

## Original Research Article

# Enhancement of solubility and release profile of simvastatin by co-crystallization with citric acid

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### Abstract

**Purpose:** To enhance the solubility and dissolution profile of simvastatin (SIM) via co-crystallization with varying levels of citric acid using various techniques.

**Method:** Simvastatin-citric acid (SIM-CA) co-crystals were prepared using dry grinding, slurry, liquid-assisted grinding, and solvent evaporation techniques, and their various properties were compared. A total of twelve formulations (CC01 to CC12) were prepared. Optimized formulations were selected on the basis of dissolution profiles. Flow properties were evaluated using micromeritic analysis, yielding angle of repose, Carr's index and Hausner's ratio. Zeta sizer was employed to evaluate particle size distribution, while surface morphology was determined using scanning electron microscopy (SEM). Melting temperature, stability and physical interaction of simvastatin-citric acid co-crystals were determined by thermal analysis and FTIR. The crystalline nature of the co-crystals was evaluated by powder x-ray diffraction analysis, while solubility and dissolution studies were performed to determine in vitro drug release behavior.

**Results:** Micromeritic analysis revealed good flow properties of SIM-CA co-crystals. Results of Zeta sizer analysis showed that the particle sizes of the co-crystals were in the nanometer range, while SEM revealed that the co-crystals had regular cubical shape. Thermal stability studies with TGA and DSC showed that the co-crystals were stable at temperatures exceeding 400 °C. FTIR results revealed minor shifts in 2956 and 1706 cm<sup>-1</sup> peaks. Co-crystal formation was confirmed by PXRD data. The drug release profiles of the optimized formulations (CC02, CC07 and CC11) were 11.36 - 94.46, 12.36 - 95.46 and 13.36 - 96.46 %, respectively. There was significant improvement in solubilities of the optimum formulations, with values of 310.18, 427.21 and 522.02 % for CC02, CC07 and CC11, respectively.

**Conclusion:** Citric acid improves the solubility and dissolution profile of the poorly water-soluble drug, simvastatin, which suggests that co-crystallization can potentially enhance the bioavailability of the drug.

**Keywords:** Zeta sizer, Solubility Enhancement, Simvastatin, Citric acid, Co-crystal

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## INTRODUCTION

Co-crystal technology is used for enhancement of solubility of drugs, and it has gained acceptance in drug product development [1,2].

Excipients listed as "generally regarded as safe" (GRAS, including organic acids and nutraceuticals) can be used as co-formers [1]. Drugs and co-formers interact mostly through hydrogen bonds [3]. Indeed, co-crystallization is

now a popular concept in drug product development [3].

Diabetes is a complex disease, and Type-2 diabetes is a vital risk factor for cardiovascular disease [4,5]. The statin simvastatin (an inhibitor of hydroxymethylglutaryl coenzyme A reductase) reduces high glucose levels and significantly mitigates vascular events in Type-2 diabetic patients [6]. In previous studies, attempts were made to enhance the solubility of simvastatin using different techniques and different dosage forms [7-9]. In the present study, co-crystallization technique was used to enhance the solubility of simvastatin, with citric acid as co-former. Increases in solubility and dissolution were studied with respect to increases in molar ratio of citric acid. Co-crystals of drug and co-former were formulated using four different techniques. The formulated co-crystals were characterized using micromeritics, *in vitro* drug release, solubility studies, zeta sizer, FTIR, thermal analysis [i.e. thermogravimetric analysis (TGA) and Diffraction Scanning Calorimetry (DSC)]; X-ray Powder diffraction analysis (XRPD), and Scanning Electron Microscopy (SEM).

Various techniques are used to enhance solubility. These comprise particle size reduction (micronisation), solid dispersion (emulsification), salt formation, solid evaporation, nanosuspension formation and lyophilization. Traditional techniques like micronisation, emulsification and salt formation have practical limitations. Solid dispersion is a simple technique but is suitable only for hydrophobic drugs. Fusion technique requires miscibility and thermostability of drug. The newer technique of solid evaporation prevents thermal decomposition of drugs, but it has drawbacks such as inconvenience associated with removal of organic solvents, and challenges in crystal re-production.

Modern techniques such as nanosuspension formation, high pressure homogenization and lyophilization are promising methods that increase bioavailability of drugs. However, these methods are time-consuming. Moreover, nanosuspension is not applicable to drugs which are poorly soluble in water and oil; homogenization needs several cycles, while lyophilization needs specialized equipment, giving rise to poor yield [7]. Pharmaceutical co-crystallization is a simple and inexpensive technique for increasing bioavailability of Active Pharmaceutical Ingredients (APIs). It can be applied to all APIs, including acidic, basic and non-ionizable molecules [8,9].

## EXPERIMENTAL

### Materials

Simvastatin ( $C_{25}H_{38}O_5$ ) was provided by Bio Fine Pharmaceuticals (Pvt.) Ltd (Pakistan). Citric acid ( $C_6H_8O_7$ ) was purchased from Sigma Aldrich (Germany). Sodium hydroxide (NaOH) was purchased from Sigma Aldrich (Netherlands). Methanol (MeOH), potassium hydroxide (KOH), hydrochloric acid (HCl) and potassium dihydrogen phosphate ( $KH_2PO_4$ ) were bought from Merck (Germany).

### Methods

#### *Co-crystallization of simvastatin with citric acid*

Co-crystals of SIM-CA were synthesized using various methods viz: co-grinding, liquid-assisted grinding (LAG), solvent evaporation and slurry technique. The drug and co-former were taken in equimolar ratios for development of formulations as indicated in Table 1. In co-grinding method, SIM and CA were milled or mixed together at the stated stoichiometric ratios for 45 min, using pestle and mortar without adding any solvent. In the LAG method, SIM and CA were milled at the indicated stoichiometric ratios for 30 min using pestle and

**Table 1:** Compositions of SIM-CA co-crystals in molar ratios

Co-crystal	Molar ratio		Method
	SIM	CA	
CC01	1	1	Dry grinding
CC02	1	1	Liquid-assisted grinding
CC03	1	1	Solvent evaporation
CC04	1	1	Slurry
CC05	1	2	Dry grinding
CC06	1	2	Liquid-assisted grinding
CC07	1	2	Solvent evaporation
CC08	1	2	Slurry
CC09	1	4	Dry grinding
CC10	1	4	Liquid-assisted grinding
CC11	1	4	Solvent evaporation
CC12	1	4	Slurry

mortar, with methanol addition. In co-grinding, SIM and CA were milled together using pestle and mortar for 45 min. In solvent evaporation technique, SIM and CA were solubilized in methanol (as common solvent) at the indicated stoichiometric ratios. Then, the solution was left for 24 h at room temperature to evaporate

slowly. In the slurry technique, specific ratios of SIM and CA were taken and slurried overnight at 300 rpm using a magnetic stirrer, and the solution was left to evaporate slowly for 12 h at room temperature.

### Characterization of formulated cocrystals

#### Micromeritics studies

The angle of repose, which gives the frictional force within the powder, was determined using fixed funnel method. Powdered co-crystal formulations were collected on butter paper. The angle of repose ( $\Theta$ ) was determined using the formula shown in Equation 1:

$$\text{Angle of repose } (\Theta) = \tan^{-1}(h/r) \dots\dots\dots (1)$$

where  $h$  and  $r$  are height and radius of pile, respectively. Angles of repose between  $20^\circ - 30^\circ$  indicate good flow properties [10].

Bulk density ( $\rho_b$ ) and tapped density ( $\rho_t$ ) were determined with known mass of co-crystal powder using graduated cylinder. The cylinder was tapped until the powder bed of the formulation had minimum volume.

The following formulae were used for calculating  $\rho_b$  and  $\rho_t$  (Eq. (2) and Eq. (3), respectively):

$$\text{Bulk density } (\rho_b) = \text{Mass/Bulk Volume} = M/V_b \dots\dots\dots (2)$$

$$\text{Tapped density } (\rho_t) = \text{Mass/Tapped Volume} = M/V_t \dots\dots\dots (3)$$

where  $M$  is mass,  $V_b$  is bulk volume density, and  $V_t$  is tapped volume.

Hausner's Ratio (HR) gives a prediction of flow properties related to inter-particle friction. It was calculated using bulk density and tapped density as shown in Equation 4. Values of HR less than 1.25 indicate good flowability [10].

$$\text{Hausner's Ratio (HR)} = \text{Tapped Density/Bulk Density} = \rho_b/\rho_t \dots\dots\dots (4)$$

Carr's Index (CI) is an index of flow rate, particle size and cohesiveness. It was calculated using Equation (5). Values of CI between 5 – 18 % indicate suitability of tablets [10].

$$\text{Carr's Index (CI)} = (\text{Tapped Density} - \text{Bulk Density}) \times 100 \text{ i.e. } CI = (\rho_t - \rho_b/\rho_t) \times 100 \dots\dots\dots (5)$$

### In vitro dissolution studies of SIM-CA co-crystals

The USP Type II Apparatus was used for evaluation of *in vitro* drug release. Both acidic and basic media (pH 1.2 and pH 7.4, respectively) were used for this purpose, with 50 mg equivalent of pure drug simvastatin and co-crystal formulations. The USP apparatus was operated at  $37 \pm 0.5^\circ\text{C}$  with 900 mL of media in each dissolution vessel. The sink conditions were maintained at 75 rpm. Aliquots of media were taken in labelled glass vials using adjustable pipette at various time intervals i.e. 0, 10, 15, 30, 45, 60 and 90 min. The withdrawn samples were taken in triplicate, and replaced with fresh media. The samples were filtered, diluted and statistically analyzed at 238 nm in a UV-Visible spectrophotometer (UV-1601 Shimadzu, Japan).

#### Solubility studies of SIM-CA co-crystals

Solubility studies were performed for pure drug and SIM:CA co-crystals in aqueous, acidic (pH 1.2) and basic media (pH 7.4) by adding excess amount of drug or co-crystal to 10 mL of each medium. The mixture of drug and medium was stirred at 400 rpm at room temperature for 48 h. Then, samples were withdrawn in triplicate, filtered using Whatman filter paper no. 42, and diluted prior to spectrophotometric analysis. The samples were collected in triplicate [11].

#### Zeta sizer analysis

Nano-series Zeta sizer ZEN3600 (Malvern Instruments Ltd. UK) was used for this purpose. Dynamic Light Scattering technique was used and samples were placed in cuvettes before inserting in the instrument which uses Malvern Zetasizer Ver. 7.01 to determine average particle size (Z-Average) and Polydispersity Index (PDI).

#### Fourier transform infrared (FTIR)

Fourier Transform Infrared (FTIR) spectra for pure simvastatin and moisture-free, powdered co-crystals were recorded using OPUS software (Bruker Tenser 27, Germany) with  $2 \text{ cm}^{-1}$  resolution in the frequency range of 4000 to  $400 \text{ cm}^{-1}$  [12]. The potassium bromide pellet method was applied.

#### Thermal analysis

In this study, TGA and DSC were recorded using Thermal Analysis System Q600 SDT (USA) at a temperature range of  $50 - 500^\circ\text{C}$ . Analysis was performed using 0.5 - 3.0 mg sample in DSC.

The heating rate was kept at 10 °C/min at a flow rate of 10 mL/min.

### X-ray powder diffraction analysis (XRPD)

The X-ray powder diffraction analysis for pure drug and co-crystals was performed using Bruker D8 Advance X-ray diffractometer (Germany). The analysis was performed on 2 – 5 mg sample in the temperature range of 5 – 70 °C under specific conditions [tube voltage of 40 KV, current at 40 mA, and 2 Theta ( $\theta$ ) of 0.001°] using wide angle.

### Scanning electron microscopy

Scanning Electron Microscope EVO LS 10 Carl Zeiss (Germany) was used for microscopic analysis of the pure drug and formulated co-crystals. The coating was done with spluttered atoms for in the form of gold 10 min. This served to improve emission and reduce degradation. Photomicrographs of the surface morphologies and shapes of the pure drug and co-crystals were obtained.

## RESULTS

### Micromeritics of co-crystals

The flow properties of co-crystals were studied by calculating angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index. The results are presented in Table 2.

### In vitro drug release

Pure drug release was in the range of 1.69 - 12.16 % at pH 1.2, and in the range of 1.71 - 15.12 % at pH 7.4. Spectrophotometric results showed that

maximum drug release was obtained from co-crystal CC02 in both media (pH 1.2 and 7.4). The order of drug release from all SIM:CA formulated co-crystals and pure drug in both media was CC02 > CC03 > CC04 > CC01 > SIM (for SIM:CA ratio of 1:1); CC07 > CC06 > CC08 > CC05 > SIM (for SIM:CA ratio of 1:2), and CC11 > CC10 > CC12 > CC09 > SIM (for SIM:CA ratio of 1:4). The *in vitro* drug release patterns at pH 7.4 and pH 1.2 are shown in Figure 1 and Figure 2, respectively.

Drug release values for the formulated co-crystals CC01, CC02, CC03 and CC04 at pH 1.2 were 2.69 - 27.16 %, 5.12 - 43.91%, 4.98 - 40.78 % and 3.36-33.95% respectively. In contrast, the drug release profiles of these co-crystals (CC01 – CC04) at pH 7.4 were 7.71 - 65.12%, 11.36 - 94.46 %, 10.66 - 82.56 % and 9.07 - 78.47 %.

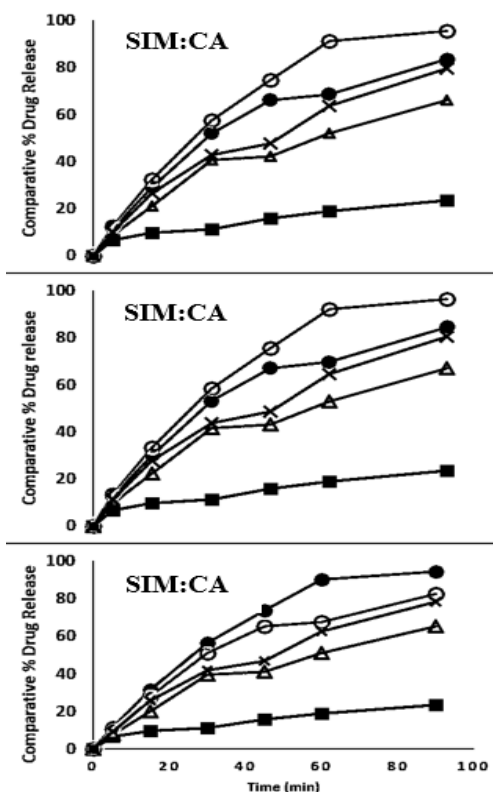
Similarly, drug release from SIM:CA (1:2) co-crystals was higher in basic medium than in acidic medium. At pH 1.2, the drug release profiles for co-crystals CC05, CC06, CC07 and CC08 were 3.69-28.16%, 5.98-41.78%, 6.12-44.91% and 4.36-34.95%, respectively. In contrast, the drug release profiles of these co-crystals (CC05-CC08) at pH 7.4 were 8.71-66.12%, 11.66-83.56%, 12.36-95.46% and 10.07-79.47%, respectively.

In the same way, there were higher increases in drug release from SIM:CA (1:4) co-crystals at pH 7.4 than at pH 1.2. At pH 1.2, drug release profiles from CC09, CC10, CC11 and CC12 were 4.69 - 29.16 %, 6.98 - 42.78 %, 7.12 - 45.91 % and 5.36 - 35.95 %, respectively. At pH 7.4, drug release profiles of these formula-

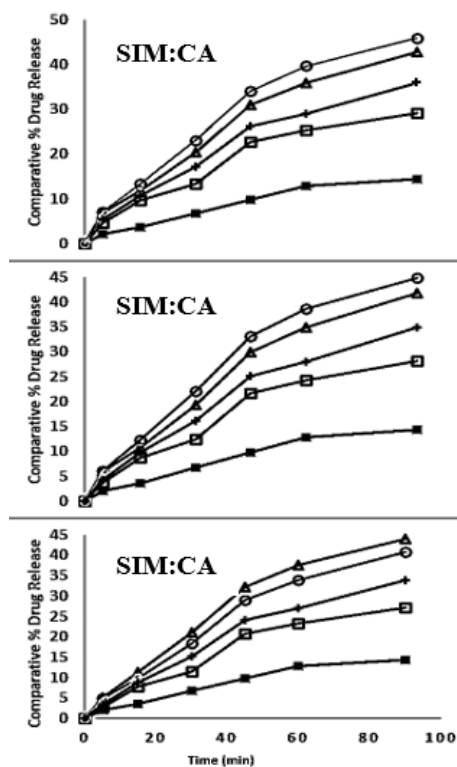
**Table 2:** Micromeritic properties of SIM-CA co-crystals

Parameter	Pure Drug	CC01	CC02	CC03	CC04
Bulk density	1.11±0.008	1.10 ± 0.015	0.95 ± 0.010	0.88 ± 0.006	0.78 ± 0.012
Tapped density	1.13±0.017	1.22 ± 0.023	1.12 ± 0.027	0.90 ± 0.014	0.85 ± 0.001
Angle of repose	31.47±0.287	21.21 ± 0.006	25.09 ± 0.002	24.85 ± 0.248	25.00 ± 0.131
Hausner's ratio	1.18±1.599	1.11 ± 0.010	1.18 ± 0.041	1.03 ± 0.014	1.09 ± 0.015
Carr's index	15.58±1.395	9.70 ± 0.853	15.08 ± 2.904	3.01 ± 1.336	8.52 ± 1.267
		<b>CC05</b>	<b>CC06</b>	<b>CC07</b>	<b>CC08</b>
Bulk density	1.11±0.008	0.94 ± 0.003	0.85 ± 0.002	0.81 ± 0.003	0.77 ± 0.003
Tapped density	1.13±0.017	1.15 ± 0.044	0.88 ± 0.011	0.92 ± 0.002	0.88 ± 0.001
Angle of repose	31.47±0.287	25.64 ± 0.002	24.70 ± 0.004	25.17 ± 0.001	24.70 ± 0.001
Hausner's ratio	1.18±1.599	1.22 ± 0.044	1.04 ± 0.011	1.13 ± 0.004	1.14 ± 0.004
Carr's index	15.58±1.395	17.91 ± 2.885	3.62 ± 1.001	11.83 ± 0.280	12.45 ± 0.294
		<b>CC09</b>	<b>CC10</b>	<b>CC11</b>	<b>CC12</b>
Bulk density	1.11±0.008	0.87 ± 0.003	0.81 ± 0.009	0.75 ± 0.005	0.68 ± 0.003
Tapped density	1.13±0.017	0.98 ± 0.001	0.86 ± 0.002	0.82 ± 0.001	0.78 ± 0.003
Angle of repose	31.47±0.287	27.92 ± 0.001	27.90 ± 0.028	27.92 ± 0.002	28.37 ± 0.003
Hausner's ratio	1.18±1.599	1.12 ± 0.004	1.06 ± 0.014	1.09 ± 0.006	1.15 ± 0.003
Carr's index	15.58±1.395	10.90 ± 0.305	5.71 ± 1.218	8.05 ± 0.540	13.04 ± 0.191

Data are presented as mean ± SD



**Figure 1:** *In vitro* drug release of pure drug (+); CC01, CC05 and CC09 ( $\Delta$ ); CC04, CC08 and CC12 (x); CC03, CC07 and CC11 ( $\circ$ ), and CC2, CC06 and CC10 ( $\bullet$ ) at pH 7.4.



**Figure 2:** *In vitro* drug release of pure drug (+), CC01, CC05 and CC09 ( $\square$ ); CC04, CC08 and CC12 (+); CC03, CC07 and CC11 ( $\circ$ ); and CC2, CC06 and CC10 ( $\Delta$ ) at pH 1.2.

tions were 9.71 - 67.12 %, 12.66 - 84.56 %, 13.36-96.46 % and 11.07-80.47 %, respectively.

Drug release for the formulated co-crystal SIM:CA (1:1) drug were up to 4.98 - 40.78 % at pH 1.2, and 9.07 - 78.47 % at pH 7.4.

Similarly, for SIM:CA (1:2) co-crystal, drug release in basic medium was higher than that in acidic medium. At pH 1.2, values of drug release from CC08 were in the range of 4.36 - 34.95 %. Similarly, at pH 7.4, drug release profile was 10.07-79.47 %. In the same way, a higher drug release from SIM:CA (1:4) co-crystal was obtained at pH 7.4 than at pH 1.2. Drug release profiles for CC12 were 5.36 - 35.95 % and 11.07 - 80.47 % at pH 1.2 and at pH 7.4, respectively.

### Solubility

Solubility studies were conducted on the optimized formulations. For this purpose, CC02, CC07 and CC11 were selected from SIM:CA (1:1), SIM:CA (1:2), and SIM:CA (1:4) CC11, respectively. Significant increases in solubility were observed in the formulated co-crystals, when compared to the pure drug. Moreover, CC02 from SIM:CA (1:1) showed percentage solubility increases of 149.33, 248.44, and 310.18% in water, acidic medium and basic medium, respectively. Similarly, CC07 from SIM:CA (1:2) had enhanced solubility, with 329.33% in water, 390.99% in acidic medium, and 427.21% in basic medium. The percentage increases in solubility of CC11 SIM:CA (1:4) in water, acidic medium and basic medium were 410.67, 480.54 and 522.02 %, respectively.

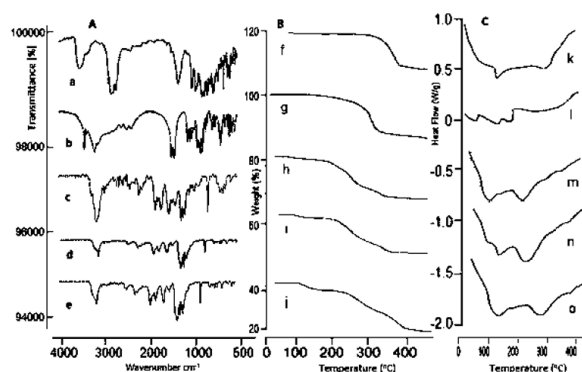
### Particle size distribution

The average particle sizes (Z-Average) of SIM:CA (1:1), SIM:CA (1:2) and SIM:CA (1:4) were  $358.7 \pm 26.1$ ,  $298.8 \pm 39.6$  and  $231.5 \pm 50.7$  nm, respectively, and their Polydispersity Index (PDI of cocrystals) values were 0.126, 0.154 and 0.195, respectively.

### FTIR spectra

FTIR spectra for pure SIM, CA, SIM:CA (1:1), SIM:CA (1:2) and SIM:CA (1:4) were obtained to ascertain any intermolecular interactions between drug and co-former. These spectra are shown in Figure 3. Pure simvastatin exhibited characteristic peaks at  $3558 \text{ cm}^{-1}$  (hydroxyl stretching);  $3011$ ,  $2956$  and  $2872 \text{ cm}^{-1}$  (methine stretching), and  $1706 \text{ cm}^{-1}$  (ester and lactone carbonyl stretching). In contrast, citric acid

showed characteristic major peaks at  $1756\text{ cm}^{-1}$ ,  $1704\text{ cm}^{-1}$  (carboxyl group) and  $3496\text{ cm}^{-1}$  (hydroxyl group) [13,14].



**Figure 3:** (A) FTIR spectra; (B) DSC and (C) TGA of pure drug SIM (a, f and k); CA (b, g and l); SIM:CA co-crystals (1:1) CC02 (c, h and m); SIM:CA co-crystals (1:2) CC07 (d, l and n); and SIM:CA cocrystals (1:4) C11 (e, j and o)

### Thermal properties

Pure SIM is characterized by a sharp endothermic peak in DSC curve at  $138.8\text{ }^{\circ}\text{C}$  which indicates the melting point of the drug [12]. As shown in Figure 3, the DSC thermogram of optimized formulation SIM:CA (1:1) showed initial endothermic peak at  $128.6\text{ }^{\circ}\text{C}$  and a second peak at  $221.8\text{ }^{\circ}\text{C}$ . In DSC curves of the optimized formulations SIM:CA (1:2) and SIM:CA (1:4), the first endothermic peak appeared at  $107.4$  and  $104.2\text{ }^{\circ}\text{C}$ , respectively, followed by other endothermic peaks at  $226.9$  and  $223.7\text{ }^{\circ}\text{C}$ , respectively.

The TGA thermogram of pure SIM showed maximum mass loss ( $58.37\%$ ) at  $> 300\text{ }^{\circ}\text{C}$  after 14.36 min, while a little mass loss ( $5.89\%$ ) was observed at  $> 400\text{ }^{\circ}\text{C}$  after 16.54 min. The TGA thermograms of optimized formulation SIM:CA (1:1) showed initial mass loss ( $8.45\%$ ) at  $> 75\text{ }^{\circ}\text{C}$ , with maximum mass loss ( $46.37\%$ ) at  $> 175\text{ }^{\circ}\text{C}$ . Maximum mass loss of  $3.12\%$  was observed at  $> 325\text{ }^{\circ}\text{C}$ . For optimized formulations SIM:CA (1:2) CC07 and SIM:CA (1:4) CC11, little mass losses ( $07.21$  and  $6.89\%$ , respectively) were observed at  $> 80\text{ }^{\circ}\text{C}$ , while maximum mass losses ( $37.12$  and  $35.28\%$ , respectively) occurred at  $> 185\text{ }^{\circ}\text{C}$ , with some mass losses ( $03.54$  and  $03.12\%$ , respectively) at  $> 310\text{ }^{\circ}\text{C}$ . The TGA thermograms are shown in Figure 3.

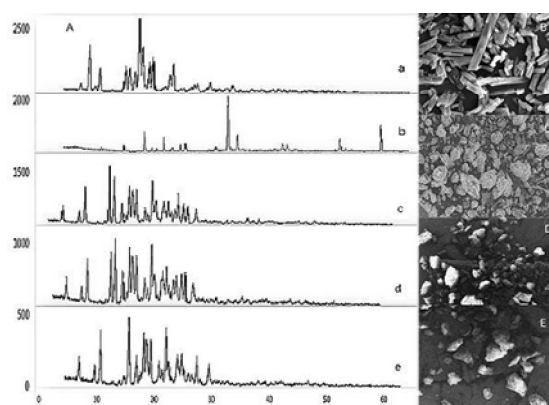
### XRD

The XRD data revealed crystallinity of the formulated co-crystals. The XRD analysis of the pure drug showed sharp peaks at diffraction

angles of  $9.46^{\circ}$ ,  $10.08^{\circ}$ ,  $10.72^{\circ}$ ,  $15.02^{\circ}$  and  $17.64^{\circ}$  [9]. However, increases in crystallinity were observed [15], with more intense and sharper peaks of the formulated co-crystals at diffraction angles of  $9.75^{\circ}$ ,  $10.21^{\circ}$ ,  $10.92^{\circ}$ ,  $14.78^{\circ}$ ,  $15.58^{\circ}$  and  $18.82^{\circ}$  for CC02;  $9.73^{\circ}$ ,  $10.16^{\circ}$ ,  $10.89^{\circ}$ ,  $14.67^{\circ}$ ,  $15.59^{\circ}$  and  $18.22^{\circ}$  for CC07; and  $9.73^{\circ}$ ,  $10.19^{\circ}$ ,  $10.87^{\circ}$ ,  $14.65^{\circ}$ ,  $15.61^{\circ}$  and  $18.23^{\circ}$  for CC11, as shown in Figure 4.

### Morphological features

SEM analysis was used for microscopic evaluation of the pure drug and formulated co-crystals. The results are shown in Figure 4.



**Figure 4:** (A) XRD diffractograms of (a) SIM, (b) CA, (c) SIM:CA co-crystals (1:1) CC02, (d) SIM:CA cocrystals (1:2) CC07, (e) SIM:CA cocrystals (1:4) CC1; and SEM analysis of (B) pure simvastatin, (C) CC02, (D) CC07 and (E) CC11

### DISCUSSION

Most of the formulated co-crystals had compressibility index values in the range of  $5 - 18\%$ . Thus, they are suitable for compression. Likewise, values of Hausner's ratio were less than 1.25 for all the formulated co-crystals. All formulations exhibited good flowability properties, when compared to micromeritic properties of the pure drug. The dissolution and release profiles of various low soluble drugs in different media can be improved with co-crystallization [16,17]. In this study, for all formulations, dissolution and solubility were increased in aqueous phase, acidic medium and basic medium. Furthermore, it was observed that drug release profiles from all SIM:CA formulations (1:1, 1:2 and 1:4) and pure drug were higher at pH 7.4 than the corresponding drug release profiles at pH 1.2. In basic medium, salt formation for simvastatin is not feasible [18]. Thus, the increase in drug release is most likely due to co-crystallization.

Polydispersity index (PDI) value confirms size uniformity within a formulation. Values of PDI > 1 indicate low uniformity, and vice versa [19]. The formulated co-crystals had low PDI values ranging from 0.126 to 0.195, indicating good uniformity in particle size. The FTIR spectra of the formulated co-crystals showed new peaks. The peak shifts indicate new bond formations. Co-crystallization may cause interactions among various single-component crystalline phase molecules. It is most likely that these interactions were responsible for the new molecular conformations seen in the FTIR of the formulated SIM:CA co-crystals [20].

The DSC and TGA curves for the formulated co-crystals differed from those of the original components. Formation of new phase was further confirmed by the fact that the co-crystals showed distinct thermal behaviors, and transition was observed relative to individual components. The peak in DSC curve of the pure drug was retained in all formulations, indicating compatibility of drug and co-former [8,21]. The multiple endothermic peaks with broad endotherms may be due to different crystal structures with different degrees of crystallinity [22]. It has been reported that co-crystals with different preparation methods show different endothermic peak temperatures, to some extent [23]. The TGA analysis showed thermal stability of formulated co-crystals, since minimum mass losses were observed at very high temperatures, when compared to original components.

The co-crystals showed distinct XRD patterns which may reflect differences in the processes used in their preparations. The results from XRD analysis further support the formation of new and different crystalline structures [20]. Further screening using different techniques may be helpful in obtaining a clearer understanding of the structures of the formulated cocrystals.

Simvastatin (SIM) appeared as rod-shaped crystals [9]. In contrast, co-crystal CC02 seemed to be crystalline aggregates, while the SEM analysis of optimized formulated co-crystals CC07 and CC11 showed cubical crystals. These analyses provide further support for the formation of crystals, and also support the results from XRD and DSC. It can also be concluded from the images that particle size was reduced, a feature which may contribute to increased solubility.

## CONCLUSION

The formulated SIM:CA co-crystals demonstrate enhanced dissolution, drug release and solubility profiles, when compared to pure simvastatin. The characteristics of the formulated co-crystals indicate their stability and compatibility. Thus, the solubility and dissolution of poorly soluble SIM can be enhanced by formulation as co-crystals with citric acid, using solvent evaporation method.

## DECLARATIONS

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### Conflict of interest

No conflict of interest is associated with this work.

### Contribution of authors

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