Journal of Thermal Analysis and Calorimetry, Vol. 95 (2009) 3, 891–894

THERMOSTABILITY AND POLYMORPHISM OF THEOBROMA OIL AND PALM KERNEL OIL AS SUPPOSITORY BASES

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Thermal stability of pharmaceutical ingredients is an important aspect. In this study, we adopted differential scanning calorimetry (DSC) to investigate thermal stability of suppository bases, theobroma oil (cocoa butter) and a palm kernel oil (PKO) blend. The study shows theobroma oil possesses six polymorphic forms whilst the palm kernel oil blend has three. Upon rescanning, the PKO blend does not show changes in the enthalpy of fusion and the melting point with time, whilst the theobroma oil shows significant reduction, and only regained its thermal stable state after 10 days. This indicates that PKO blend possesses better thermal stability.

Keywords: *cocoa butter, DSC, palm kernel oil, pharmaceutical, polymorphism, stability, suppository, theobroma*

Introduction

The ability of a molecule to crystallize into more than one arrangement is termed polymorphism and it has profound effect on the shelf life, solubility and formulation [1]. In fat polymorphism, it is the result of different lateral packing of the fatty acid chains and the longitudinal stacking of molecules in the lamellae [2]. Many studies have been conducted to investigate the polymorphism profile of various oil and fats products [3–6]. There are three main polymorphic organizations frequently observed in fat, where the arrangement of their molecules determine the thermal stability of the fat [7, 8]

Polymorphism in a fatty suppository base affects both the manufacturing process and the quality of the finished product, and this has been shown with theobroma as a suppository base [9]. For example, incorrect storage of theobroma (cocoa butter) based suppositories at an elevated temperature, such as above 30°C, causes the suppositories to melt. Upon cooling, the suppositories harden and metastable polymorphic forms appear, and this causes the suppositories to melt at a lower temperature. This problem will be further complicated if the incorporated drug is also prone to polymorphism [10].

The crystallization kinetics of fats including theobroma have been studied, however, the time required for the fats to regain their stable polymorphic forms after melting has not been widely reported [7, 8, 11–13]. In this study, we investigated the recovery time of theobroma and a palm kernel oil blend to their thermostable polymorphic forms. We also determined their suitability as suppository bases using differential scanning calorimetry (DSC), which is an important tool for the study of fat stability [14, 15].

Experimental

Materials

The hydrogenated palm kernel stearin (Batch No. 0091420002), palm kernel stearin (Batch No. 0091420002) and virgin palm kernel oil (Batch No. 0091420002) were obtained from Cargill (M) Sdn. Bhd., Kuala Lumpur, Malaysia. Theobroma (Batch No. BD.80.10HF01.0152) was supplied by KL Kepong, Kuala Lumpur, Malaysia. Other chemicals of analytical grade were obtained from either Sigma Chemical Company or Fisher Scientific, U.S.

Preparation of palm kernel oil suppository base

The palm kernel oil suppository base was prepared by mixing hydrogenated palm kernel stearin (50%), palm kernel stearin (20%) and virgin palm kernel oil (30%) using an Erweka mixer (Model No. AR 402, 45°C, paddle stirrer speed: 100 rpm). The blend was allowed to solidify at 25°C for one week and thereafter kept at 4°C until use.

DSC analysis

The differential scanning calorimeter (DSC 6, PerkinElmer, US) was connected to a chiller (C6, PerkinElmer, US) and a thermal analysis gas station

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1388–6150/$20.00

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(PerkinElmer, US) to control the flow of the purge gas, nitrogen at a flow rate of 20 mL min^{-1}. The DSC pans used were 50 μL aluminum pans (lids with holes), and indium and zinc (PerkinElmer, US) were used to calibrate the DSC. Each sample weighing between 2.5–4.0 mg (Mettler Toledo UMT2 Microbalance, Switzerland) was scanned from 3.5 to 70°C at 5 K min^{-1} using DSC to give the 'first melt DSC curve'. The sample was then cooled from 70 to 3.5°C at –5 K min^{-1}, followed by storage for 0, 15 min, 1, 2, 4, 32, 64 h, 5, 10, 20 or 30 days at 22.5°C before rescanned from 3.5 to 70°C at 5 K min^{-1} to give the 'remelt DSC curve'. The 'first melt' and 'remelt' scans were determined for each of the three individual samples at each storage condition for theobroma oil and palm kernel oil blend.

Results and discussion

The thermal profile of theobroma clearly shows the presence of 6 polymorphs, which concurs with the work reported by Loisel *et al.* (1998) [2], whilst an earlier report suggested the existence of between 4 to 6 polymorphs for cocoa butter [15]. The DSC curve shows that Form I polymorph melts at about 16°C followed by the crystallization of Form II before it melts at about 21°C. The Form III polymorph then crystallizes before melting at about 26°C followed by the crystallization of Form IV before it melts at about 29°C Form V then crystallizes and melts at about 33°C and this is followed by melting of the Form VI polymorph at 36.6°C, which gives a dominant peak compared to others (Fig. 1). After cooling, the same theobroma sample was subjected to immediate remelt, it produced one main peak (Form II) with a melting point of 18°C, and a smaller hump (Form III) at 26°C. Upon storage, the melting peak increased in temperature and only recovered to the original state after storage of 10 days or longer (Table 1 and Fig. 3). This clearly suggests upon melting the crystal structure of the theobroma only regains its original arrangement, thermal stable form after storage at 22.5°C for 10 days. Previously, Davis and Dimick (1989) [11] had reported an isothermal study on the crystallization

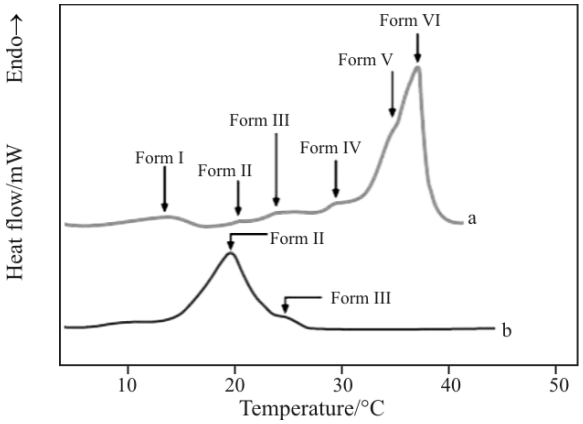

Fig. 1 Comparison of the DSC curves from the a – first melt and the b – immediate remelt (0 min storage) of theobroma. Arrows showing the melting peaks of the six forms of polymorphs

Table 1 The melting peak, enthalpy change of fusion and % difference of the enthalpy change of fusion compared to the first melt of theobroma and palm kernel oil blend samples after storage at time intervals at 22.5°C

Curves[#]	Storage time	Peak of melting/°C		Enthalpy change of fusion, ΔH/J g^{-1}		% difference of enthalpy change of fusion, ΔH relative to the first melt	
		Theobroma	PKO	Theobroma	PKO	Theobroma	PKO
a	First melt	36.6±0.3	32.6±0.4	111.9±4.3	102.1±2.6	–	–
b	0 min	20.1±0.2*	31.3±0.2	55.1±1.0*	98.3±1.7	56.8	3.7
c	15 min	15.5±0.4*	31.7±0.2	44.4±1.4*	98.9±1.9	60.3	3.1
d	1 h	27.8±0.3*	31.7±0.3	62.5±0.8*	100.9±2.0	44.1	1.2
e	2 h	27.8±0.4*	31.8±0.3	76.5±0.6*	101.1±1.3	31.6	1.0
f	4 h	27.9±0.4*	31.8±0.3	81.5±0.7*	101.5±1.3	27.2	0.6
g	32 h	32.7±0.3*	31.8±0.6	102.0±0.4*	101.6±2.0	8.8	0.6
h	64 h	32.8±0.4*	31.9±0.3	102.8±0.5*	101.6±0.6	8.1	0.5
i	5 days	32.9±0.2*	31.9±0.6	103.7±0.4*	101.7±0.3	7.3	0.4
j	10 days	33.1±0.1*	31.9±0.1	106.0±1.2	101.9±2.0	5.3	0.3
k	20 days	33.4±0.4	32.0±0.5	111.6±1.6	102.4±2.0	0.2	0.3
l	30 days	33.3±0.4	31.1±0.4	111.0±2.8	102.4±2.6	0.8	0.3

[#]Representative curves are as depicted in Fig. 3. Each value was expressed as mean (n=3)±SD. PKO: Palm kernel oil blend. Independent Student's t-test: * p<0.05 compared to the first melt

characteristics of isolated seed crystals of theobroma at interval of 0 to 21 h. However, the recovery time to thermal stable form had not been reported.

Tan and Che Man (2000) [16] in their study found that there are 4 polymorphic forms for pure PKO, but our study on the PKO blend indicates the existence of 3 polymorphs in the first scanning using DSC. The second scan shows a single peak, close to the original Form II polymorph peak. The difference in the melting point of this peak compared to the Form III peak from the first scan is small (1.9±0.2°C) (Fig. 2). As with theobroma, the palm kernel oil blend was kept at 22.5°C for various time intervals before being rescanned. However, unlike theobroma, the enthalpy change of fusion for palm kernel oil blend between the first melt and subsequent remelts were found to be statistically similar (Fig. 3 and Table 1) (p>0.05). Similar studies on palm kernel oil have not been reported, except Siew *et al.* (2000) [17] had investigated the thermal characteristics of palm olein upon short (2 months) and prolong (2 years) storage.

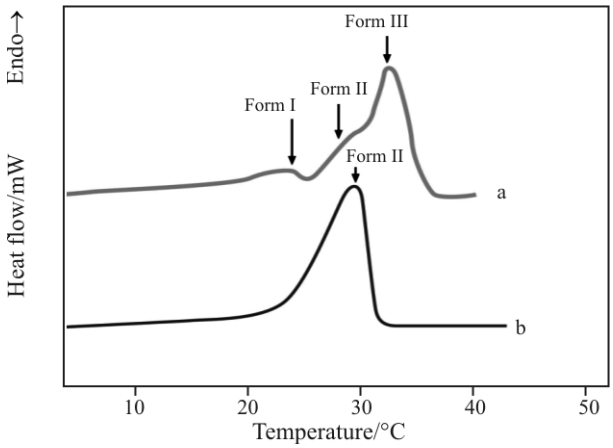

Fig. 2 Comparison of the DSC curves from the a – first melt and the b – immediate remelt (0 min storage) of a selected palm kernel oil blend. Arrows showing the melting peaks of the three forms of polymorphs

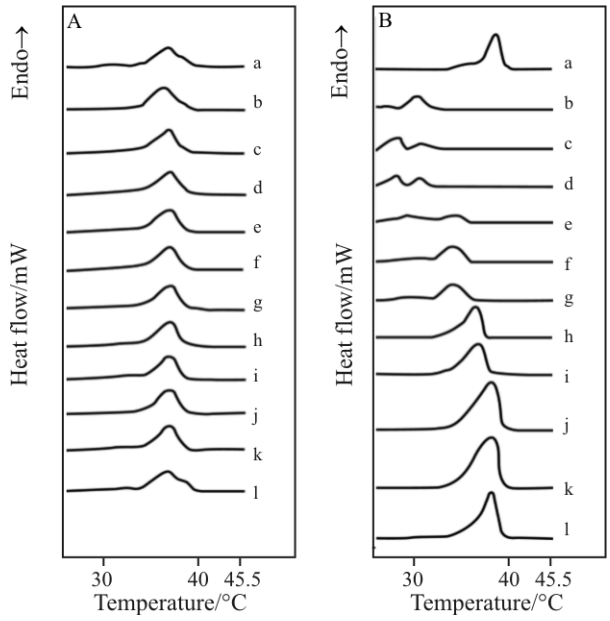

Fig. 3 Representative DSC curves of A – palm kernel oil blend and B – theobroma with various storage time intervals at 22.5°C. a – First melt, b – 0 min storage, c – 15 min storage, d – 1 h storage, e – 2 h storage, f – 4 h storage, g – 32 h storage, h – 64 h storage, i – 5 days storage, j – 10 days storage, k – 20 days storage, l – 30 days storage

The melting range for theobroma is higher but narrower (34–39°C) compared to that of palm kernel oil blend (27–35°C). This suggests unlike complete melting of palm kernel oil, this theobroma oil may not afford complete melting in the rectum, as the rectal temperature is 35–36°C, and this may lead to incomplete release of drug.

Conclusions

The study supports the use of DSC as a simple method to investigate the thermal stability and polymorphism of suppository bases. It also indicates palm kernel oil blend as a superior alternative to theobroma as a suppository base, as it is more thermal stable, and hence, more robust to temperature change during preparation and storage.

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Received: March 21, 2008
Accepted: June 24, 2008
OnlineFirst: October 12, 2008

DOI: 10.1007/s10973-008-9152-6