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Original Article

Co-crystallization: A Tool to Enhance Solubility and Dissolution Rate of Simvastatin

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ABSTRACT

Objective : The aim of this study was to explore co-crystallization to enhance the solubility of simvastatin (SV) as a drug of choice for hypercholesterolemia using saccharin (Sacch) as co-former. **Methods:** Molecular modeling of sacch against SV has been conducted by *in silico* using auto dock 4.2. Preparation of co-crystal has carried out by solvent evaporation (SE) using an equimolar ratio of SV and Sacch. Co-crystal of SV- Sacch was evaluated by the saturated solubility test and intrinsic dissolution test. Afterward, the co-crystal was characterized by infrared spectrophotometry (FT-IR), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), binary phase diagram and stability studies in storage condition 400C and relative humidity (RH) 75% for three months. **Results:** *In silico* studies showed that the interaction of SV against sacch has hydrogen bonding as molecular synthon. Evaluations of solubility and intrinsic dissolution have shown an increased in rate properties significantly of co-crystal as compared to pure SV and its physical mixer (PM). Characterizations of a co-crystal SV: sacch (1: 1) has indicated the formation of different new solid crystal phase as compared to SV, sacch, and its PM, and stable for 40^{0}C and RH 75% in 3 months. **Conclusion:** Co-crystallization has been used to increase the solubility and dissolution rate of simvastatin and all characterization has shown the formation of co-crystal SV: sacch (1: 1).

Key words: Co-crystal, Simvastatin, Saccharin, Solubility, Dissolution.

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INTRODUCTION

The effectiveness of drug therapy highly depends on the level of the drug in the blood, thus it directly depends on the nature of drug solubility.[1] Solubility and dissolution is important factors in pharmacological effect of the drug.[2] A drug with good solubility properties will show good absorption, which in turn will lead to better bioavailability. However, almost 40% of the drug in the market shows low solubility in water. Due to the low solubility, the drug is absorbed slowly and the levels of the drug in the blood are lower than the required levels.[3] In the pharmaceutical industry, the shortage of properties of biopharmaceutical drugs such as ineffective medication constitutes 1% of the major cases in the market.[4] These issues are the direct results of the solubility property of the drug. Approximately 70% of candidate drugs have problems with the solubility, therefore, it is a big challenge in the field of pharmaceuticals to developing drugs and drug dosage forms to show a good profile of solubility and dissolution rate, especially for oral preparations.[5]

Based on the nature of solubility and permeability of the biopharmaceutical classification system (BCS), drugs are classified into four classes; including drugs have low solubility (BCS class II) such as SV. SV has a low solubility of about 30 µg/ml and its bioavailability is only 5%.[6] However SV is the drugs of choice for the management of hypercholesterolemia due to their recognized efficacy and safety profile.[7] Several methods have been developed to increase the solubility, such as the technique of forming an SNNEDS,[8] the addition of a surfactant, and particle size reduction by microemulsion technology,[9] these methods have been somewhat inadequate. They have drawbacks such as the following: they involve the use of a number of matrices; the energy of the process is high, and the up-scaling process is complicated.[7] To the best knowledge of the present researchers, co-crystallization has not been investigated as a potential method to increase the solubility of SV.

Co-crystallization is a simple technique that can improve the physicochemical properties of the active pharmaceutical ingredient (API), such as solubility, dissolution rate, bioavailability, and stability.[10] It can be applied to acidic, alkaline, neutral and ionic compounds including SV.[11] Co-crystallization technique is widely used in the pharmaceutical field to change the features of a pharmaceutical solid substance, thus thereby develop it into a material with the desired properties.[12] Co-crystal is becoming an important class of pharmaceutical solid that can improve the solubility and dissolution of the API by forming a complex crystal. It consists of a drug and co-crystal former (co-former) with a defined stoichiometric ratio and connected by a synthon.[13] A synthon in co-crystals are a non-covalent interaction involving hydrogen bonds, Van der Waals, and π-π electrons.[14] The interaction of synthon can be expected by the *in silico* method. It is useful to ensure and understand the interaction the type of the interaction of API and co-former.[15]

A number of techniques had been investigated to synthesize co-crystals, such as the following: melting extrusion,[16] forming slurry with ultrasound,[17] particle size reduction,[18] sprays drying,[19] and the solvent evaporation (SE).[1] Co-crystal's synthesis based on solution method (SE) might be more effective and efficient for refinement; furthermore, the SE method is commonly used in the pharmaceutical industry.[20] In the pres-

ent work, we developed co-crystallization as a simple approach in terms of process and procedures to produce an excellent improvement in the solubility of the API as previous studies.[21]

MATERIALS AND METHODS

Materials

Simvastatin obtained from Teva with purity > 99% (Belgium), methanol pro analysis purchased from Merck, (Germany), saccharin pro analysis from Merck (Germany), and potassium dihydrogen phosphate pro analysis (Merck, Germany).

Methods

In silico Molecular Docking

The 3D-structures of the SV and Sacch were proposed using Hyperchem 7.0 and energy minimization by MM+. Additionally, the compound conformations were produced using the Discovery Studio 2.5 with CATALYST finest conformation module. CHARMM forced field was applied for energy optimization. The compounds which had higher than 20 kcal/ mole as compared to the total lowest for conformation l minimum were rejected; the highest number of conformations was adjusted to 255. Docking simulations of the molecules were done by AutoDock 4.2. The AutoDockTools (ADT) script was directed to transform the ligand PDB to the PBQ format finished adding Gasteiger charges, setting ligand flexibility and inspecting polar hydrogen.

Preparation of cocrystal

Accurately weighed SV and Sacch equivalent to a molar ratio (1:1), afterward carried by dilution of the mixture of SV and Sacch assisted by methanol as a solvent, shaken for 10 minutes, later stored in a water bath at 30^{0}C for 24 hours for drying and next keep in to vial in room temperature (25^{0}C).

Evaluation of co-crystal

Saturated solubility studies

Accurately weigh of dried co-crystal equivalently to SV 100 mg, then input into the vial and reconstituted with 50 ml of distilled water, later shaken for 24 hours using an agitator shaker, afterward calculate the concentration of dissolved SV using verified spectrophotometry UV-Vis method (Analytical zena, Germany). The same procedure was repeated for pure SV and physical mixture (SV: Sacch).

Intrinsic dissolution studies

The intrinsic release behaviors of the SV and its co-crystals were measured during a dissolution test (USP type two). A sample with equal consisted of 250 mg SV in co-crystal powders was made in pellet form, then put into a 900 ml simulated intestinal fluid pH 4.5 (less enzyme) and stirred at 100 rpm. Sampling (5 mL) was done until 60 minutes sat pre-determined time points, and a fresh 5 mL SIF solution was added into the system after each sampling. Dissolution's samples were filtered through a syringe filter of 0.45 µm pore size, and its UV absorbance was measured at 240 nm (Analytical Zena, Germany). SV concentration was calculated using a validated pre-constructed calibration curve and the same way was done for the pure SV intrinsic dissolution procedure.

Characterization of Co-crystal

FT-IR analysis

Samples in the form of powder mixed with potassium bromide crystal with the molar ratio (1: 10), crushed until homogeneous and then compressed to a pressure of 20 psi. The spectra were analyzed over a range of wavenumbers 4000-400 cm $^{-1}$ using FT-IR (Specord 200, Germany).

Thermal measurement

Thermal analysis of the samples was performed on a DSC/TGA apparatus (Linseis PTA ST 1600, Germany) which was standardized for temperature and cell constants using indium. Samples (1–3 mg) crimped in the aluminum pan were analyzed from 50 to 300^{0}C with a heating rate of 10^{0}C/ min. Samples were continuously removed with nitrogen at 50 ml/ min.

XRPD studies

The x-ray powder diffractometer (X Philips Analytical PW1710, Germany) patterns were collected using Cu Ka radiation (l = 1.54 Å), a tube stage of 40 kV and a tube current of 40 mA. Data were collected from 2□ angle 5^0-48^0 at a continuous scan rate of 4^0/ minute.

Binary diagram phase studies

The binary phase diagram is made by making the mixture with SV: Sacch with mol fraction comparison among SV- Sacch (0:10) until (10:0), then each mixture was measured at its melting point and it was plotted in the chart form.

Stability Studies of Co-crystal

Profile of co-crystal stability SV: Sacch (1:1) was examined by observing the melting point of co-crystal that were kept in a storage condition 40^{0}C and RH 75% for three month.

RESULTS AND DISCUSSION

In silico Simulation Modeling

In silico studies based on molecular modeling Figure 1 are performed as simple procedures to confirm the hydrogen bonding between SV and Sacch. The lowest Gibbs-free energy of the molecular conformation was -3 kcal/mole. The negative value indicates the possible occurrence of the interaction between SV and SAC.[22] This interaction results in the formation of a hydrogen bond with a short bond distance of 1.982 Å (green line on the Figure 1).

Preparation of Co-crystal SV-Sacch (1:1)

The preparation of the SV–Sacch (1:1) co-crystal was carried out by SE, since this method affords high purity of crystallinity.[23] The SE method is also reliable in the discovery of new co-crystals when the presence of a solvent as a liquid phase can improve the rate of co-crystal formation and is suitable for co-crystal constituents with the equimolar ratio.[24] In this work, Sacch was chosen as the coformer because of its stability, polarity, and ability to form a synthon. Synthon in co-crystal would form a hetero-synthon and thereby would be very effective in enhancing the solubility of the API

Evaluation of Co-crystal SV-Sacch (1:1)

Solubility saturation studies

Tests of saturated solubility were conducted on SV, a PM of the SV-Sacch, and co-crystal of SV–Sacch (1:1). The saturated solubility of the co-crystal (83 ppm) was up to 10 times higher than those recorded for SV (8 ppm) and the PM (58 ppm). This is because of the affinity of the solvent towards SV was stronger in the presence of the co-former, which led to a decrease in the energy of crystal lattice by the formation of co-crystal. This finding can also be attributed to the pH changes that can lead to the formation of a formed stable ion that is soluble in a water environment.[25]

Intrinsic dissolution measurement

Intrinsic dissolution studies were carried out on pure SV and co-crystal SV–saccharine (1:1) Figure 2. The dissolution value of co-crystal SV–TA (1:1) was approximately four times that of the pure SV in 60 minutes. The increase in the dissolution rate correlated with the diffusion constant, function of the surface area, boundary-layer thickness, and solubility. SE also could modify the diffusion of a molecule of the API by affecting its hydrodynamic properties and influence the release behavior of API.[26]

Co-crystal Characterization

FT-IR studies

FT-IR analysis of co-crystal was employed to determine the hydrogen bonding between the SV and Sacch Figure 3. The spectrum overlay of the pure SV, Sacch and co-crystal SV-sacch (1:1) has shown the widening of the co-crystal absorption at wavenumber 3600-3200 cm^{-1}. It is specifically for the intermolecular hydrogen bonding formation.

Thermal analysis

DSC studies are undertaken to observe the co-crystal formation from the difference in the melting point of co-crystal as compared to its own constituent by the endotherm phase. DSC has been used to rapid screening of the co-crystal. The thermogram Figure 4 showed that the melting point (endotherm phase) of co-crystal SV-Sacch (112°C) was less than that of pure SV (122°C). The enthalpy of SV (87 Joule/g) was greater than that of co-crystal SV- Sacch 1:1 (-201.65 Joule/g). A decrease in the melting point and heat content of the co-crystal will directly correlate with increased solubility of API in the co-crystal. The melting point of the co-crystal will fall between those of API and its coformer and the physiochemistry of the co-crystal could be predicted by a polarity of co-former.[27]

XRPD

An XRPD was performed to verify the formation of the co-crystal of SV: Sacch (1:1) as compared to that of SV and its PM. The diffractogram showed that the total number of peaks for the co-crystal was 54, although the peak number of the physical mixture was 43 Figure 5. The difference in the number of co-crystal peaks and PM indicates a difference in the structure of the two. The overlay of the diffractogram showed distinct peaks and intensity at an angle of 2□: 17–20°, 20–30°. The X-ray powder diffraction is a specific technique to confirm the new solid state and the pharmaceutical co-crystal is prone to forming isostructural phases. All crystal forms of a compound to produce own characteristic x-ray diffraction pattern.[28] Generally, the difference of peaks indicates the formation of new solid crystalline phases and the intensity of the peaks of SV and co-crystal showed decreases in intensity, thus, it was due to changes in crystal habits.

Binary phase diagram

The results of the binary phase diagram analysis, indicating the eutectic point at the mole fraction comparing (4:6) and (5:5), and (4:6) co-crystals. At this point, the melting point decreases and reaches the lowest point. The three lowest points formed a W pattern. Generally, the W pattern was contributed by hydrogen bonding between SV and Sacch, and it must be presented co-crystal habits.[29]

Stability Studies

The melting points Table 1 were used to observe the stability of the co-crystal. Testing with the application of temperature and relative humidity stress are the most established methods to exhibit the stability of a substance in the solid state.[30] The melting point on days 30, 60, and 90 showed consistency in the value. Consequently, it showed the indicated stability of co-crystal in condition 40°C and relative humidity of 75%.

Table 1: Melting point stability of co-crystal SV: Sacch (1:1) under condition (40°C ; RH 75%) after 3 months

Days	0	30	60	90
Melting	147.02	147.2	147.2	147.2
point (°C)	147	147.6	147	147
(n=3)	147	147	147	147
Mean±SD	147.05 ± 0.2	147 ± 0.282843	147.5 ± 0.235702	147.05 ± 0.02357

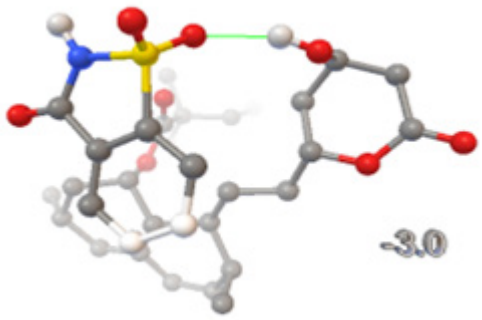

Figure 1: *In silico* molecule modeling simulation of SVand Sacch.

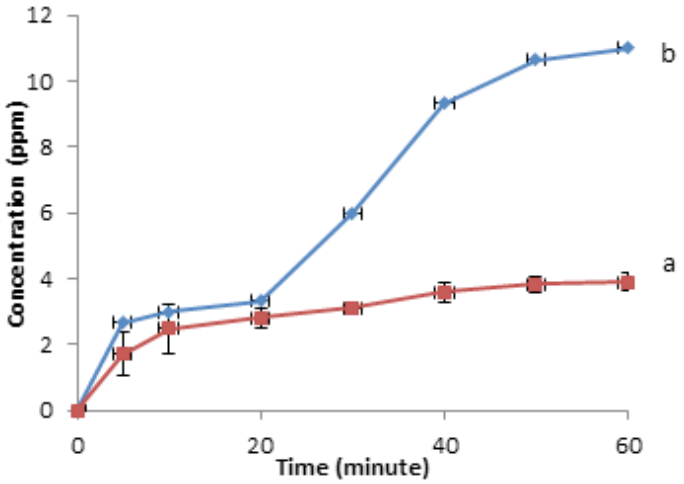

Figure 2: Intrinsic dissolution profile of (a) SV and (b) co-crystal SV: Sacch (1:1) (n=6).

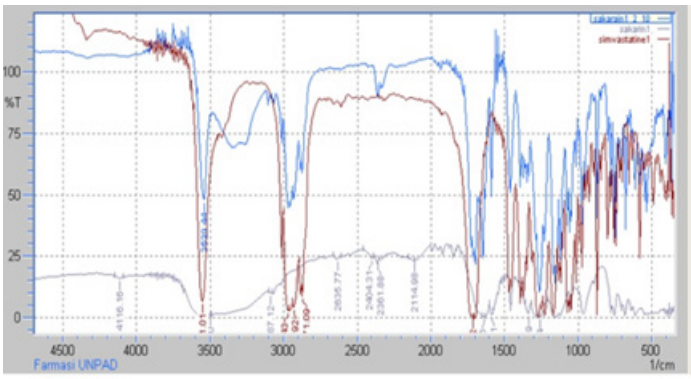

Figure 3: FT-IR spectrum overlay of SV (-), Sacch (-), and co-crystal SV: sacch 1:1 (-).

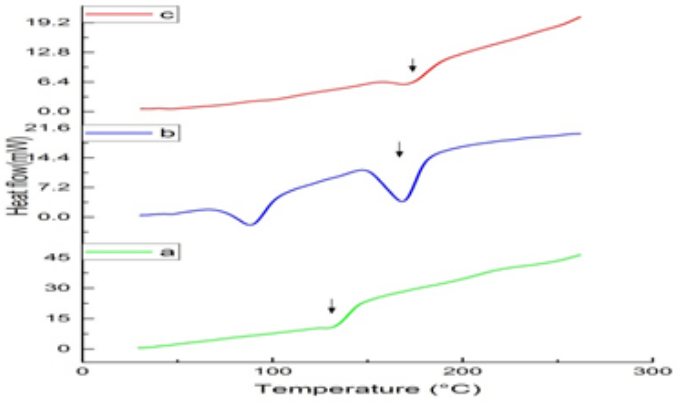

Figure 4: Thermogram of SV (a), PM (b), co-crystal SV-Sacch (1:1) (c).

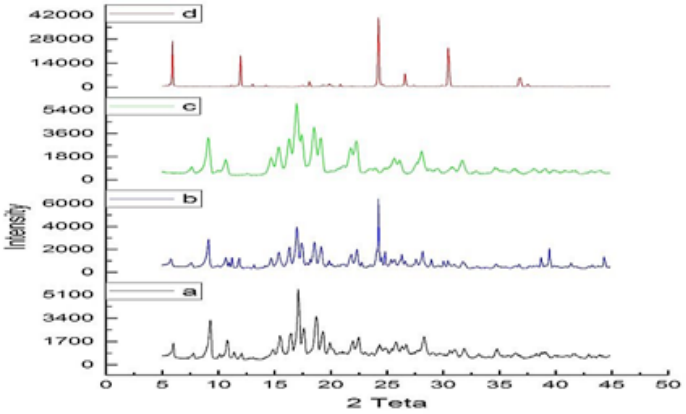

Figure 5: Diffractogram of SV(a), PM (b), Co-crystal SV : Sacch (1:1) (c), and Sacch (d).

CONCLUSION

Preparation of co-crystal SV: Sacch (1:1) had been conducted using SE. The saturated solubility and intrinsic dissolution evaluation of co-crystal had presented an significantly increasing of the rate of solubility and release behavior and all characterization against co-crystal SV: Sacch (1:1) indicated the formation new solid crystalline phases that change from SV, Sacch, and its PM.

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CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATION USED

SV: Simvastatin; **Sacch:** Saccharine; **API:** Active Pharmaceutical Excipient; **SE:** Solvent evaporation; **DSC:** Differential Scanning Calorimetry; **SEM:** Scanning Electrons Microscopy; **FT-IR:** Fourier Transform Infra Red Spetroscopy; **PXRD:** Powder X-ray Diffraction.

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