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Der Pharmacia Lettre, 2017, 9 [6]:18-27
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ISSN 0975-5071
USA CODEN: DPLEB4

Dissolution Rate Repairing of Simvastatin as A New Approach in Cocrystallization

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ABSTRACT

Simvastatin (SV) is a cholesterol-lowering drug of choice classified into a class II of drugs based on bbiopharmaceutical cclassification ssystem (BCS), which is a drug that has a poor solubility but high permeability. Low solubility drug caused a low bioavailability in the blood before it reached its workplace. Cocrystallization is one way to enhance the solubility and dissolution rate of SV with aspartame (ASP) as the conformer. Cocrystals was being examined on its solubility and dissolution test. Afterward, cocrystal was characterized by fourier ttransform iinfrared (FT-IR), X-ray powder ddiffraction (XRPD) and ddifferential scanning ccalorimetry (DSC). Co-crystalline simvastatin with co-former ASP equimolar enhances solubility of simvastatin by 193.28% and it enhances the rate of dissolution by 153.53%. Characterization of the cocrystals shown there were a resultant of functional groups from SV and ASP, and it is also shown a different pattern of the thermogram, and difractogram, consequently, it has indicated the formation of cocrystals.

Key words: Solubility, Dissolution, Simvastatin, Cocrystals, Conformers

INTRODUCTION

Solubility is a rate limiting dissolution process for a drug included in a BCS class II system to increase the bioavailability [1]. Drug which has a low solubility but high permeability needs to be improved and modified so it would have a better therapeutically impact. Simvastatin is a statin group used to decrease the hypercholesterolemia by inhibiting the HMG-CoA reductase enzyme which has a role in forming a cholesterol [2]. Simvastatin is a white powder crystalline, non-hygroscopic, 418.56 molecular weight. Practically insoluble in water (30 µg/ml) easily dissolved in methanol, ethanol and chloroform. It has a

bioavailability in 3 hours and 5% [3, 4]. Simvastatin included in class II based on Biopharmaceutical Classification System (BCS) which has a low solubility in water but has a high permeability [1]

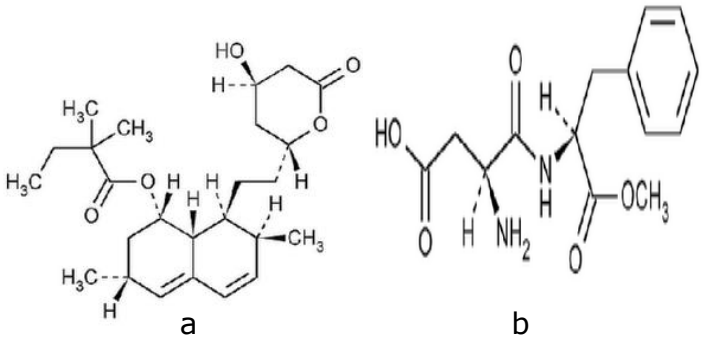

Figure-1: SV (a) and ASP (b)

Some methods have been investigating to improve the solubility, such as the technique of forming an SNNEDS [5], solid dispersion [5], the addition of a surfactant, particle size reduction by microemulsion technology [6], and supercritical antisolvent (SAS) [7], these methods have been somewhat inadequate. They have problems such as the following: they take in the use of a number of matrices; the up-scaling process is complicated, and the energy of the process is high [3]. Accoording to the best understanding of the current researchers, co-crystallization has not been studied as a potential method to increase the solubility of SV.

Cocrystals is one of the methods which can be used to increase the solubility and chemical stability of simvastatin. Cocrystals is a solid material consisting of two or more solid material formed a new difference lattice crystal which connected by a hydrogen bond like Van der Waals [7]. The advantages of this method are not influencing the pharmacological activity of active pharmaceutical ingredients and it can increase physical properties such as solubility, dissolution, and compressibility. Moreover, cocrystallization could be used potentially to all active pharmaceutical ingredients including; acid, base, and unionized molecule [8].

Cocrystals is a combination between an active pharmaceutical ingredient (API) and its cocrystals former. Cocrystals former chosen by its ability to form a hydrogen bond with its API. The requirements for the cocrystals former are; the ability to form a hydrogen bond, inert, and has a low toxicity [9]. Slurry method was used by mixing the API and its cocrystals former added using a properly solvent in room temperature. The mixture was being evaporated until all the methanol was gone from the solid mixture and was consider as simple method [10].

MATERIALS AND METHODS

Preparation of ccocrystals

SV and cocrystals former was mixed in an equimolar ratio (1:1) and (1:2) by adding methanol until a slurry formed and agitated for about 10 minutes. Put the mixture on a water bath in 50^{o}C for 24 hours [11].

Saturated ssolubility studies

The cocrystals solubility test applied on every cocrystals by every cocrystals former by weighing 20mg equal to simvastatin and dissolved it into 10 ml. aquadest inside the vial and shake it using agitator for 24 hours in a room temperature (25^{o}C) [11]. The result measured by a spectrophotometry UV in a wavelength range from 200 – 300 nm.

Cocrystals ddissolution test

Dissolution was done in a phosphate buffer at pH 4.5 which contained 13.61 g KH_2PO_4 in 1L aquadest [12]. Dissolution test using Apparatus 2 (paddle) in 50 rpm for 90 minutes [11]. Dissolution test done in a 500ml medium phosphate buffer pH 4.5 in 37± 0,5^{0}C [12]. Take 10 ml of samples periodically every 10, 20, 30, 45, and 60 minutes while adding the same medium volume into dissolution apparatus. The result measured by a spectrophotometry UV in a wavelength range from 200 – 300 nm.

Cocrystal ccharacterization

Ccocrystals with the best solubility and dissolution profile was characterized using FT-IR, DSC and XRPD and compared towards SV and PM. Its was conducted to know the difference of crystal characterization based on the slurry method.

X-RPD analysis

The structure of crystal was examined by Powder X-Ray Diffractometer (Philips PW 1835), with several conditions: target/filter (monochromator) Cu, tension 40 kV, current 30 mA, width slit 0,2 inch, scanning velocity 0,2Ɵ - 0,5Ɵ per minute and scanning distance 2θ = 5 – 50. This procedure was done to compare the SV with the formed cocrystals simvastatin.

FT-IR sspectrophotometry test

A powder sample was mixed up with potassium bromide in 1:10 equimolar ratio and grinded to form a homogeneous mixture. The mixture was compressed in 20 Psi pressure to form a potassium bromide plate. The spectrum was measured in the range of 4000-400 cm^{-1} wavenumber using FT-IR spectrophotometry. Its was done to compare the functional group between pure simvastatin toward the formed SV cocrystal.

DSC anlaysis

Thermal analysis of the sample was done using a calibrated DSC (Linseis) by an indium. 5-10 mg sample was put on an aluminum closed pan. It was managed at the range 50-350 ^{o}C in the speed of 10 ^{o}C per minutes. This procedure was done to compare the thermogram between initial SV to SV cocrystals.

RESULT AND DISCUSSION

Molar comparing was used for cocrystal SV-ASP syntesis were 1:1 and 1:2. Its was used based on the synthon between SV and ASP [13,14] This dominant sinton connection involves non-covalent interaction like a hydrogen bond [15]. Simvastatin have some lactones functional group which contains carbonyl, hydroxyl, and ether thus possible in making a hydrogen bond with the aspartame. Saturated solubility studies was examined to know how it could enhance the solubility in water with the result fig 2;

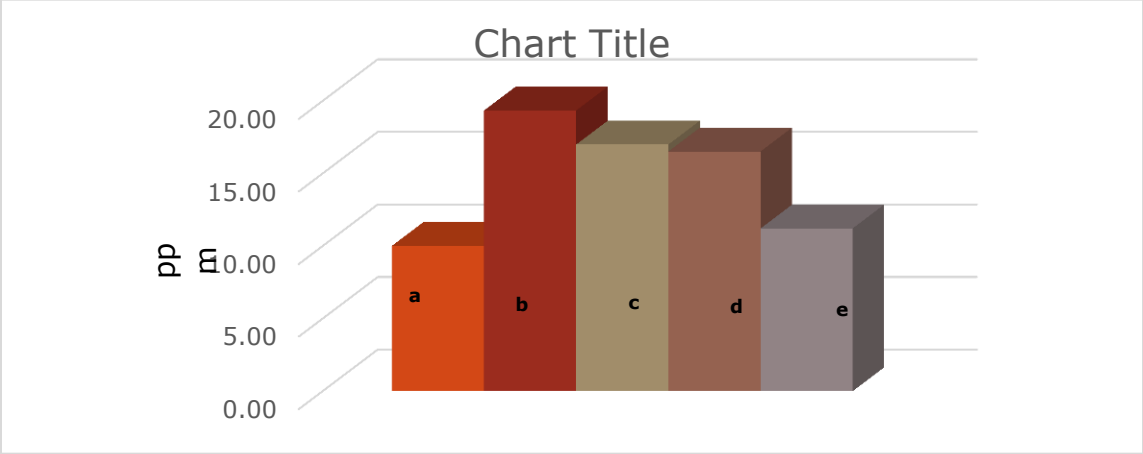

Figure 2. Solubility profile of SV (a), cocrystals SV:ASP 1:1 (c), cocrystals SV: ASP 1:2, PM 1:1 (d), and PM 1:2 (e)

The result of saturated solubility has shown that the highest solubility enhancement was given by cocrystals SV: ASP with an equimolar ratio, it is 193.29% increase from the pure SV. The polar functional group from ASP has bounded through a hydrogen bond with SV and it enhances the solubility of simvastatin in water [1]. The best solubility enhancement as a result of SV: ASP cocrystals was analyzed statistically in order to know a molar ratio gives the best solubility enhancement. Solubility analysis was done using a univariate analysis with $\alpha = 0.05$. Normality data was done using Shapiro- Wilk test for an SV, cocrystals SV: ASP 1:1, and cocrystal SV: ASP 1:2.

The normal data were shown by a significantt value $p > 0.05$ so it can be continued to test the homogeneous variants using Levene's Test. The homogeneity test result shown the significance value $p > 0.05$ which indicated that all data was homogen and

so it can be continued to analyze using univariate analysis to know was there any significance contribute to the differentiation of molar ratio in the cocrystal form to SV solubility enhancement results (Table 1).

Table 1: Univariate test result of cocrystal SV solubility enhancement

Dependent Variable: Solubility					
Source	**Type III sum of squares**	**df**	**Means square**	**F**	**Sig.**
Corrected Model	265826.255[a]	2	132913.128	1233.502	0.000
Intercept	166382.410	1	166382.410	1544.114	0.000
Simvastatin	265826.255	2	132913.128	1233.502	0.000
Error	646.516	6	107.753		
Total	432855.181	9			
Correction total	266472.771	8			
a. R squared = 0.998 (Adjusted R squared = 0.997)					

The statistical test undertaken to find out a significant value of the solubility differentiation of two comparing molar ratios in the cocrystal form to SV. The univariate analysis test of Post Hoc test using Tukey HSD and Scheffe was done to veryfied whether it has a significance difference between those both molar ratios. The result of Post Hoc test given a no significance value of p = 0.522 whereas p> 0.05 for a cocrystal SV: ASP 1:2 and a significance value for a cocrystal SV: ASP 1:1 to SV. Dissolution profile (figure 2) was exhibited that cocrystal SV: ASP 1:1 as a highest concentration in 60 minutes. ASP is stable in acidic medium at pH 4.5 [16,17]. It caused by an affinity force of a polar molecule from aspartame as a solute in the dissolution medium with a dipole interaction [10]. Consequently, it could be enhance the dissolution rate of SV [1].

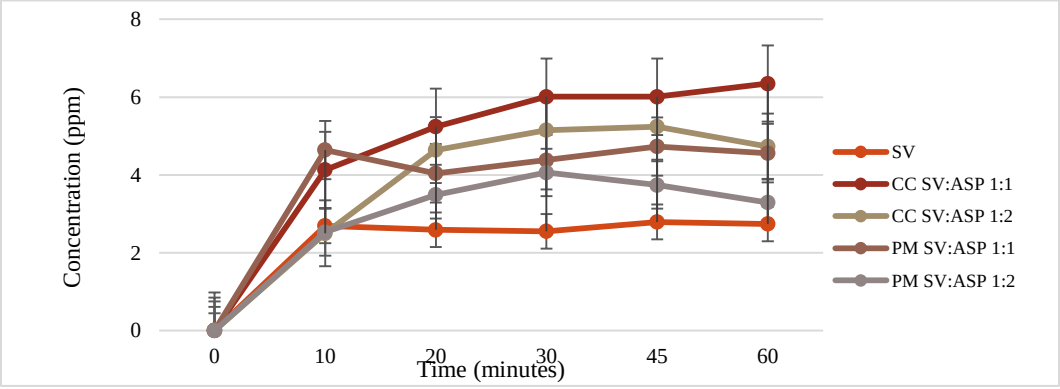

Figure-3: Dissolution profile of SV, Cocrystal SV: ASP, and PM

Characterization of cocrystal

FT-IR spectrum of initial SV with the SV which was being solved in a methanol shown almost similar and it doesn't mean a forming new functional group and interpreted that there was no chemical interaction between SV to methanol. Moreover, the functional group shown by the FT-IR was appropriate with the structure of simvastatin. Infrared spectrum was absorbed at 3656.12cm^{-1} (OH stretch, hydroxyl free alcohol), 3340.91 cm^{-1} (NH stretch 1^{o}, 2^{o} amine, amide), and 1737.29 cm^{-1} (C=O stretch ester, saturated aliphatic) [18]. ASP functional group was appropriate to the structure of aspartame based on USP30-NF25 as below:

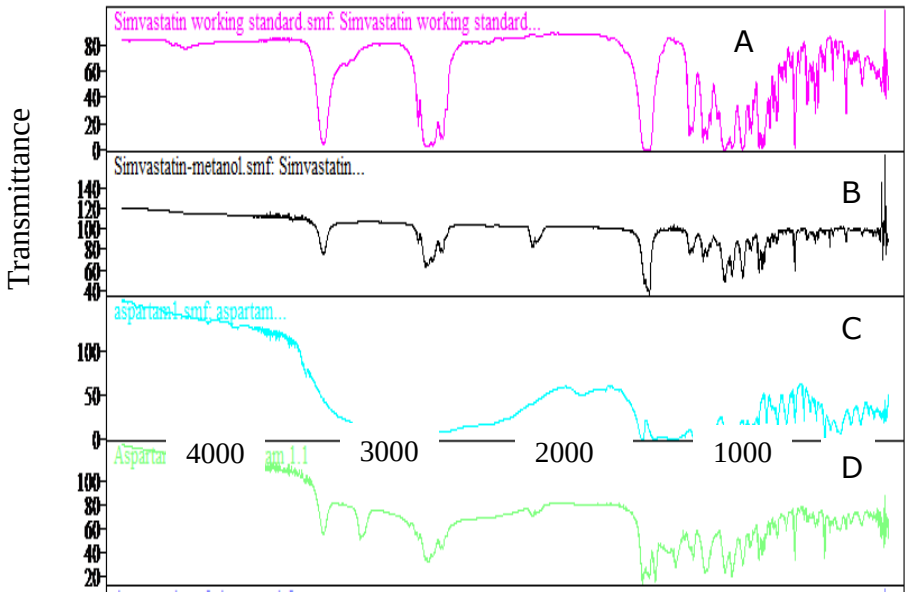

Figure-4: FT-IR pattern of SV (a), ASP (c) and cocrystal (d)

FT-IR spectrum shown cocrystal SV-ASP 1:1 compared to the SV shown almost the same characteristic in both aspartame and simvastatin. There was a combination between those two components, so it could have predicted that there was no any chemical interaction happened in slurry method cocrystallization. FT-IR spectrum shown (%T) to the wavelength (cm^{-1}) from cocrystal SV-ASP 1:2 compared to the SV shown almost the same characteristic in both ASP and SV which it absorb at 3550,69 cm^{-1} (OH-fenol), and 3340,83 cm^{-1} (N-H stretch 1^{o}, 2^{o} amine, amide) which was belongs to the aspartame, 2970,13 (=C-H stretch alkene, C-H stretch aromatic), and 2871,43 (C-H stretch alkane), also 1735,92 (C=O stretch)[18] so it could predicted that there was no any chemical interaction happened in slurry method cocrystallization.

Cocrystal SV and SV was then characterized by using an XRPD to know whether there was a difference in the crystal structure or not between those two if there was any new crystalline phase from the interaction of those two components it could be shown from the difference of x-ray diffractogram compared to the PM, SV, and its cocrystal [19].

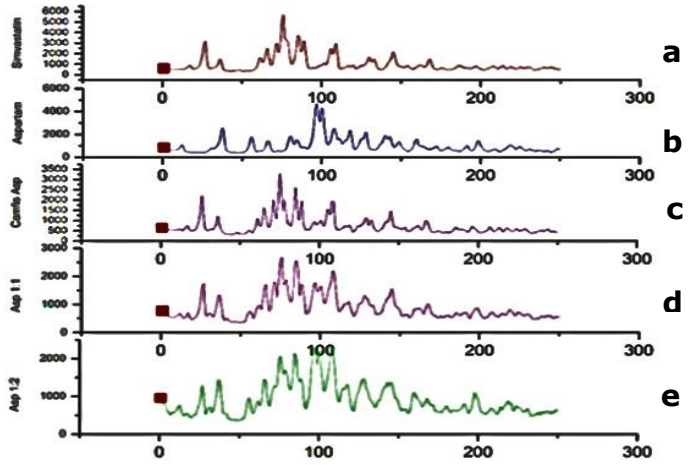

Figure-5: XRPD patterns of SV (a), ASP (b), Physical mixture (c), ccocrystals SV:ASP (1:1) (d), and ccocrystals SV: ASP (1:2) (e)

Simvastatin diffractogram shown the highest intensity of diffraction on 9.08^o; 10.66^o; 14.72^o; 15.32^o; 16.28^o; 16.96^o; 17.42^o; 18.5^o; 19.1^o; and 22.22^o shown that simvastatin was stated at its crystalline form. So does aspartame, shown the highest intensity on 6.72^o; 10.88^o; 13.78^0; 15.48^o; 17.7^o, 20.3^o; 20.86^o; dan 22.14^o. The diffraction pattern of the physical mixture SV: ASP shown the similarity with the combination of both components and it has more diffractions. So does the cocrystal SV-ASP 1:1 and 1:2 ratios almost have the same diffractogram with its physical mixture. The difference of cocrystal SV-ASP 1:1 was that it has a new highest intensity on 22,16^o which indicated that it was forming a new crystalline phase of simvastatin. The peak intensity of cocrystal SV-ASP diffraction was decreased relatively if compared to initial simvastatin, this could be happened because of the changes in crystal habit [20].

DSC thermal analysis is an analytical instrument that very beneficial in characterizeing the solid-state interaction between two or more chemical materials [21]. This analysis was used to evaluate the thermodynamic property changes such as thermal energy, recrystallization, melting point, desolvation, and solid phase transformation, which shown by the endothermic and exothermic pick on thermogram [21.]

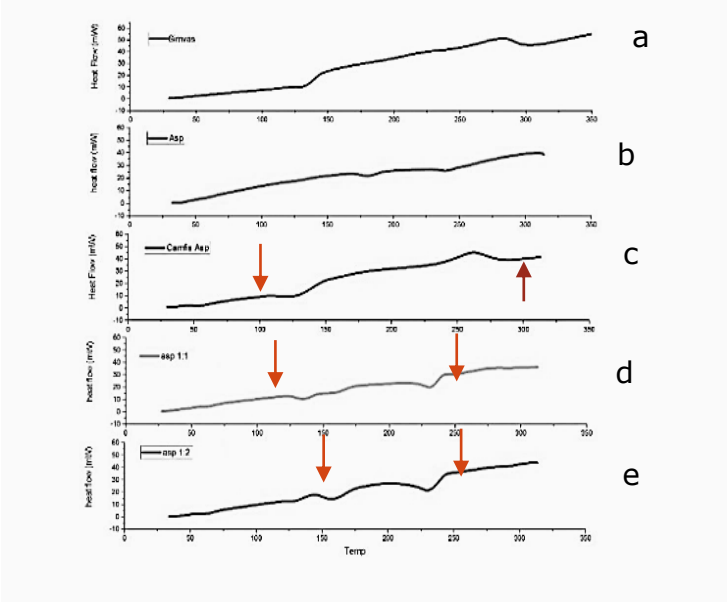

Figure-6: hermogram of SV (a), ASP (b), PM (c), ccocrystals SV-ASP 1:1 (d), and ccocrystals SV-ASP 1:2 (e)

SV thermogram has shown an endothermic peak in range 122^{o}C- 143.4^{o}C and exothermic peak at a temperature range 248.3^{o}C-297.9^{o}C (fig 6). Meanwhile, ASP has shown two endothermic peak at temperature range 170^{o}C-192.5^{o}C and 230.4^{o}C-249.5^{o}C. The PM of SV- ASP has shown the endothermic peak at temperature range 104.5^{o}C – 148.4^{o}C and 234.2^{o}C- 282.2^{o}C. The thermogram of PM was similar to the SV but has lower temperature. Thus, indicated that it has the interaction between SV and ASP and the difference in thermogram happened with the decreased at its melting point [22.] Cocrystal SV-ASP 1:1 presented three peaks of endothermic. First endothermic peak was at temperature range 124.6^{o}C- 145.7^{o}C which it has similiar melting point to SV, the second endothermic peak 149.2^{o}C - 170.6^{o}C, and the third endothermic peak was at temperature range 216.9^{o}C - 240^{o}C which it was included at the crystal ASP melting point. Cocrystal SV-ASP 1:1 also shown the exothermic peak at temperature range 253^{o}C - 291,9^{o}C which it was the stable SV crystalline temperature. Thus, indicated that it has the interaction between SV and ASP. The difference in thermogram caused by the decreasing of its melting point [23].

CONCLUSION

Cocrystal SV-ASP has been done well by slurry method. Cocrystal simvastatin enhance the solubility and dissolution rate best at an equimolar ratio. All characterization of cocrystal has shown the formation new solid phase crystal of cocrystal

ACKNOWLEDGMENT

I thank all the Padjadjaran University Academician and PT. Gracia Phamrindo for all support in this project.

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