Volume 19 Nomor 2, Juli 2018 pISSN: 1411-5735 eISSN: 2442-5613

Jurnal ILMU DASAR

Terakreditasi SINTA Kemenristekdikti No. 21/E/KPT/2018

Jurnal ILMU DASAR	Vol. 19	No. 2	Hlm. 71 - 148	Jember Juli 2018	ISSN 1411-5735

Jurnal ILMU DASAR
FMIPA Universitas Jember
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eISSN 2442-5613 pISSN 1411-5735

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eISSN 2442-5613 pISSN 1411-5735

Vol. 19 No. 2 (2018)

Published: 2018-07-31

GENERAL

Phase Diagram and Thermodynamic Properties of Ketoprofen-Succinic Acid Binary Mixtures

Diagram Fase dan Sifat Termodinamik Campuran Biner Ketoprofen-Asam Suksinat

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ABSTRACT

The equilibrium phase diagram and thermodynamic properties of a mixture of drugs and additives are information related to various possible interaction processes between components. Therefore, we conducted a study of the phase diagrams and thermodynamic properties of binary mixtures of ketoprofen-succinic acid to estimate the types of interactions that may occur between these materials. The solid-liquid phase diagram of ketoprofen-succinic acid binary mixtures was determined by differential scanning calorimetry and composition of eutectic system was determined accurately using a Tamman diagram. The measurement of binary mixtures of ketoprofen-succinic acid with differential scanning calorimeter obtained the value of melting temperature and heat of fusion of ketoprofen- succinic acid system. The solid-liquid phase diagram of ketoprofen- succinic acid showed the formation of eutectic type phase diagram. The Tamman diagram showed accurately composition of the eutectic system of the Kp-SA binary mixtures at the mole fraction of Kp 0.87 and temperature 96.9°C.

Keywords: ketoprofen, phase diagram, eutectic system, Tamman diagram

INTRODUCTION

The drugs are often physically and chemically modified in order to improve its properties. In modifying the physical-chemical properties, the drugs are often combined with one or more other materials (Blasi et al. 2007, *Wicaksono et al. 2016, Wicaksono et al. 2017a). The* solids resulted from modifications by combining two or more components typically have significantly different physical or chemical properties with the original solid (Umeda et al. 2009, Ainurofiq et al. 2018). This is because the new solid is the result of interaction from various processes such as the formation of eutectic melts or stable chemical compounds. Information relating to possible interactions between components in pharmaceutical mixtures should be extracted from the equilibrium phase diagrams (Klimova & Leitner 2012). Therefore, the study of the phase diagrams and thermodynamic properties of mixture of drugs and additional ingredients is essential prior to the process of incorporation or modification (Klimova & Leitner 2012, Meltzer & Pincu 2012, *Wicaksono et al. 2017b).*

Ketoprofen (Kp) is a drug used as an analgesic, antipyretic and anti-inflammatory agent. It is a weak acid (pKa = 4.45) of propionic acid derivative that is slightly soluble in water. Kp has poor absorption and bioavailability related to its solubility in water (Patil et al. 2005, Shohin et al. 2012).

Modification of the physical-chemical properties of Kp to improve its solubility through incorporation with other ingedients has been frequently performed. The new modified solids by combining the Kp with other ingedients are solid dispersions (Salman et al. 2015) and multicomponent crystals (Vaghela et al. 2014). The additional ingredients used to combine with Kp are mannitol, urea, povidone, tween, cinnamic acid, maleic acid, nicotinamide, oxalic acid and p-amino benzoicacid (Khaleel et al. 2011, Vaghela 2014).

The purpose of the study was to investigate the phase diagram and thermodynamic properties of Kp and succinic acid (SA). SA is an inactive ingredient that classified as generally regarded as safe, so it is often used as a material for modifying the physical-chemical properties of the drugs (Felix-Sonda et al. 2013, Jung et al. 2014, Lahtinen et al. 2013). The results of the study are expected to be used to modify Kp by using SA as additional ingredients.

METHODS

Materials and Instruments

Kp (purity ≥98.7%) obtained from PT Dexa Medica (Palembang, Indonesia) and SA (purity ≥99.0%) purchased from Merck (Darmstadt, Germany). The instruments in experiment were analytical balance (Precisa ES 225SM-DR) and differential scanning calorimeter (Rigaku Thermo Plus EVO II).

Methods

Preparation of Kp-SA Binary Mixtures

The binary mixtures of Kp-SA were prepared with mole composition of Kp 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0, respectively. Each material before the mixing process sieved with 80 mesh size sieve to produce the particles in the same of size range. Subsequently each material was weighed according to the mole fraction ratio and carefully mixed using a mortar to produce a homogeneous mixture.

DSC Measurements

Each binary mixture of Kp-SA is transferred into aluminium crucibles (with lid rested on the sample) and then weighed approximately 2 mg using an analytical balance with precision of 10 µg. The DSC measurements were determined at temperature range 30–200 °C with heating rate 10 degrees per minute. DSC testing is done under conditions of dry nitrogen atmosphere..

RESULTS AND DISCUSSION

Solid-Liquid Phase Diagram

The solid-liquid phase diagram is formed from the results of DSC measurement of Kp, SA and the binary mixtures. The physical properties of Kp and SA results from testing with DSC are shown in Table 1. Kp and SA are pure materials where their DSC curves each have one peak showing melting point in accordance with the literature (*Wicaksono et al.* 2017b, Tita et al. 2011, Patel et al. 2012, Ober et al. 2012). Kp has a melting point at 96.1 °C with an enthalpy value ($\Delta_{fus}H$) 103.9 J/g. The DSC curve of SA showed an endothermic peak which indicated a melting point at 186.8 °C with an enthalpy value ($\Delta_{fus}H$) 327.8 J/g. In addition to the DSC curves, the thermograms of Kp and SA show only one endothermic peak, related to the melting event, which indicated that under the conditions used, the materials are stable and do not decompose (Trache et al. 2013).

Table 1. The Result of DSC Experiment of Kp and SA

Samples	T_f (°C)		$\Delta_{fus}H$ (J/g)	
	Experiment	Literature	Experiment	Literature
Kp	96.1	96.10 (*Wicaksono et al.* 2017b) 96.80 (Tita et al. 2011)	103.90	343.10 (Tita et al. 2011)
SA	186.8	187.60 (Patel et al. 2012) 191.30 (Ober et al. 2012)	327.80	168.00 (Ober et al. 2012)
Eutectic point	96.9	-	92.90	-

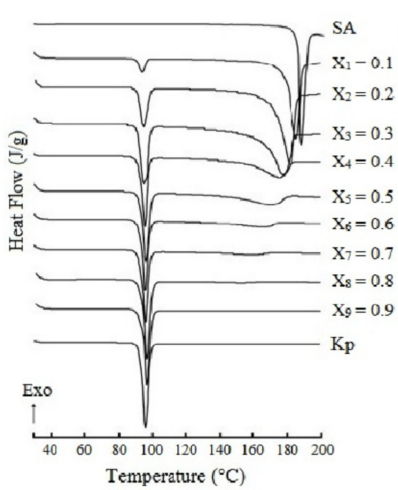

Figure 1. DSC curves of Kp, SA and binary mixtures of Kp-SA (Xn = mole fraction of Kp)

The overlay of the DSC curves of Kp, SA and Kp-SA binary mixtures is shown in figure 1. The DSC curves of the binary mixtures each showed the presence of two endothermic peaks. The first endothermic peak showed the melting point of the eutectic mixture and the second represented the melting point of the major component (Meltzer & Pincu 2012, Trache et al. 2013). The results of the DSC experiment of the Kp-SA binary mixtures are summarized in the table 2.

Table 2. The Melting Point and Enthalpy of Binary Mixtures of the Kp-SA binary mixtures

Mole fraction of Kp (X_n)	1st DSC peak		2nd DSC peak
	T (°C)	$\Delta_{fus}H$ (J/g)	T (°C)
0.0	-	-	188.5
0.1	94.6	18.3	185.4
0.2	95.1	34.8	181.7
0.3	95.3	53.9	177.5
0.4	95.9	64.6	175.0
0.5	96.3	73.0	170.2
0.6	96.1	81.2	166.3
0.7	96.1	91.2	159.3
0.8	96.9	105.1	152.1
0.9	96.9	92.9	96.9
1.0	-	-	96.1

The solid-liquid phase diagram of the Kp-SA binary mixtures is obtained from plotting the mole fraction of Kp against temperature (Sharma et al. 2012). Figure 2 showed the solid-liquid phase diagram of the Kp-SA binary mixtures. The curve of the solid-liquid phase diagram showed the formation of eutectic type phase diagram (Singh et al. 2014). From the solid-liquid phase diagram, the Kp-SA binary mixture considered exhibit a simple eutectic system. In this system, only solid phases as immiscibility mixture (S_1+S_2) exist below the solidus curve and only a liquid phase as complete miscibility mixture (L) exists above the liquidus curve. The areas between these curves show the equilibrium coexistence of both solid and liquid phases (Rice & Suuberg 2010, Sharma et al. 2012).

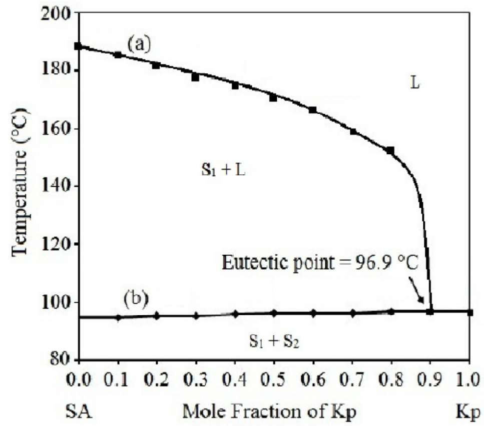

Figure 2. Solid-liquid Phase Diagram of Kp-SA Binary Mixtures (a) liquidus curve (b) solidus curve

The phase diagram of the Kp-SA has a eutectic point at 96.9 °C with mole fraction of Kp 0.9. The result showed that at high concentrations of Kp, eutectic formation is limited by the availability of SA. This means that addition of SA at low concentrations will lead to the formation of the eutectic phase. The transition liquid temperature of the binary mixtures of Kp-SA is indicated by solidus curve formed by the second endothermic peaks of each Kp-SA binary mixture. The solidus curve showed transition liquid temperatures of the Kp-SA binary mixtures at the temperature range of 96.9-188.5 °C.

Tamman Diagram

The eutectic system is a thermodynamically preferred phase which its formation limited by the stoichiometry system (Rice & Suuberg 2012). Based on this characteristic can be obtained more information from the enthalpy of fusion of the eutectic composition. The enthalpy data ($\Delta_{fus}H$) at eutectic temperature of each binary mixture can be used to arrange a characteristic triangle curve that known as Tamman diagram (Meltzer & Pincu 2012, Rice & Suuberg 2012).

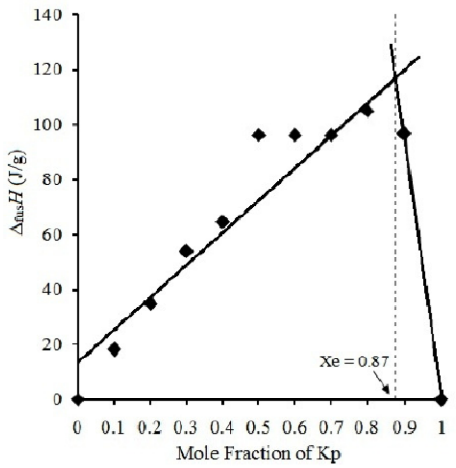

Figure 3. Tamman Diagram of Binary Mixtures of Kp-SA

From the solid-liquid phase diagram (Figure 2), the eutectic point is obtained at the 0.9 mole fraction of Kp. Therefore, the triangle curve of Tamman diagram is formed by linear regression of the $\Delta_{fus}H$ of binary mixtures 0.0-0.9 mole fraction of Kp and linear regression of the $\Delta_{fus}H$ of binary mixtures 0.9-1.0 mole fraction of Kp. The result of construction of Tamman diagram of the binary mixtures of Kp-SA is shown in Figure 3. From the Tamman diagram, composition of the eutectic system of the Kp-SA binary mixtures was obtained accurately at the mole fraction of Kp 0.87. Based on solid-liquid phase diagram (figure 2), temperature of the eutectic point at mole fraction of Kp 0.87 is 96.9 °C.

CONCLUSION

The DSC curve of Kp and SA indicates that both materials are stable and do not decompose under the conditions used. The curve of the solid-liquid phase diagram showed that the Kp-SA binary mixture formed the eutectic type phase diagram. The phase diagram showed that at high concentrations of Kp, formation of eutectic system is limited by the availability of SA. The Tamman diagram showed accurately composition of the eutectic system of the Kp-SA binary mixtures at the mole fraction of Kp 0.87 and temperature 96.9°C.

ACKNOWLEDGEMENT

This work was supported by Ministry of Research, Technology and Higher Education of the Republic of Indonesia through Doctoral Dissertation Research Grant (Hibah Penelitian Disertasi Doktor) under contract number 0553/UN25.3.1/LT/2017. Thanks to PT Dexa Medica for providing ketoprofen for this study.

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