples were analyzed at a 2θ angle range of 2–45°. Step time was 0.5 sec, and acquisition time was 1 h.

Differential Scanning Calorimetry (DSC)

The DSC thermograms were recorded using a differential scanning calorimeter (DSC 823E, Mettler Toledo, Japan). Approximately 2–5 mg of each sample was heated in a pierced aluminum pan from 30 to 300 °C at a heating rate of 10 °C/min under a stream of nitrogen at a flow rate of 50 mL/min. Thermal data analyses of the DSC thermograms were conducted using STARe software (version 5.21).

Fourier Transform Infrared Spectroscopy (FTIR)

The IR spectra were recorded using an FTIR spectrophotometer (Jasco-450 Plus, Japan) with diffuse reflectance principle. The samples were scanned over the frequency range 4000–400 cm^{-1}.

Scanning Electron Microscopy (SEM)

The surface morphology of samples was determined using an analytical scanning electron microscope (JSM-6360A, JEOL, Tokyo, Japan). The samples were lightly sprinkled on a double-sided adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold-sputter module in a high-vacuum evaporator. Afterwards, the stubs containing the coated samples were placed in the scanning electron microscope chamber.

In Vivo Pharmacodynamic Study Using Rats

Approval to carry out an in vivo study was obtained from the Institutional Animal Ethical Committee, AISSMS College of Pharmacy, Pune, and their guidelines were followed for the study. The SSD that showed highest release profile for SIM and the maximum saturation solubility (i.e., SSD with CCS 1:3) was selected for the in vivo studies. The animals used for the in vivo experiments were adult Wistar male albino rats (250–300 g), which were divided into three groups with six rats in each group. Animals were kept in air-conditioned rooms (24–25 °C) with constant humidity and were allowed food and water ad libitum before they were distributed by weight into experimental groups. The rats were fasted overnight and were then injected intraperitoneally with 250 mg/kg Triton WR 1339 (Tyloxapol, Sigma Chemical Co., St. Louis, MO) dissolved in 0.9% saline (*20*). The control group of rats was given the vehicle (plain saline), and the reference group was given plain SIM (10 mg/kg body weight). SSD (equivalent to 10 mg/kg SIM) was given to the test group. Rats were given a light ether anesthesia and were restrained by hand; oral dosing was performed by
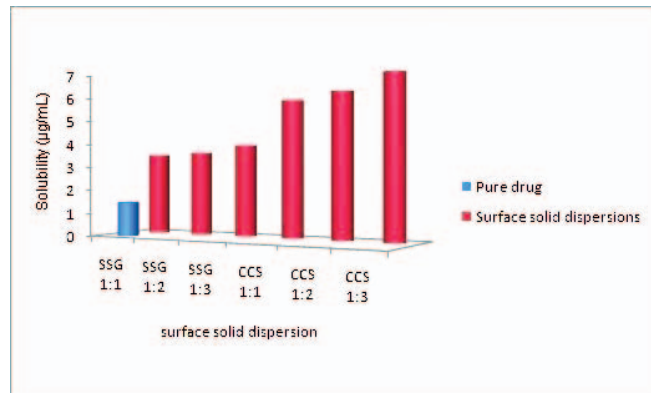

Figure 1. Saturation solubility of surface solid dispersions.

intubation using an 18-gauge feeding needle. The volume fed was 1.0 mL in all cases. To study the effect of formulation components on lipid lowering, blood samples were withdrawn after 24 h by retro-orbital puncture (*21*). The serum samples were analyzed for total cholesterol, triglycerides, low-density lipoprotein, and very low-density lipoprotein cholesterol levels by the in vitro diagnostic kit (Pathogen Diagnostics Pvt. Ltd., Mumbai, India).

Dosage Form Development

The SSD that showed maximum drug release and increase in saturation solubility was further formulated in Size 0 hard gelatin capsules containing SSD equivalent to 20 mg, lactose as capsule filler, and magnesium stearate as a glidant. The blend was evaluated for drug content and micromeritic properties such as bulk density, tapped density, and angle of repose. Filled capsules were evaluated for content uniformity, disintegration time, and weight variation.

RESULTS AND DISCUSSION
Drug Content

Drug content for all SSDs were in the range of 98.54–100.87%, which is acceptable according to the *United States Pharmacopeia* (*22*).

Saturation Solubility Studies, pH Solubility Profile

Figure 1 represents the saturation solubility of the SSDs and plain SIM. SIM showed a solubility of 1.45 µg/mL in distilled water, 14.5 µg/mL in pH 1.2 buffer, and 24.4 µg/mL in pH 7.0 buffer. The saturation solubility increased with an increase in carrier proportion for both carriers. This might be due to better wetting ability associated with CCS over SSG surface solid dispersions. SSG and CCS have very fine particle size and, hence, large surface area, so as the proportion of carrier increases, a larger surface is presented for adsorption of the drug crystals. Evaporation of solvent leads to an increase in interfacial area of contact between the drug particles and dissolution medium. The affinity between the hydrophilic inert carriers of the
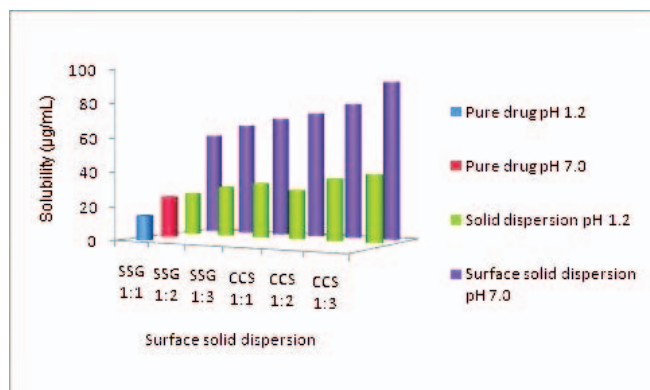
Figure 2. pH-dependent solubility studies (pH 1.2 and pH 7.0).
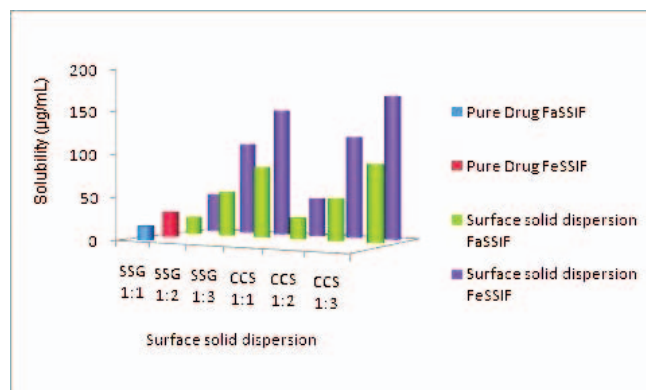

Figure 3. Solubility in biorelevant media.

dissolution fluids facilitates rapid penetration into the particles, further enhancing the dissolution process.

The percent increase in saturation solubility with CCS (1:3) was higher than with SSG (1:3). This might be due to better wetting ability of CCS over SSG. The ratio with CCS (1:3) showed the highest solubility at 6.88 µg/mL (i.e., a 374.48% increase as compared with pure drug).

The solubilities of prepared dispersions in distilled water, 0.1 N HCl (pH 1.2), and phosphate buffer (pH 7.0) are presented in Figure 2. SIM exhibits maximum solubility in phosphate buffer pH 7.0 (i.e., SIM solubility increases with an increase in medium pH). In short, SIM exhibits pH-dependent solubility. The SSDs showed marked improvement in all three media as compared with SIM.

Solubility in Biorelevant Media

The solubility of SIM in FaSSIF (pH 5.0) was 16.4 µg/mL, whereas in FeSSIF (pH 6.5), it was 29.90 µg/mL, indicating that simvastatin exhibited higher solubility in biorelevant media. SIM, being lipophilic in nature, can be considered to be entrapped in the lipophilic micellar core of surfactants (i.e., sodium taurocholate and lecithin present in the media), and hence the possibility of micellar solubilization effect cannot be ruled out. All surfactants above a particular concentration aggregate in a specific orientation depending on the external environment to form micelles (3). The core of spherical micelles is lipophilic. The log P of SIM is 4.38, indicating its high lipophilicity. Hence, we can attribute the higher solubility of SIM in biorelevant media to micellar solubilization.

Solubility increased with an increase in carrier proportion. A 1:3 proportion with CCS surface solid dispersion showed a maximum increase in solubility (i.e., 89.49 µg/mL in FaSSIF and 169.25 µg/mL in FeSSIF), equivalent to increases of 445.67% and 466.05%, respectively, with respect to pure drug simvastatin (Figure 3). Also the percent increase in solubility in biorelevant media was seen to be higher as compared with pH 1.2 and pH 7.0 buffers for a 1:3 proportion with CCS (i.e., in the pH 1.2

buffer 37.79 µg/mL), whereas in pH 7.0 buffer, a solubility of 92.83 µg/mL was observed (i.e., increases of 160.62% and 280.45%, respectively). This might be due to a synergistic effect of natural surfactants, sodium taurocholate, and lecithin present in the biorelevant media that led to significant improvement in solubility of SIM.

In Vitro Dissolution Studies

The dissolution profiles of the solid dispersions are shown in Figures 4 and 5. The dissolution rate of SIM in physical mixtures as well as in SSDs was higher for both carriers as compared with plain simvastatin. Plain SIM showed a poor dissolution profile (i.e., only 27 % of drug was released at the end of 120 min), whereas physical mixtures showed slight improvement due to the presence of carrier in the respective mixtures.

Dissolution profiles of all the SSDs for both carriers were almost similar (i.e., no significant improvement in dissolution was observed with an increase in carrier proportion). Surface solid 1:3 dispersions with both carriers showed maximum drug release; the SSD with CCS showed almost 99.68% drug release within 90 min, whereas SSD with SSG required 120 min for 93.21% release, indicating that SSD with CCS showed better a dissolution profile than SSG. The capsule dosage form also showed a better dissolution profile; 99.50 % of drug was released within 90 min (Figure 6).

The improved dissolution could be attributed to a reduction in particle size of the drug, its deposition on the surface of the carrier, and improved wettability. SSG and CCS have very fine particle sizes and hence large surface areas. As the proportion of carrier increases, more surface is available for adsorption of drug crystals on evaporation of solvent, leading to an increase in interfacial area of contact between the drug particles and dissolution medium. The affinity between the hydrophilic inert carriers of the dissolution fluids facilitates rapid penetration into the particles, which further enhances the dissolution process.
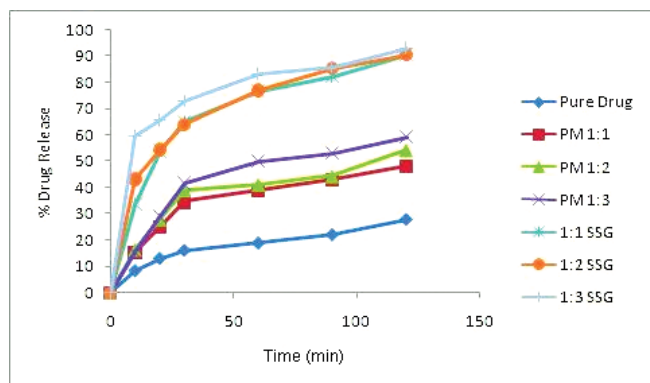
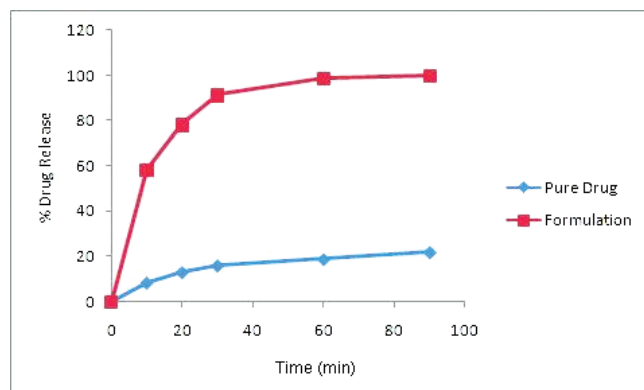*Figure 4. Dissolution profiles of surface solid dispersions of simvastatin with SSG.*

Figure 6. Dissolution profiles of capsule formulation.

Powder X-Ray Diffractometry (PXRD)

The PXRD patterns of pure drug and solid dispersions are depicted in Figure 7. The diffraction patterns of the physical mixture and SSD indicate changes in the crystal-line nature of the drug. The diffraction pattern of the pure drug simvastatin shows a highly crystalline nature, indicated by numerous distinctive peaks at a diffraction angle of 2θ (28.4°, 22.6°, 18.8°, 17.2°, 10.9°, and 9.3°) throughout the scanning range; on the other hand, PXRD of surface solid dispersions shows a significant decrease in the degree of crystallinity, as evident by the disappearance of sharp distinctive peaks. It can be predicted that a larger proportion of simvastatin has been converted to the amorphous form. The relative reduction in the diffraction intensities in the surface solid dispersions can be attrib-uted to the change in orientation during the crystal growth phase. The shearing force applied by the stirrer produces intimate mixing of drug solution with carrier. Additionally, as the solution becomes supersaturated due to solvent evaporation, the turbulence generated by the stirrer interferes with the nucleation and crystal-growth
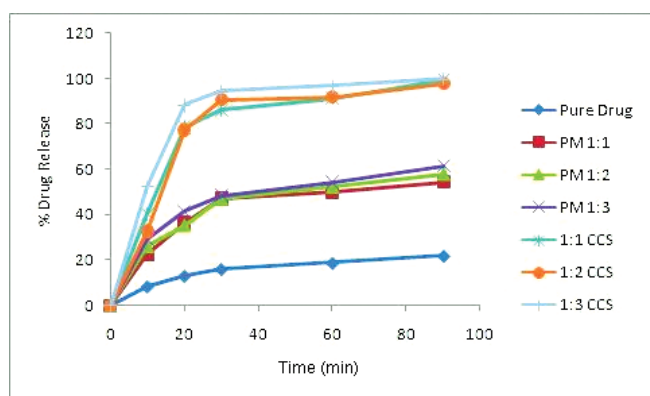
phases, leading to formation of imperfect crystals or amorphization.

Degree of crystallinity of the product was calculated using the following equation (*23*)

$$DC = \left\{ \frac{Scr}{Scr + Sam} \right\} \times 100$$

where *Scr* is the total area of peaks of the crystalline phase and *Sam* is the area of halo from the amorphous phase.

The degree of crystallinity for plain SIM was 53.82%. SSD with CCS showed a significant decrease in crystallinity (i.e., retaining only 1.47% degree of crystallinity).

Differential Scanning Calorimetry (DSC)

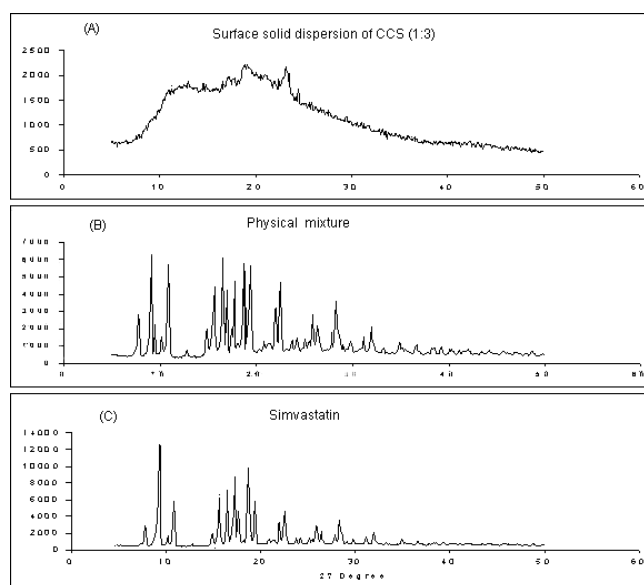The DSC thermogram of SIM exhibits a sharp melting endotherm at 138 °C (Figure 8B). In SSD prepared with

Figure 7. PXRD pattern of (A) surface solid dispersion of CCS, (B) physical mixture, and (C) simvastatin.

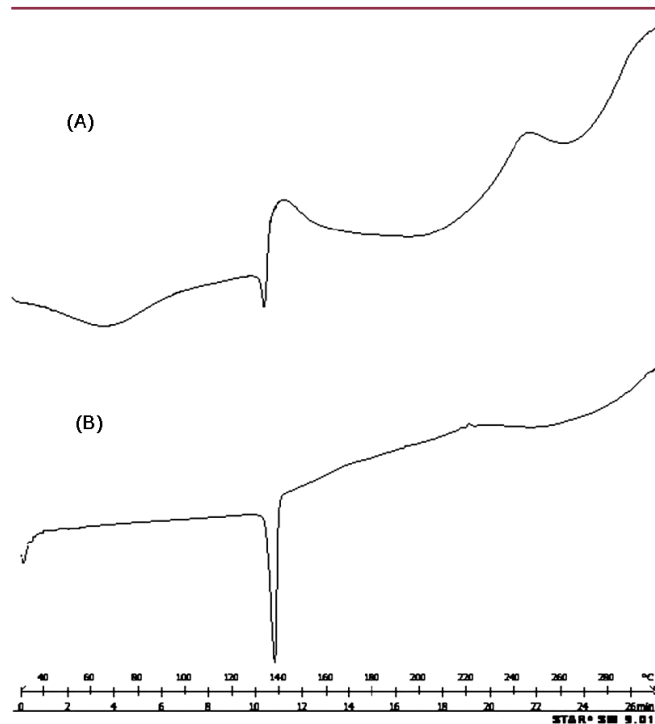*Figure 5. Dissolution profiles of surface solid dispersions of simvastatin with CCS.*

Figure 8. DSC thermograms of (A) surface solid dispersion of CCS and (B) simvastatin.

CCS, the melting endotherm of CCS is evident in the temperature range of 48.24–99.70 °C and simvastatin in the temperature range of 137.53–142.56 °C (Figure 8A), suggesting that there was no physical or chemical interaction in between CCS and SIM SSD.
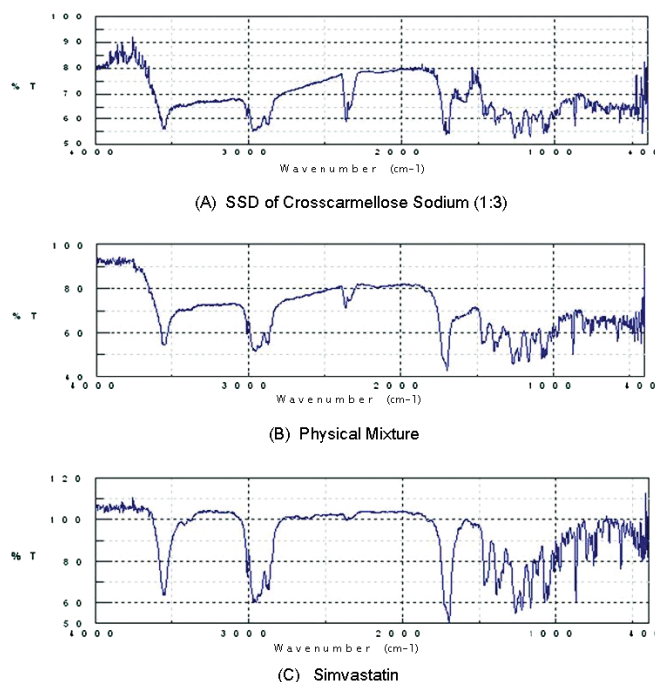

Figure 9. FTIR spectra of (A) surface solid dispersion of CCS, (B) physical mixture, and (C) simvastatin.
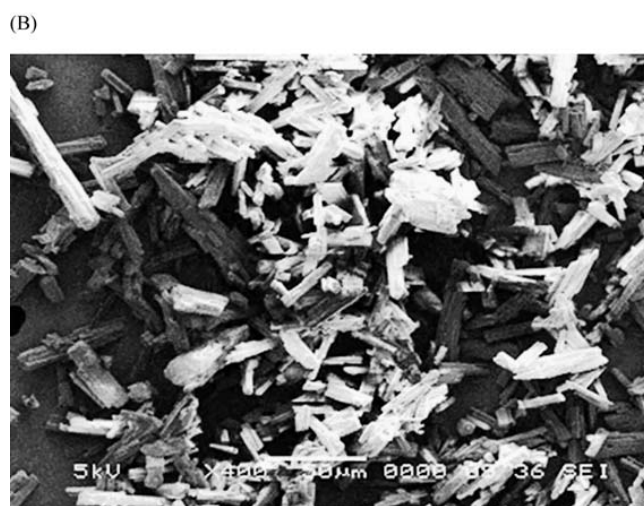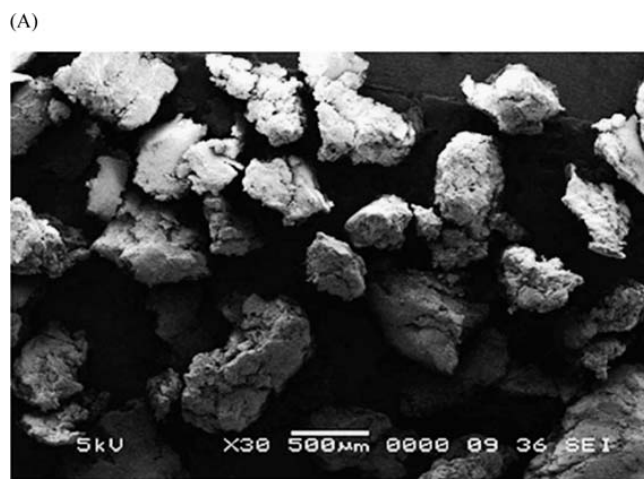

Figure10. SEM microphotographs of (A) surface solid dispersion of CCS and (B) simvastatin.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy was used to study the possible interactions between SIM and CCS in the SSD. There is no significant difference in the FTIR spectra of pure drug, physical mixture, and SSD (Figure 9). All major peaks of SIM observed at wavenumbers 3553 cm^{-1} (free O–H stretching vibrations); 3011, 2959, and 2872 cm^{-1} (C–H stretching vibrations); and 1714 cm^{-1} (stretching vibration of ester and lactone carbonyl functional groups) were retained in physical mixtures and SSDs, which clearly indicate that no interaction exists between pure drug and CCS in SSD.

Scanning Electron Microscopy (SEM)

SEM photomicrographs that reveal the surface morphology of the samples are shown in Figure 10. Characteristic needle-shaped crystals of simvastatin were observed in the photomicrograph of pure drug SIM (Figure 10B). SEM of the SSD (Figure 10A) reveals irregular particles with several microscopic cracks and crevices, which provide additional surface for deposition of the

Table 3. Lipid-Lowering Profile for In Vivo Bioavailability Study in Rats

Parameter	Control[a] (mg/dL)	Reference[b]		Test[c]	
		Value (mg/dL)	% decrease	Value (mg/dL)	% decrease
Cholesterol	281.5 ± 2.566	188.33 ± 3.073 **	33.09	101.16 ± 1.973**	64.06
Triglycerides	448.33 ± 2.824	438 ± 2.517 *	2.3	180.66 ± 2.333**	59.70
LDL	125.5 ± 1.821	41.5 ± 0.9916 **	66.93	27.66 ± 1.406**	77.96
VLDL	30.16 ± 1.195	23.5 ± 0.9916 **	22.09	22.4 ± 1.478**	25.72

[a]Triton (WR1339)
[b]Pure drug
[c]Surface solid dispersion of CCS (1:3)
*$p < 0.05$, **$p < 0.01$

drug particles. There is no evidence of drug crystals, which confirms the previous findings based on PXRD patterns.

In Vivo Studies

The serum lipid profiles of all the experimental groups after a 24-h interval are presented in Table 3 along with the corresponding percent changes in lipid profiles. A comparison among groups was carried out by one-way analysis of variance (ANOVA) followed by Dunnets test ($n = 6$). $P < 0.05$ was considered as significant. As expected, after 24 h of treatment with Triton (WR1339), the control group showed a significant increase in total cholesterol, TG, LDL, and VLDL, whereas the reference group showed a 33.9% decrease in total cholesterol, a 2.3% decrease in TG, a 66.93% decrease in LDL, and a 22.9% decrease in VLDL. The test group showed a 64.06% decrease in total cholesterol, a 59.70% decrease in TG, and 77.96% and 25.72% decreases in LDL and VLDL, respectively, relative to the control group, thus the test group exhibited an almost twofold decrease in total cholesterol and TG in comparison with the control group. Thus, SSD with CCS (13) performed better than pure drug SIM in reducing total cholesterol and TG levels, which could be attributed to the improved solubility and dissolution associated with amorphization of the drug and wetting effect of CCS.

CONCLUSION

In conclusion, SSDs of SIM with two different superdisintegrants prepared by a coevaporation method showed significantly higher drug dissolution in comparison with pure drug and physical mixtures. FTIR and DSC studies showed no evidence of interaction between the drug and carrier. PXRD study confirmed amorphization of drug, which was further corroborated by SEM studies. In vivo studies of the SSD in rats showed a higher percentage inhibition of cholesterol and triglyceride levels in rats than those achieved with plain drug. This is attributed to improved bioavailability due to enhancement in rate and extent of drug release when drug was administered as an SSD using CCS as a carrier.

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