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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-