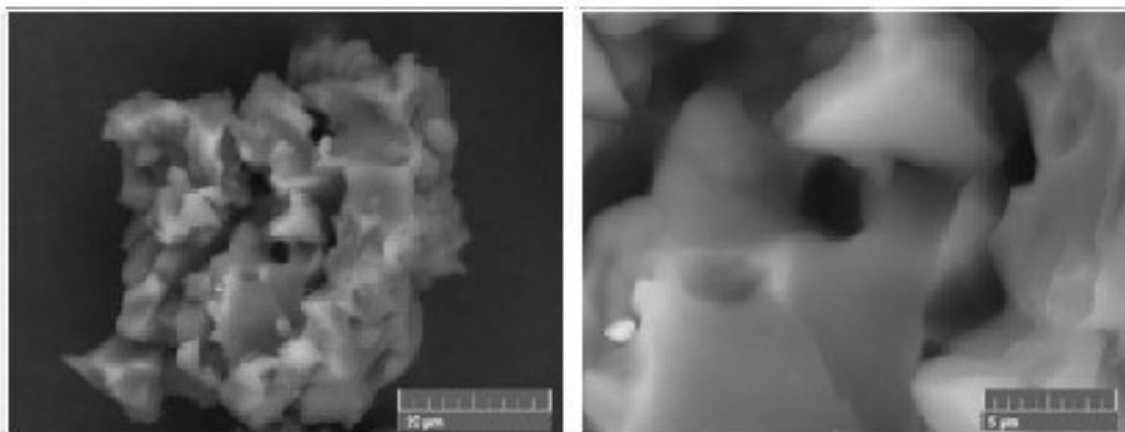




# Indonesian Journal of Chemistry































































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# Table of Contents

## Articles

<p><b>Adsorption of Remazol Brilliant Blue R Using Amino-Functionalized Organosilane in Aqueous Solution</b> <span style="float: right;">343-350  </span></p> <p> .....</p> <p> .....  Abstract views : 258    views : 103    views : 157</p>
<p><b>Bilayer-Structured Regenerated Cellulose/Chitosan Films Prepared with Ionic Liquid</b> <span style="float: right;">351-359 </span></p> <p> .....</p> <p> .....  Abstract views : 201    views : 153</p>
<p><b>A New Polyketide from the Endophytic Fungus</b> ..... <span style="float: right;">360-364 </span></p> <p> .....</p> <p> .....  Abstract views : 91    views : 46</p>
<p><b>Design and Optimization of Self Nano-Emulsifying Drug Delivery System Containing a New Anti-inflammatory Agent Pentagamavunon-0</b> <span style="float: right;">365-375 </span></p> <p> .....</p> <p> .....  Abstract views : 81    views : 38</p>
<p><b>Preponderance of Bioactive Medicinal Compounds and ATR-FTIR Spectroscopy of Coriander and Mustard Floral Honey from</b> ..... <span style="float: right;">376-384 </span></p> <p> .....</p> <p> .....  Abstract views : 57    views : 60</p>
<p><b>Recovery of Fermented Spinach (<i>S. .... sp.</i>) Concentrate Through Ultrafiltration Membrane Process as Source of Folic Acid for Smart Food Formula</b> <span style="float: right;">385-393 </span></p> <p> .....</p> <p> .....  Abstract views : 83    views : 59</p>
<p><b>Distribution and Source of Sedimentary Polycyclic Aromatic Hydrocarbon (PAHs) in River Sediment of Jakarta</b> <span style="float: right;">394-400 </span></p> <p> .....</p> <p> .....  Abstract views : 71    views : 41</p>
<p><b>Preliminary Study on the Synthesis of Phosphorylated Mung Bean Starch: The Effect of pH on the Physicochemical and Functional Properties</b> <span style="float: right;">401-406 </span></p> <p> .....</p> <p> .....  Abstract views : 57    views : 16</p>
<p><b>..... Leaf Extract for Green Synthesis of Silver Nanoparticles</b> <span style="float: right;">407-414 </span></p> <p> .....</p> <p> .....  Abstract views : 72    views : 50</p>
<p><b>PCR Primer Specific CaMV 35S Promoter to Detect Transgenic Soybean in Indonesia Commercial Soy Bean and Tempeh</b> <span style="float: right;">415-421 </span></p> <p> .....</p> <p> .....  Abstract views : 60    views : 53</p>
<p><b>Detection of Taste Change of Bovine and Goat Milk in Room Ambient Using Electronic Tongue</b> <span style="float: right;">422-430 </span></p> <p> .....</p> <p> .....  Abstract views : 86    views : 52</p>
<p><b>Influence of Macrocyclic Ring Size on the Corrosion Inhibition Efficiency of Dibenzo Crown Ether: A Density Functional Study</b> <span style="float: right;">431-438 </span></p> <p> .....</p> <p> .....  Abstract views : 116    views : 111</p>



**Investigation on the Effect of Addition of Fe<sup>3+</sup> Ion into the Colloidal AgNPs in PVA Solution and Understanding Its Reaction Mechanism**

439-445



Abstract views : 70 | views : 61

**Adsorption and Desorption of Na<sup>+</sup> and NO<sub>3</sub><sup>-</sup> Ions on Thermosensitive NIPAM-DMAAPS Gel in Aqueous Solution**

446-452



Abstract views : 83 | views : 40

**Synthesis of Fulvic Acid-Coated Magnetite (Fe<sub>3</sub>O<sub>4</sub>-FA) and Its Application for the Reductive Adsorption of [AuCl<sub>4</sub>]<sup>-</sup>**

453-460



Abstract views : 83 | views : 38

**The Development of Reproducible and Selective Uric Acid Biosensor by Using Electrodeposited Polytyramine as Matrix Polymer**

461-470



Abstract views : 55 | views : 76

**Synthesis of Zeolite-X Supported on Kapok Fiber for CO<sub>2</sub> Capture Material: Variation of Immersion Time during Fiber Activation**

471-476



Abstract views : 498 | views : 93

**Synthesis of Polyurethane/Silica Modified Epoxy Polymer Based on 1,3-Propanediol for Coating Application**

477-484



Abstract views : 93 | views : 69

**Thermodynamic and Thermomicroscopy Study of Atorvastatin Calcium-Succinic Acid Binary Mixtures**

485-490



Abstract views : 74 | views : 45

**New Trident Molecule with Phosphoric Acid Functionality for Trivalent Rare Earth Extraction**

491-499



Abstract views : 63 | views : 69

**The Addition of N-Butanol in Ethanol-Isooctane Mixture to Reduce Vapor Pressure of Oxygenated-Gasoline Blend**

500-508



Abstract views : 102 | views : 51

**Transesterification of Used Cooking Oil Using CaO/MCM-41 Catalyst Synthesized from Lapindo Mud by Sonochemical Method**

509-515



Abstract views : 76 | views : 43

**Determination of Effective Functional Monomer and Solvent for R(+)-Cathinone Imprinted Polymer Using Density Functional Theory and Molecular Dynamics Simulation Approaches**

516-522



Abstract views : 97 | views : 78

**Study of Proton Transfer and Hydration in Phosphorylated Nata de Coco**

523-530



Abstract views : 72 | views : 50

**Investigation of the Structural and Dynamical Properties of Cu<sup>+</sup> in Liquid Ammonia: A Quantum Mechanical Charge Field (QMCF) Molecular Dynamics Study**

531-537



Abstract views : 100 | views : 72

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## Thermodynamic and Thermomicroscopy Study of Atorvastatin Calcium-Succinic Acid Binary Mixtures

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### ABSTRACT

Binary mixtures of pharmaceuticals significantly affect the physical-chemical properties of each component. Understanding the behavior of pharmaceutical ingredients in binary mixtures will assist in formulating the pharmaceutical ingredients into good dosage forms. The aim of this work was to explore the thermal behavior and solid state transformation of binary mixture of atorvastatin calcium and succinic acid. The thermodynamics of binary mixtures were determined by differential scanning calorimeter. Meanwhile, thermomicroscopy and microstructure were determined by a polarized microscope. The results showed that melting points of atorvastatin calcium and succinic acid respectively were 159.35 and 188.51 °C. The solid-liquid phase diagram of atorvastatin calcium - succinic acid indicates the existence of two eutectic points at 136.57 and 120.96 °C respectively on the mole fraction of atorvastatin calcium 0.3 and 0.5. The Tamman diagram accurately shows mole fraction of atorvastatin calcium at eutectic point 0.33 and 0.46 respectively for eutectic points 130.0 and 134.0 °C. Determination of Jackson's roughness parameter showed the interfaces of all remelting crystals were smooth. The results can be used to modify the properties of atorvastatin calcium as well as the development of the formula into good pharmaceutical preparations.

**Keywords:** thermodynamic; atorvastatin calcium; binary mixtures; phase diagram

### ABSTRAK

Campuran biner bahan obat sangat mempengaruhi sifat fisika-kimia masing-masing komponen. Memahami perilaku bahan farmasi dalam campuran biner akan membantu dalam memformulasi bahan farmasi tersebut menjadi sediaan obat yang baik. Tujuan dari penelitian ini adalah mengetahui sifat panas dan transformasi padatan campuran biner kalsium atorvastatin dan asam suksinat. Termodinamika campuran biner kalsium atorvastatin-asam suksinat ditentukan dengan differential scanning calorimeter. Sedangkan termomikroskopi dan mikrostruktur ditentukan dengan mikroskop terpolarisasi. Hasil penelitian menunjukkan kalsium atorvastatin dan asam suksinat mempunyai titik lebur masing-masing 159,35 dan 188,51 °C. Diagram fase padat-cair dari kalsium atorvastatin-asam suksinat menunjukkan adanya dua titik eutektik pada suhu 136,57 dan 120,96 °C yaitu masing-masing untuk fraksi molar kalsium atorvastatin 0,3 dan 0,5. Diagram Tamman secara lebih akurat menunjukkan molar fraksi dari kalsium atorvastatin pada titik eutektik yaitu 0,33 dan 0,46 masing-masing untuk titik eutektik 130,0 dan 134,0 °C. Penentuan parameter Jackson's roughness menunjukkan antarmuka semua kristal adalah halus. Hasil penelitian dapat digunakan untuk memodifikasi sifat-sifat atorvastatin kalsium maupun pengembangan formulasi atorvastatin menjadi sediaan farmasi seperti yang baik.

**Kata Kunci:** termodinamika; kalsium atorvastatin; campuran biner; diagram fase

### INTRODUCTION

Pharmaceutical properties of mixture of substances are generally influenced by molecular interactions between components. Most studies have shown that interaction model among components of pharmaceutical

mixtures can be obtained from solid-liquid phase equilibrium and it is significantly different from physical and chemical properties of each component [1]. Therefore, investigations of solid-liquid phase equilibrium of mixture of substances are an important step for pharmaceutical development. With the phase

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diagram we can know the thermodynamic properties of the mixture relating to the interaction model that occurs between the components in the mixture. And this is an important data for the process of modification or formulation of a pharmaceutical ingredient. Recently, the various phase changes of binary mixtures of materials can rapidly be characterized by differential scanning calorimetry method [2].

The interactions between the molecules affect microstructure of their mixtures and are related to the value of enthalpy and entropy of fusion of pure substances and eutectic mixtures. Thus, value of entropy of fusion can be used to estimate the solid-liquid interface morphology of substance. The entropy of fusion is calculated base on Eq. 1 [3]:

$$\Delta_{\text{fus}}S = \frac{\Delta_{\text{fus}}H}{T_{\text{fus}}} \quad (1)$$

where  $\Delta S$  is the entropy of fusion,  $\Delta H$  is the enthalpy change and  $T$  is the melting temperature. The characters of growth morphology from melt of binary mixture depend on the nature of solid-liquid interface and can be predicted from value of entropy of fusion. The predicted structure is related to roughness factor known as Jackson's roughness parameter ( $\alpha$ ) and is closely related to entropy of fusion by the Eq. 2 [3]:

$$\alpha = \xi \frac{\Delta_{\text{fus}}H}{RT_{\text{fus}}} = \xi \frac{\Delta_{\text{fus}}S}{R} \quad (2)$$

where  $\xi \{T_c/T = (T - \Delta T)/T\}$  is a crystallographic aspect depending upon the geometry of the molecules; it usually has a value  $\leq 1$ .  $\Delta S$  is entropy of fusion, and  $R$  is gas constant. Smooth interface appears when  $\alpha > 2$  for both phases while the interface is rough and many sites if  $\alpha < 2$ .

Thermomicroscopy is a synergy of microscopy and thermal analysis to analyze the physical properties of materials as a responsibility of temperature and time. It allows characterization of little amount of substances to acquire solid-state properties of substances. In the field of pharmaceuticals, thermomicroscopy has been used to obtain visual and semi-quantitative data with respect to transition of pharmaceutical polymorphs. Therefore, thermomicroscopy is commonly used to support thermal analysis method of DSC [4].

Atorvastatin is a drug that is classified as statin group, used to reduce blood cholesterol levels [5]. There are 42 crystalline structures of atorvastatin [6]. However, chance to create atorvastatin into another polymorphic or different crystal structure is still fully open [7]. For this reason, verification of crystal phase and thermodynamic changes of atorvastatin in binary mixtures is important to do. Succinic acid (SA) is a dicarboxylic acid. In this research, it was used to form a binary mixture with atorvastatin because it is often used as ingredient in modification of pharmaceuticals [8]. The aim of this work

was to *explore* the thermal behavior and solid state transformation of binary mixture of atorvastatin calcium (AC) and succinic acid (SA). The results of the study are useful for the modification process in order to improve the properties of atorvastatin calcium and also for the formulation of atorvastatin calcium into ready-to-use pharmaceutical preparations such as tablets, capsules and others.

## EXPERIMENTAL SECTION

### Materials

Atorvastatin calcium (AC) was obtained from PT Dexa Medica (Palembang, Indonesia) and succinic acid (SA) was supplied by Sigma-Aldrich.

### Instrumentation

The instruments used were differential scanning calorimeter (Rigaku Thermo Plus EVO II), polarized microscope (Olympus BX41), camera (Olympus DP21), heating stage (Scilogex MS7-H550-Pro), and analytical balance (Precisa ES 225SM-DR).

### Procedure

#### Physical mixtures of AC and SA

AC and SA were sifted to obtain particle size in similar range and each was weighed according to desired mole fraction. These materials were mixed carefully using a mortar to form a homogeneous mixture [9].

#### DSC measurements

Physical mixtures of AC-SA at different composition were transferred into aluminium crucibles (with lid rested on the sample) and then weighed approximately 5 mg using a balance with precision of 10  $\mu\text{g}$ . The differential scanning calorimetry (DSC) measurements were determined at temperature range 30-200  $^{\circ}\text{C}$  with heating rate 10 degrees per minute. The dry nitrogen was used as atmosphere of experiments.

#### Microstructure

Each sample of AC and SA was placed on an object glass then heated to melt. The melt was covered with cover-slip and placed at room temperature in order to crystallize again. The crystal was observed by a polarized microscope equipped with a camera [3].

#### Thermomicroscopy

Thermomicroscopy was performed using a polarized microscope equipped with heating stage and camera. Each physical mixture of AC-SA with different

**Table 1.** Melting point and enthalpy of binary mixtures of AC-SA at different composition

Mole fraction of AC ( $X_1$ )	1 <sup>st</sup> DSC peak		2 <sup>nd</sup> DSC peak	
	T (°C)	$\Delta H$ (J/g)	T (°C)	$\Delta H$ (J/g)
0.0	-	-	188.51	320.77
0.1	128.24	1.06	167.54	38.12
0.2	123.48	12.67	156.91	0.12
0.3	136.57	46.44	136.57	-
0.4	122.24	58.58	153.10	0.22
0.5	120.96	47.78	120.96	-
0.6	123.05	42.74	151.37	0.16
0.7	132.42	15.52	149.48	5.61
0.8	152.94	13.85	160.79	7.00
0.9	153.45	17.66	160.92	15.21
1.0	-	-	159.35	101.90

composition was placed on an object glass and then heated at 30-180 °C. Phase transitions and eutectic point of sample were observed, and images were taken [4].

## RESULT AND DISCUSSION

### Solid-Liquid Phase Diagram

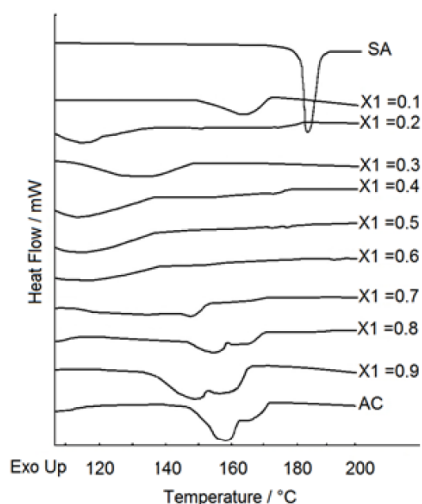
Phase diagram of binary mixtures of AC-SA was constructed from DSC curves of each pure substance and its binary mixtures. DSC curves of AC, SA and binary mixtures at different composition are shown in Fig. 1. DSC curves of each pure substance are showing only one endothermic peak, corresponding to its melting point. Binary mixtures of AC-SA have two endothermic peaks; the first peak appearing at lower temperature is attributed to melting point of eutectic composition and second one, at higher temperature, correlated with melting point of major component [3].

DSC curve of AC exhibited a sharp endothermic peak at 159.35 °C due to melting point of AC. The melting point of AC has enthalpy 101.90J/g confirming that crystal the substance of AC consists solely of form I [10]. The melting point of SA is 188.51 °C according to the literatures [11-12]. The melting point of AC decreased with additional mole fraction of SA and attained minimum melting point at 120.96 °C when the mixture had 0.5 mole fraction of SA. The melting point and enthalpy of binary mixtures obtained from DSC curves are presented in Table 1.

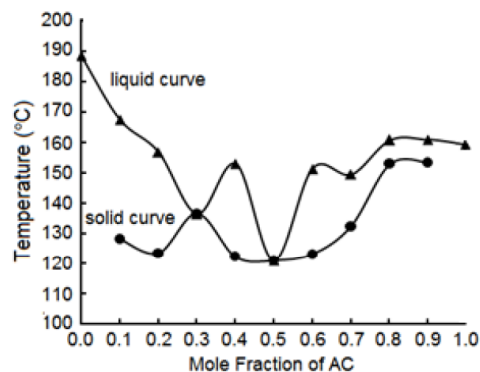
DSC curves of binary mixtures of AC-SA were used to create the solid-liquid phase diagram by plotting temperature versus mole fraction (Fig. 2). Phase diagram shows two eutectic points at temperature of 136.57 and 120.96 °C respectively on the mole fraction of AC 0.3 and 0.5.

This phase diagram is characterized as a congruent melting point that shows the binary mixture of AC-SA capable to form a cocrystal [13]. Phase diagram of cocrystal was a typical W-shaped phase diagram

exhibit two eutectic points and a cocrystal region between the two eutectic points [14]. Melting point and enthalpy of AC, SA and eutectic mixture of AC-SA are given in Table 2.



**Fig 1.** DSC curves of AC, SA and binary mixtures of AC-SA at different composition



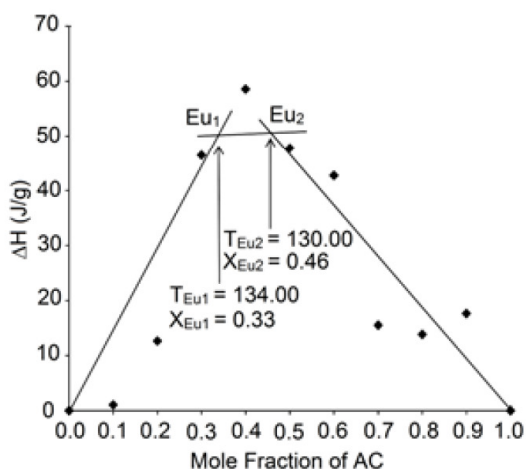
**Fig 2.** Solid-liquid phase diagrams of binary mixtures of AC-SA

**Table 2.** Melting point and enthalpy of AC, SA and eutectic mixture of AC-SA

Compound	$T_{fus}$ (°C)		$\Delta_{fus}H$ (Jg <sup>-1</sup> )	
	Experiment	Literature	Experiment	Literature
AC	159.35	158.80 [9]	101.90	86.85 [9]
SA	188.51	187.60 [10] 191.30 [11]	320.77	168.0 [11]
Eutectic 1	136.57	-	46.44	-
Eutectic 2	120.96	-	47.78	-

**Table 3.** The entropy of fusion and  $\alpha$  value of AC, SA and binary mixtures of AC - SA

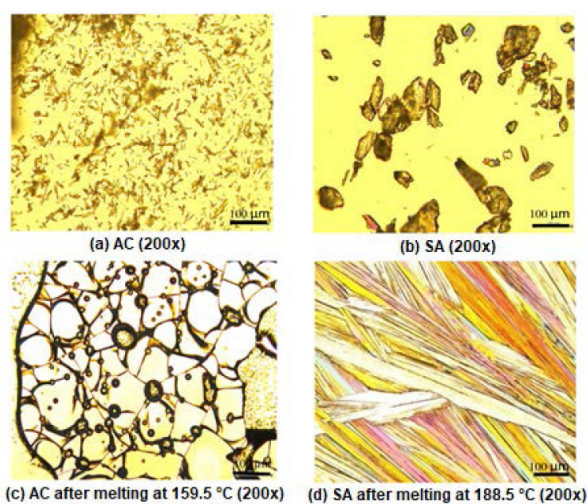
Compound	$\Delta_{fus}H$ (Jg <sup>-1</sup> )	$\Delta_{fus}H$ (kJ mol <sup>-1</sup> )	$T_{fus}$ (K)	$\Delta_{fus}S$ (J mol <sup>-1</sup> K <sup>-1</sup> )	$\alpha$
AC	101.90	123.24	432.50	284.95	35.03
SA	320.77	37.88	461.66	82.05	10.09
Eutectic 1	50.00	23.92	409.72	58.38	7.02
Eutectic 2	50.50	31.32	394.11	79.47	9.56

**Fig 3.** Tamman diagram of binary mixtures of AC-SA

Determination of eutectic composition can be significantly improved using Tamman diagram by plotting mole fraction of AC versus enthalpy  $\Delta H$  (J/g) of eutectic point of binary mixtures [15]. The results of plotting of Tamman diagram (Fig. 3) accurately show mole fraction of AC at eutectic point 0.33 and 0.46 respectively for eutectic temperature 130.0 and 134.0 °C. These results indicate that the mixture of AC and SA in the molar fractions of AC 0.33 and 0.46 gives the eutectic mixture with different physical properties with the origin components indicated by the decrease of the melting point of the mixture to 130.0 and 134.0 °C.

#### Microstructure

The values of entropy of fusion and of AC, SA and binary mixtures of AC - SA are presented in Table 3. Calculation of Jackson's roughness parameter shows that AC, SA and eutectic mixtures have  $\alpha$  value more than 2 which indicates that the interfaces of crystals are

**Fig 4.** Microstructure of AC and SA after melting

smooth. The microstructures of remelting crystal of AC and SA are shown in Fig. 4. Microstructure of remelting crystal of AC is irregular while SA crosses plates. Remelting crystal of AC has different types of shape which represents polymorphism. These results are in agreement with report that AC exhibits several polymorphic forms [16].

#### Thermomicroscopy

Thermomicroscopy of eutectic mixtures of AC-SA is shown in Fig. 5. The crystals of physical mixture of AC and SA are aggregated at room temperature at all compositions. All the samples have eutectic melting at 134 °C except binary mixture at mole fraction of AC 0.9. These results are consistent with the phase diagram indicated by eutectic melting of binary mixture at mole fraction AC 0.9153.45 °C. Thermomicroscopy of binary mixtures of AC-SA have eutectic mixtures at



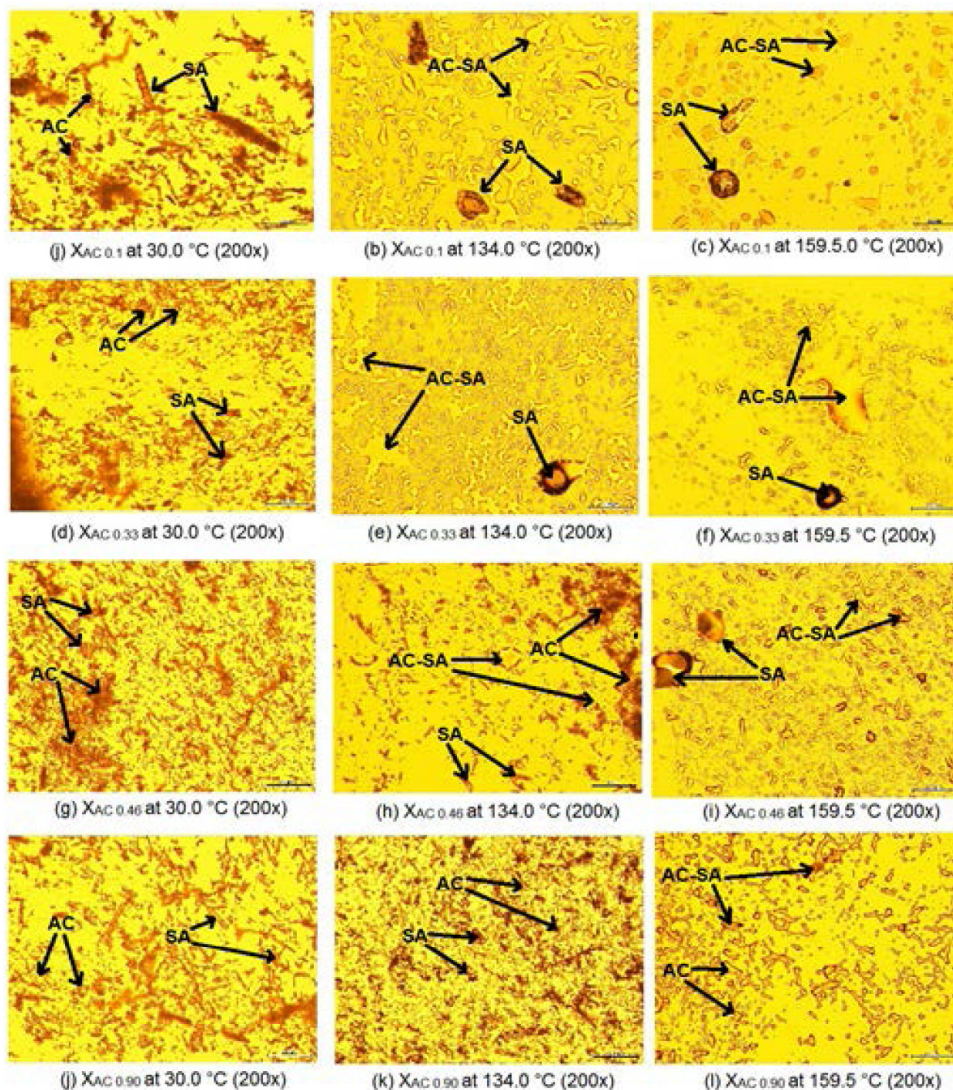


Fig 5. Thermomicroscopy of binary mixtures of AC-SA

mole fractions of AC 0.1, 0.33, 0.46, and 0.9 respectively at temperatures of 128.24, 136.57, 122.24, and 153.45 °C. At temperature of 159.5 °C, the eutectic mixtures in all samples are melting and mix with excess components in the mixture [17].

## CONCLUSION

Thermal behaviors of binary mixtures of AC-SA were investigated by DSC and thermomicroscopy technique. The phase diagram of AC-SA indicates the existence of two eutectic points at 134.00 and 130.00 °C respectively on the mole fraction of AC 0.33 and 0.46.

The values of Jackson's roughness parameter of AC, SA and eutectic mixtures were found greater than 2 which indicated smooth interfaces of remelting crystals. Thermomicroscopy of binary mixtures of AC-SA were consistent with the phase diagram

## ACKNOWLEDGEMENT

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