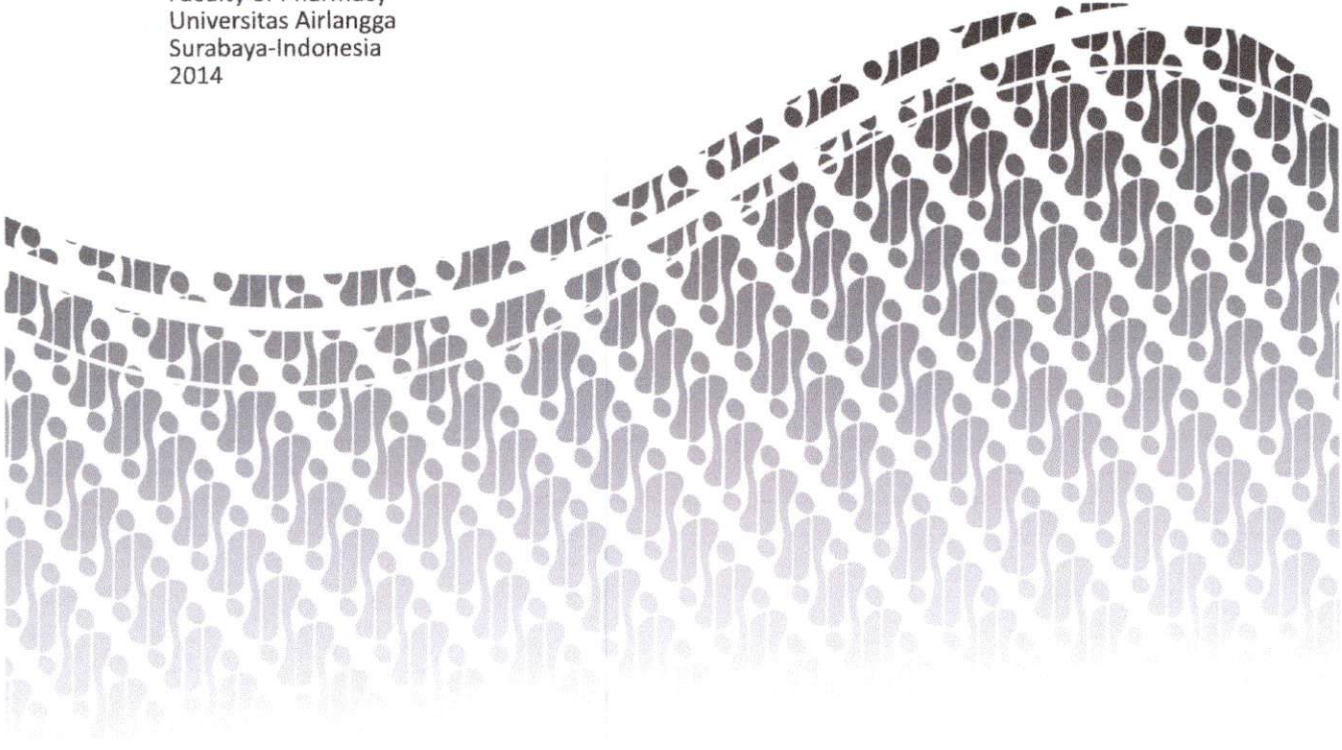
Proceeding

The 1st International Conference on Pharmaceutics & Pharmaceutical Sciences

Published and Organized by
Faculty of Pharmacy
Universitas Airlangga
Surabaya-Indonesia
2014



The 1st International Conference on Pharmaceutics & Pharmaceutical Sciences Proceedings

ISBN : 978-602-72333-0-0
(Letter of National ISBN Agency No. 4127/E.8/p/03.2015 Date 18 March 2015)

1st edition Proceeding
Published by:
Faculty of Pharmacy Universitas Airlangga
Surabaya, Indonesia

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ISBN 978-602-72333-0-0

PREFACE From Chairman

It is our pleasure to present you the proceedings of The 1st International Conference on Pharmaceutics and Pharmaceutical Sciences (ICPPS) organized by The Faculty of Pharmacy Universitas Airlangga Surabaya Indonesia.

The proceeding was produced based on papers and posters presented at The 1st International Conference on Pharmaceutics and Pharmaceutical Sciences (ICPPS), held in Surabaya, Indonesia, 14-15 November 2014.

The proceeding clearly reflects broad interest, from the participants that coming from all around the world.

The papers presented were pharmaceutics and biopharmaceutics; requirements on how to evaluate molecules in discovery and their appropriateness for selection as potential candidate; their development in context of challenges and benefits, together with associated time and cost implications and also requirements to progress through pre-clinical and clinical.

In this an opportunity, I would like to express my appreciation to the editorial team of the proceeding who have been working hard to review manuscripts, and making the first edition of this proceeding be possible.

I would like also to thanks to all invited speakers and presenters who participated in The 1st International Conference on Pharmaceutics and Pharmaceutical Sciences (ICPPS) and your contribution to this proceeding.

Finally, I hope this proceeding will give contribution to the Pharmaceutics and Pharmaceutical Sciences research.

Chairman,

Dra. Esti Hendradi, MSI., Ph.D., Apt

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KINETICS STUDY COCRYSTALS KETOCONAZOLE-SUCCINIC ACID PREPARED WITH SLURRY METHOD BASED ON POWDER X-RAY DIFFRACTION (PXRD)

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INTRODUCTION

The compounds with low solubility drugs can be a problem in the development of drugs for the pharmaceutical industry. Group of drugs that are included in the Biopharmaceutical Classification System (BCS) class II drugs can be a challenge for the preparations of pharmaceutical development because of low solubility drugs as well as the rate of dissolution. In this case to increase the solubility of drugs besides salts, pharmaceutical cocrystals opened a new dimension to search for solid forms such as solubility, dissolution rate, stability, and shelf life of active pharmaceutical ingredients (APIs) without affecting their inherent pharmacological properties1.

Pharmaceutical co crystals are materials or crystalline materials consisting of at least two different components (multicomponent crystals or mixed crystals)2-3. Co crystal could be prepared by several methods, such as solvent evaporation, slurry, melt, and grinding. Co crystals formed between ketoconazole (KTZ) as an active pharmaceutical and succinic acid (SA) as a co crystal former (co-former)4 was increased dissolution rate of pure ketoconazole in equimolar ratio (1:1)1. Physical characterization of co crystal was performed by physical mixture of binary system with molar ratio using different thermal analyzer (DTA) data from KTZ and SA. Besides that, physicochemical characterizations of cocrystal were performed by using PXRD and infrared spectroscopy (IR).

Active solid materials in the manufacture of pharmaceutical preparation suffered in various thermic or machanical proccessed such as grinding, milling, granulations (wet and dry granulations), tabletasi, and storage at various temperature, so the materials can occure transformation polymorph or hidrat/solvat5. Kinetic study of cocrystal KTZ-SA prepared with slurry method at various solvent concentrations a follows 2%, 3%, 4%, 5% and 6% (w/w). Therefore, the aim of the present study was determined the kinetics of co crystals KTZ-SA prepared with slurry method by using Powder X-ray Diffraction (PXRD) data such as the research of co crystalline phase transformation of binary mixture of trimethoprim (TMP) and sulfamethoxazol (SMZ) by slurry technique5.

MATERIALS AND METHODS

Materials

Ketoconazole was purchased from Zhejiang East-Asia Pharmaceutical Co., Ltd, China, bacth no. DC-0101H-1209001. Succinic acid was purchased from Merck KGaA, Germany, bacth no. K43601782. Destilled water and ethanol p.a.

Methods

Preparation of Phase Diagram of Binary System

KTZ and SA were sifted and weighed to obtain particle size in similar range. The obtained physical mixtures were obtained by simply mixed KTZ with SA at different molar ratios as follows: (10:0), (9:1), (8:2), (7:3), (6:4), (5:5), (4:6), (3:7), (2:8), (1:9) and (0:10) respectively. The mixtures were gently mixed in mortar for 5 minutes. The melting point of physical mixtures of KTZ-SA was determined by DTA. Endothermic peak was plotted against molar

fraction of mixture to obtain the phase diagram of KTZ-SA.

Preparation of KTZ-SA Physical Mixture

KTZ and SA equimolar carefully weighed; 0.5314 grams and 0.1181 grams respectively. Both powders were mixed homogenously in a mortar.

Preparation of Cocrystal Using Solvent Evaporation Method

KTZ and SA equimolar carefully weighed; 0.5314 grams and 0.1181 grams respectively. Each compound was dissolved in ethanol separately. KTZ was dissolved in approximately 30 mL of ethanol to form a clear solution. SA was dissolved in approximately 8 mL of ethanol to form a clear solution. The two solutions were mixed and stirred for a few minutes. The solvent evaporated at room temperature for 48 hours. Co crystal solids stored in a desiccators under vacuum6.

Preparation of Cocrystal Using Slurry Method

KTZ and SA equimolar carefully weighed; 0.5314 grams and 0.1181 grams respectively. Both powder were mixed homogeneously with various solvent concentration added in mortar. Slurry method used water distilled as a solvent. Various solvent concentration added to the mixture mixed slurry samples formed as follows: 2%, 3%, 4%, 5% and 6% (w/w), it means waters added to the mixture mixed slurry samples formed as follows: 2 mL, 3 mL, 4 mL, 5 mL and 6 mL. The mixtures were gently mixed in mortar for 10 minutes. Co crystal formed was dried at room temperature for 48 hours. Co crystal solids stored in a desiccators under vacuum.

Physicochemical Characterization Co crystals

Differential Thermal Analyzer (DTA) was used to analyze the thermal properties. The DTA (Metller Toledo FP 85, Switzerland) was calibrated with indium before analysis. Certain amount of samples i.e. 5-7 mg samples were placed in a sealed aluminum pan. The analysis was performed in a temperature range of 50-300oC with heating rate of 10oC per minute.

Characterization By Powder X-Ray Diffraction

Method

Powder X-Ray Diffraction (Philips X'Pert Diffractometer) analysis performed at room temperature. Condition of measurement was set as follows: Cu metal target, Kα filter, voltage of 40 kV, 40 mA. Performed analysis on the range of 2θ (theta) of 5-40o. Sample placed on the sample holder and lattes to prevent particle orientation during preparation.

Characterization Using Fourier Transform Infrared Spectroscopy (FTIR)

Approximately 1% (w/w) dispersion of sample powder in potassium bromide (KBr) was prepared by mixing the sample powder with KBr. The infrared spectrum was obtained using infrared spectrophotometer (Spectrum One, Perkin Elmer) in wave length range 400-4000 cm-1.

PXRD Calibration Curve

Prepared calibration curve of co crystal with mixed physical mixture KTZ-SA equimolar and co crystal KTZ-SA equimolar at various percentage comparation as follows: (0/100), (10/90), (30/70), (50/50), (70/30), (90/10) and (100/0). A value percentage of zero percent is a KTZ-SA physical mixture of binary system and a hundred percent is KTZ-SA co crystalline phase. Both of mixed powders characterized with PXRD, choose the unique interference peaks or different peaks among co crystal, physical mixture and pure each component material, and than choose a unique peak with the highest maximum intensity made calibration curve of co crystal and calculated kinetics of co crystal. The calibration curve of co crystal plotted the value of maximum intensity (intensity-background) against percentage of co crystal in binary mixture. We get a value of linier regression equation ($y = ax \pm b$), a value of x showed co crystal percentages.

Kinetics Study of Co crystal Prepared with Slurry Method Using PXRD

The results of characterization prepared with slurry method used PXRD at each various solvent concentration were calculated maximum

intensity respectively to linier regression equation from calibration curve of co crystal.

RESULT AND DISCUSSION

Phase Diagram of Binary System

The phase diagram of KTZ-SA mixture was made using different molar ratio (i.e. (10:0), (9:1), (8:2), (7:3), (6:4), (5:5), (4:6), (3:7), (2:8), (1:9) and (0:10)) respectively presented in figure 2 and the result of DTA thermogram respectively presented in figure 1. KTZ melted at 152.4oC and SA melted at 192.3oC. The result showed two eutectics (E1 and E2), it means that the type of phase diagram of binary mixture is a congruently melted point of molecular compound (co crystal). First eutectic (E1) at molar ratio (3:7) has a melting point temperature of 143,9oC ΔH = 68.7 J/g and second eutectic (E2) at molar ratio (9:1) has a melting point temperature of 147,9oC ΔH = 56.0 J/g. KTZ melted at 152.4oC was decreased until minimum melting point temperature of E1 when it was added in SA into the mixture and melting point of E1 increased because SA added in the mixture until maximum melting point temperature of 164.7oC ΔH = 20.0 J/g, it was called congruently melting point of molecular compound7. Increasing the number of fraction mol of SA will further cause a decrease in melting point of binary mixture at minimum temperature of SA, it was called second eutectic (E2)

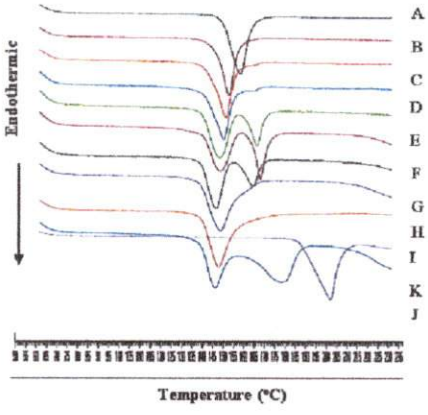

Figure 1: DTA thermogram KTZ (A), SA (K), KTZ-SA physical mixture (9:1) (B), (8:2) (C), (7:3) (D), (6:4) (E), (5:5) (F), (4:6) (G), (3:7) (H), (2:8) (I), (1:9) (J).

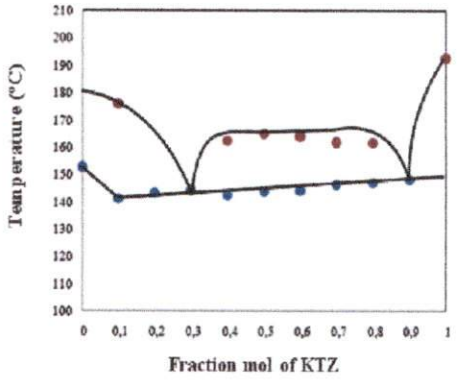

Figure 2: Phase diagram of binary system KTZ-SA with various compared of fraction mol.

DTA Analysis

DTA analysis was performed to characterize thermal behavior of KTZ-SA co crystal phase in relation to intact component and KTZ-SA physical mixture of binary system presented in figure 3. KTZ and SA showed a single endothermic peak at 152.4oC ΔH = 63.3 J/g and 192.3oC ΔH = 199.0 J/g respectively. KTZ-SA physical mixture showed two endothermic peaks at 143.5oC ΔH = 26.2 J/g and 164.7oC ΔH = 20.0 J/g . KTZ-SA co crystal showed only a single endothermic peak at 165oC indicated co crystalline phase formed between KTZ and SA5. It was occurred fusion of eutectic mixture in KTZ-SA physical mixture due to KTZ-SA co crystal phase5.

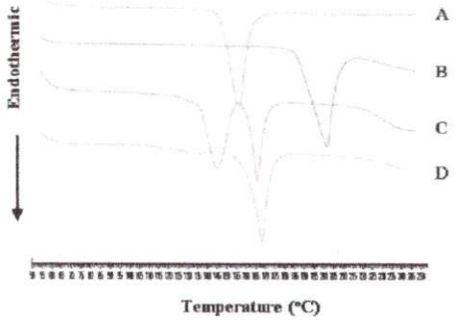

Figure 3: DTA Thermograms of KTZ (A), SA (B), KTZ-SA physical mixture (1:1) (C), KTZ-SA cocrystal (1:1) (D).

PXRD Analysis

PXRD analysis used to characterize a new crystalline phase formed in solid state and showed superposition of two materials, it means that there is an interaction between two materials, such as interactions between KTZ and SA in this case, the interactions may produce new diffraction peaks as compared the constituent materials6. In this case, PXRD analysis performed at the angle of 2θ = 5-50o. PXRD difractograms of KTZ, SA, KTZ-SA physical mixture (1:1) and KTZ-SA co crystal (1:1) solvent evaporation were showed at figure 4.

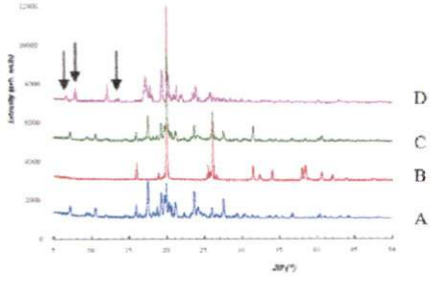

Figure 4: PXRD diffractograms of KTZ (A), SA(B), KTZ-SA physical mixture (1:1) (C) and KTZ-SA co crystal (1:1) (solvent evaporation) (D).

Based on these data, PXRD diffractogram of KTZ was showed at the angle of 2θ = 5.3o, 7.1o, 9.4o, 10.4o, 11.9o, 14.3o, 15.9o, 16.4o and 17.4o. PXRD diffractogram of SA was showed at the angle of 2θ = 15.8o, 16.0o, 18.0o, 18.8o and 19.9o. KTZ-SA physical mixture (1:1) diffractogram was specific angle of 2θ = 5.4o, 6.7o, 7.2o, 7.8o, 9.4o, 10.5o, 12.0o, 13.5o, and 14.6o. KTZ-SA co crystal (1:1) (solvent evaporation) diffractogram was specific angle of 2θ = 6.6o; 7.8o and 13.3o whereas no peaks were found in KTZ-SA physical mixture diffractograms,

FTIR Spectroscopy Analysis

FTIR spectroscopy analysis used to study the chemical and physical structure changed in the molecular structure of substance6. Infrared spectra of KTZ, SA, KTZ-SA physical mixture (1:1) and KTZ-SA cocrystal (1:1) solvent evaporation were showed at C=O, O-H and N-H stretch bend (figure 5). KTZ has a C-H alkana stretch bends at 2883 cm-1, C-H amine stretch bends at 1290, 1244, 1224, and 1201 cm-1, C-N stretch bends at 1546 and 1512 cm-1, C=O stretch at 1755 and 1647 cm-1, C=C aromatic stretch bends at 1647, 1546 and 1512 cm-1, C-Cl stretch bends at 815 cm-1, O-H stretch at 3448, 3176, 3118 and 2883 cm-1 and N-H stretch at 3448 cm-1. SA has a peak O-H stretch at bends 2931 cm-1, C-H alkana stretch at 2931 cm-1, C=O stretch at 1691 cm-1, C-C stretch at 1203, 1074 and 916 cm-1. The interactions of KTZ-SA were showed at 1755 and 1647 cm-1 referred peaks of C=O stretch from KTZ and at 1691 cm-1 referred peak of C=O stretch from SA shifted peaks 1710 and 1691 cm-1 referred peaks of C=O stretch from KTZ-SA physical mixture of binary system and shifted peaks at 1787 and 1714 cm-1 referred C=O stretch from KTZ-SA co crystalline phase. Second, the interactions of KTZ-SA were showed peaks at 3448, 3176, 3118 and 2883 cm-1 referred peaks of O-H stretch from KTZ and at 2931 cm-1 referred peaks of O-H stretch from SA shifted at 3431 and 2885 cm-1 for KTZ-SA physical mixture of binary system and shifted at 3421, 3271 and 2893 cm-1 for KTZ-SA co crystalline phase. The last, interactions of KTZ-SA were showed at 3442 cm-1 referred peak of N-H stretch, and there was no peak in SA, the peak of N-H stretch was appeared at 3431 cm-1 for KTZ-SA physical mixture of binary system and appeared at 3421 for KTZ-SA co crystalline phase8.

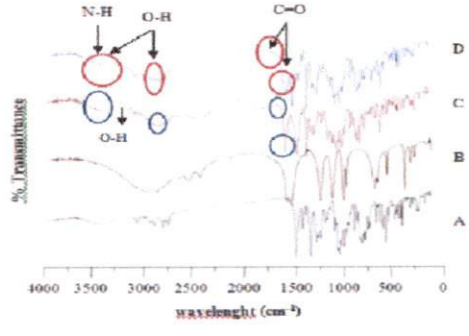

Figure 5: Infrared spectra of KTZ (A), SA (B), KTZ-SA cocrystal (1:1) (solvent evaporation) (C) and KTZ-SA physical mixture (1:1) (D).

PXRD Calibration Curve

Based on the data from PXRD diffractogram, KTZ-SA cocrystal (1:1) (solvent evaporation) diffractogram was specific angle of 2θ = 6.6o; 7.8o and 13.3o whereas no peaks were found in KTZ-SA physical mixture diffractograms, Selected a unique interference peak from three specific peaks from the angle of 2θ = 6.6o; 7.8o and 13.3o which have highest maximum intensity. The angle of 2θ = 6.6o; 7.8o and 13.3o have maximum intensity at 213, 620 and 151 respectively. The angle of 2θ = 7.8o was selected for a unique peak for making calibration curve and reference calculated kinetic study cocrystal KTZ-SA prepared with slurry method used PXRD data.

Calibration curve of cocrystal prepared with mixed physical mixture KTZ-SA equimolar and cocrystal KTZ-SA equimolar at various percentage compare as follows: (0/100), (10/90), (30/70), (50/50), (70/30), (90/10) and (100/0). Zero percent as KTZ-SA physical mixture of binary system and a hundred percent as KTZ-SA co crystalline phase. The results of PXRD diffractogram at various percentage compare were showed at figure 6. After that, calculated maximum intensity (intensity - background) for each percent of cocrystal and than prepared the calibration curve with plotted percent of cocrystal against maximum intensity of characteristic interference peak showed at figure 7 and table 1. WinPLOTR (version march 2007) software was used to determine the maximum intensity (intensity - background) in PXRD diffractogram.

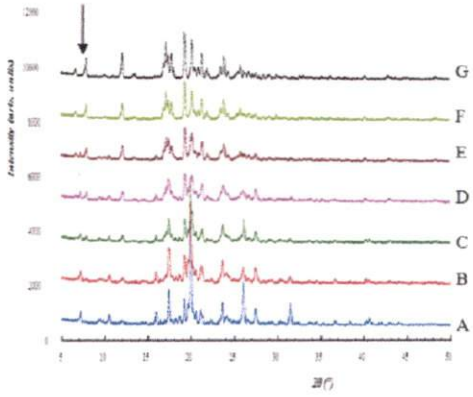

Figure 6: PXRD diffractograms of KTZ-SA mixed physical mixture of binary system and KTZ-SA co crystalline phase at various percentage of (0/100) (A), (10/90) (B), (30/70) (C), (50/50) (D), (70/30) (E), (90/10) (F) and (100/0) (G).

Table 17. Percent of maximum intensity cocrystal

% Cocrystal	0	10	30	50	70	90	100
Max. Int	0	75	146	275	362	468	620

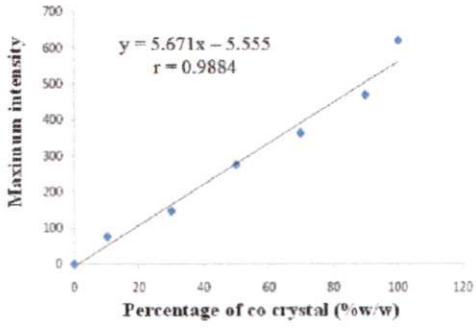

Figure 7: Calibration curve of percentage co-crystal in binary mixture against maximum intensity based on PXRD analysis data at the angle of (2θ = 7.8o).

Kinetics Study of Cocrystal Prepared with Slurry Method Using PXRD

Kinetics study of cocrystal prepared with slurry method using PXRD data from each various solvent concentration (i.e. 2%, 3%,

4%, 5% and 6% (w/w)) calculated with linier regression equation of maximum intensity calibration curve of percentage cocrystal, so we will get cocrystal percentage. PXRD diffractogram of slurry method was showed at figure 8. A good linier curve of percentage of solvent concentration prepared with slurry method obtained by plotting various solvent concentration against maximum intensity (figure 9 and table 2) and so do the curve of percentage cocrystal prepared with slurry method by plotting various solvent concentration against percentage of cocrystal (figure 10 and table 3). WinPLOTR (version march 2007) software was used to determine the maximum intensity (intensity - background) in PXRD diffractogram.

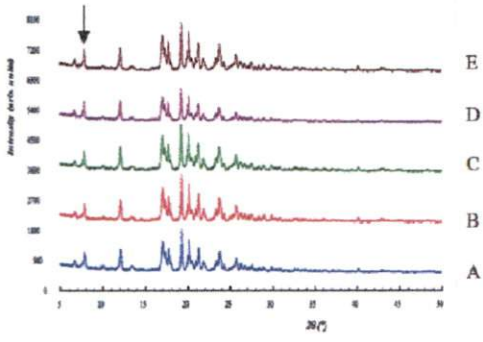

Figure 8: PXRD diffractograms of KTZ-SA slurry method with various solvent concentrations of 2% (A), 3% (B), 4% (C), 5% (D) and 6% (E).

Table 2. % Solvent concentration against maximum intensity.

% Solvent concent.	2	3	4	5	6
Max. Int	427	435	478	495	527

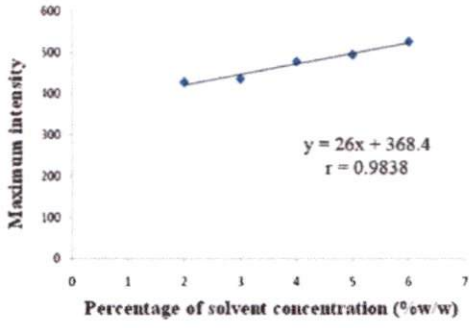

Figure 9: Curve of percentage solvent concentration (%w/w) prepared with slurry method against maximum intensity based on PXRD analysis data at the angle of (2θ = 7.8°).

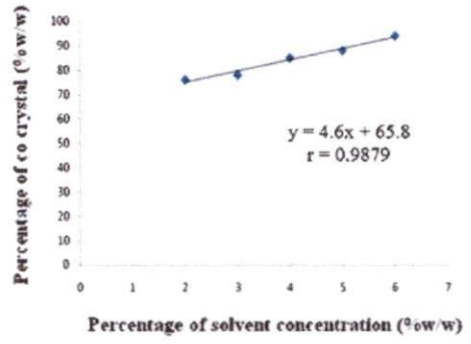

Figure 10: Curve of percentage solvent concentration (%w/w) prepared with slurry method against percentage of cocrystal (%w/w) based on PXRD analysis data at the angle of (2θ = 7.8°).

Table 3. Solvent concentration (%w/w) against cocrystal (%).

% Solvent	2	3	4	5	6
% cocrystal	427	435	478	495	527

Based on these data (figure 10 and table 3), the kinetics of cocrystals were determined based on PXRD analysis data. Cocrystal formed occur between contact of solvent activated with the molecular compounds of the energy added in the mixture during grinding both components (KTZ and SA) in mortar. So, increasing percentage solvent concentration was made contact activated with both molecular compounds increased so percentage cocrystal was produced faster. So that the number of cocrystal form were increased.

CONCLUSION

The kinetics study of cocrystals KTZ-SA prepared with slurry method were determined based on PXRD analysis data.

ACKNOWLEDGEMENT

The authors would like to thank for the advisors were given suggestion and support to finish this paper.

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