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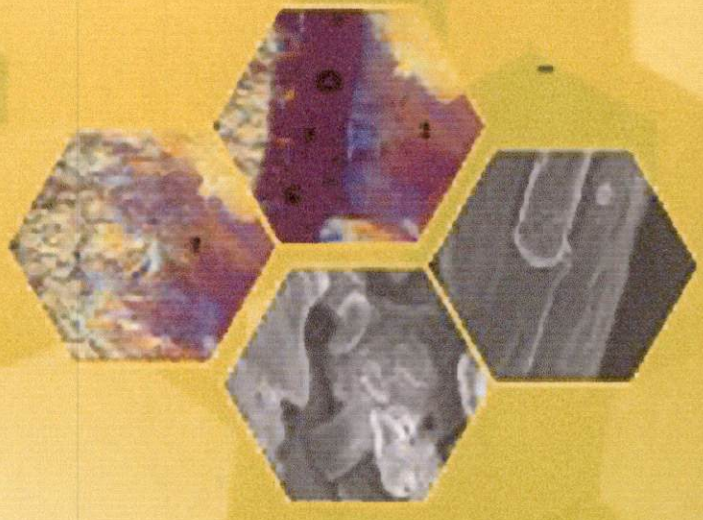

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Research Article

PHYSICAL CHARACTERIZATION OF IBUPROFEN-STEARIC ACID BINARY MIXTURE DUE TO COMPRESSION FORCE

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ABSTRACT

Aim of this research is to determine physical characteristic of ibuprofen-stearic acid due to compression force. Binary mixture of ibuprofen-stearic acid with weight ratio of 4:6, 5:5, and 6:4 was compressed under various compression force using hydraulic press with 13mm diameter flat punch. Identification of solid state interaction between these two components was performed by Hot Stage Microscopy (HSM). Physical characterization was studied using Differential Thermal Analysis (DTA), X-ray Powder Diffraction (XRPD), Scanning Electron Microscopy (SEM), and Fourier Transform Infrared (FT-IR) spectroscopy. According to hardness measurement, 4:6 weight ratio has the highest tensile strength on 170.6N/cm^2 under 19.93kN compression force. Interaction identification by HSM showed single blank line that indicates eutectic formation. Thermal analysis of DTA also revealed eutectic formation upon compression which the endothermic peak of ratio of 4:6 has the lowest melting temperature of 53.2°C. X-ray diffraction of three peaks generally showed that peak intensity decreases as compression force increases, but at particular point it begins to increase again. Sintering phenomenon at the surface of compressed tablet was observed from SEM analysis. FT-IR study confirms the formation of simple eutectic.

Key words: ibuprofen, stearic acid, binary mixture, compression force, physical characterization

INTRODUCTION

Tablet are the most widely used solid dosage form with several advantages in term of administration, formulation, and manufacturing (Yoshinari *et al.*, 2003).Tablet quality depends on formulation and process during manufacturing. Tablet manufacturing process produces thermal and mechanical energy which possibly results in physical interaction amongst components used (Hosaka *et al.*, 2005). During tablet compression, interaction can undergo between active substances, active substance with excipient, or between excipients. Crystal lattice arrangement followed by deformation or fracture can undergo during tablet compression (Bandyopadhyay *et al.*, 2005).

Ibuprofen is one of antipyretic drugs extensively produced in tablet dosage form. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) derivative of propionic acid with a melting point of 77°C (Ali *et al.*, 2010). Stearic acid is a tablet lubricant with melting point of 57.23°C (Wang *et al.*, 2010). Eutectic is known to be formed on ibuprofen-stearic acid binary mixture that is seen on phase diagram studied by Differential Scanning Calorimetric (DSC) (Lerdkanchanaporn *et al.*, 2001).

Eutectic is a mixture of one component on another. Eutectic can be formed unintended during manufacturing process, e.g. wet granulation and compression (Bi *et al.*, 2003). Compression force is known to lead to the change on the properties of drug substance and excipients such as particle size, specific surface area, crystallinity, polymorphism, crystal habit; lead to sintering and eutectic interaction (Yoshinari *et al.*, 2003; Setyawan *et al.*, 2011; Bi *et al.*, 2003). Compression force drives eutectic formation by intimate contact facilitation and decrease of thermal contact resistance that reduce separation and facilitate heat transfers. Unintentional eutectic formation on tablet dosage forms have been reported to cause unwanted changes of characteristics of tablets such as sticking, unpredictable hardness, and instability (Bi *et al.*, 2003). Zalac *et al.* (1998)

reported that wet granulated tablet formulation containing eutectic compounds of paracetamol and propyphenazone has disadvantage properties that the tablet unacceptably softened after storage at 40°C and 75% relative humidity for one month, although it was still stabile chemically.

On knowing thermally-induced eutectic formation between ibuprofen and stearic acid, this research was conducted to identify effect of compression force upon binary mixture of the eutectic compounds and determine its physical characteristics.

MATERIAL AND METHODS

Ibuprofen was purchased from Shasun Chemicals and Drugs Ltd., India, batch no. IBU0603674. Stearic acid was purchased from Hense Chemicals Manufacture Ltd., China.

Binary mixture of ibuprofen and stearic acid was prepared with weight ratio of 4:6, 5:5, and 6:4. Eutectic samples were obtained by compression using a 13mm flat punch hydraulic press on compression forces of 4.9, 9.9, 19.9, 24.9, and 28.9kN.

Hot stage microscopy study

Hot stage microscopy was conducted using polarizing microscope equipped with hot stage. The observation was made by first melting a small amount of the higher melting component on microscope slide to occupy about half the area under cover slip. After the first component had cooled and solidified, the lower melting component stearic acid was placed at the edge of cover slip near the first component, then the sample was heated until the stearic acid melted completely and contacted with the first component. Once the sample cooled and solidified, the temperature was raised gradually during the observation.

Mechanical properties

Five hundred (500) mg of each pure component and binary mixture was compressed with different applied force for 10s. Compressed tablets were stored in desiccator for 2 days for elastic recovery. Thickness and diameter were measured for each tablet. Hardness of tablets was measured using Erweka hardness tester. Tensile strength (σ) (kgf/cm^2) was calculated using following equation (Wu *et al.*, 2005).

$$\sigma = 2F / \pi D t$$

where, F= hardness (kgf), D= tablet diameter (cm), and t= thickness (cm).

Differential thermal analysis study

Differential thermal analysis was performed on differential thermal analyser (Mettler Toledo FP 85, Switzerland). ±5mg of each sample was heated in hermetically sealed aluminium pans with heating rate of 5°C/min at temperature of 30-200°C.

X-ray powder diffraction study

X-ray powder diffraction patterns were obtained using an X-ray powder diffractometer (Phillips X'Pert, Netherland) with CuKα radiation (1.54Å), at 40kV and 30mA, passing through a nickel filter with a divergence slit (0.25°C), antiscattering slit (0.5°C), receiving slit (0.15mm). Samples were scanned at rate of 2.4°C/min, over the 2θ range of 5-50°C. Obtained diffractograms were analysed with Winplotr diffraction software.

Scanning electron microscopy study

Scanning electron-micrographs of tablet surface of compressed pure components and binary mixture were obtained using a Hitachi TM3000, Japan, with magnifications of 1000.

Fourier transform infrared spectroscopy study

FTIR spectra were measured using a Shimadzu 8400s FTIR spectrometer, Japan. Samples were dispersed in potassium bromide powder and compressed on 29.4kN forces by a hydraulic press to form transparent disc. Each sample's spectrum was recorded from 4000 to 450cm^{-1}.

RESULTS AND DISCUSSION

Hot stage microscopy study

Hot stage microscopy is a simple technique to identify the type of physical interaction between two compounds by observation of phase behaviour upon heating. Crystalline phases direct the polarized light so that it will be seen under polarizing microscope with certain colour and intensity in regard to fragment orientation, thickness, and the absorbed polarized light by crystalline

fragment. In other hand, liquid phases allow the light to pass through unchanged so no light reaches microscope (Davis *et al.*, 2004; Zaini *et al.*, 2011). Thus, it will be recognized as a black line or region as crystalline phases melt to form liquid phases (Davis *et al.*, 2004).

Phase behaviour of ibuprofen and stearic acid is shown in Figure 1. Re-crystallized phase of ibuprofen is marked by number 1, re-crystallized phase of stearic acid is by number 2, and contact area is by number 3. It's clearly seen that contact area of two components is melted first than the pure component as temperature raised (Figure 1 B), leaving single blank line between crystalline phases.

In the occurrence of eutectic interaction, the contact area of two compounds exhibits different melting behaviour with lower melting point compared to the pure compounds. If a simple eutectic is formed, single blank line would be observed in the contact area when the temperature is raised (Davis *et al.*, 2004). Result shown in Figure 1 indicates formation of eutectic, the simple one, between ibuprofen and stearic acid and confirms result of previously conducted experiment (Lerdkanchanaporn *et al.*, 2001).

Simple eutectic (conglomerate mixture) has reported to be formed on hot stage microscopy study of trimethropim-nicotinamide conducted by Zaini *et al.* (2011). It was observed in the contact area new habit crystal distinguished from habit of pure compounds and it melted first as the sample was reheated, followed respectively by nicotinamide and trimethropim crystalline phase (Zaini *et al.*, 2011).

Mechanical Properties

Mechanical properties from the elastic modulus curve are shown in figure 2. Both pure compounds exhibit highest tensile strength at 19.9 kN compression force. The binary mixtures follow the same pattern with different tensile strength values and the highest one is binary mixture of 4:6 weight ratio. Since ibuprofen and stearic acid are hydrophobic substances due to long fatty acid chain, its binary mixture may have higher compactibility that results in uncontrolled tablet hardness (Bi *et al.*, 2002; Bergman *et al.*, 1965; Adeyeye and Brittain, 2008). According to figure 2, tensile strength value tends to increase in the binary mixture compared to the pure compounds. This is probably because the binary mixture forms eutectic (will be discussed further in thermal analysis) which has more plastic properties (Bi *et al.*, 2003). So, it can be concluded that compressed 4:6 weight ratio binary mixture is the most plastic characteristic.

The same result is also obtained with binary mixtures of acetaminophen-caffeine anhydrous and acetaminophen-prophylphenazone investigated by Bi *et al.* (2003). Each binary mixture is known to form eutectic, in different % formed, under compression, and the tablet properties study resulted in eutectic has no negative effect of eutectic on tablet hardness.

Based on the elastic modulus curve, binary mixture of 4:6 weight ratio and its compressed tablet under 19.9kN force is chosen for further physical characterization.

Differential Thermal Analysis

DTA analysis showed melting point of compressed ibuprofen and compressed stearic acid at 19.9kN is 78.7°C and 59.4°C respectively, and enthalpy energy of 95.3J/g and 116J/g respectively (Figure 3). Compressed 4:6 weight ratio binary mixture of ibuprofen-stearic acid gives single different endothermic peak compared to the pure components with lower melting point at 54.1°C. It confirms eutectic formation of ibuprofen-stearic acid even under compression. Melting point depression and high modulus elasticity curve of the compressed binary mixture shows physical interaction of these two components that may cause crystallinity change in its mixture (Zaini *et al.*, 2011; Putra *et al.*, 2012).

X-Ray Powder Diffraction Study

X-ray diffractions of binary mixture of 4:6 weight ratio under various compression forces are shown in figure 4. Three specific peaks at 2θ = 6.4°, 16.8° and 23.8° is used for calculation of peak intensity. Figure 5 shows that the intensity value decreases with the increasing of compression force. However,the intensity increases generally at high compression force over than 14.9kN. Intensity represents strength of lattice preferred orientation.

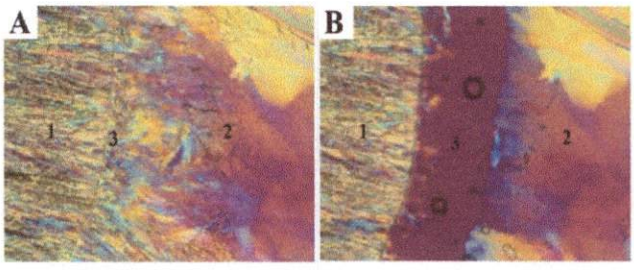

Figure 1. Observation of mixed fusion behaviour of ibuprofen and stearic acid, A. Formation of contact area, and B. First melting of contact area, (1= ibuprofen, 2= stearic acid and 3 = contact area)

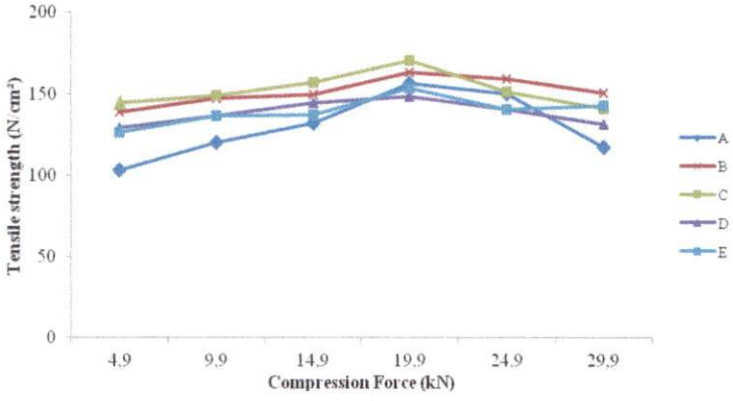

Figure 2. Elastic modulus of A. Ibuprofen, B. Stearic acid, C. Ibuprofen-stearic acid weight ratio of 4:6, D. 5:5, and E. 6:4.

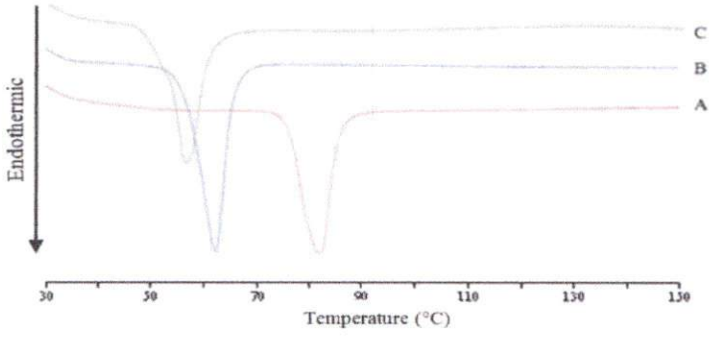

Figure 3. DTA thermograms of A. Ibuprofen, B. Stearic acid, C. Compressed binary mixture of ibuprofen-stearic acid of 4:6 weight ratio at 19.9kN.

It can be predicted that crystallite breaks after compression at low force (4.9kN), but the crystallite's breakage fills the void space between adjacent crystallites at high compression force (19.9kN), result in increasing lattice order (Rippi *et al.*, 2000).

Scanning electron microscopy study

SEM was used to evaluate the surface morphology of compressed pure components and its binary mixture of 4:6 weight ratio. It was observed that bar-shaped crystal habit of ibuprofen still remains on compressed tablet

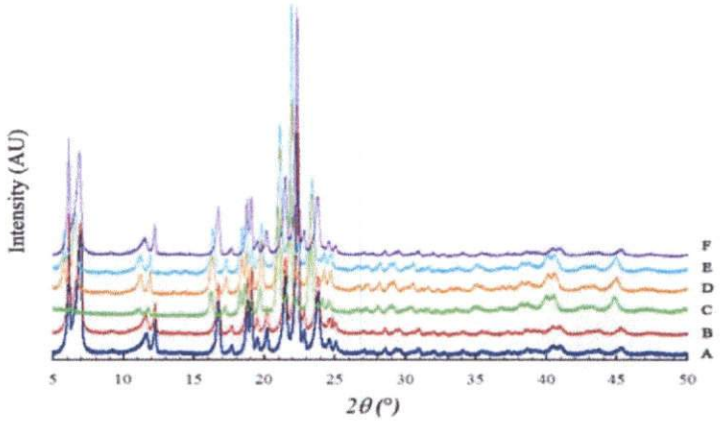

Figure 4. X-ray diffractograms of 4:6 weight ratio ibuprofen-stearic acid binary mixture under compression force of A. 4.9kN, B. 9.9kN, C. 14.9kN, D. 19.9kN, E. 24.9kN, and F. 29.9kN.

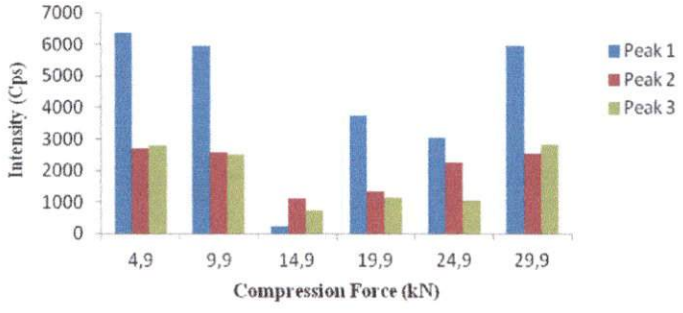

Figure 5. Intensity of three specific peaks of compressed 4:6 weight ratio ibuprofen-stearic acid binary mixture under different compression force.

(Figure 6C). However, sintering phenomenon was observed in compressed stearic acid as it losses surface border of the plate-shaped habit (Figure 6D). It was also observed on compressed binary mixture (Figure 6E).

Sintering phenomenon under compression is generally explained by impact of temperature increase due to interparticle friction during compression. The component with lower melting point melts and facilitates sintering at temperature above lower melting component by causing rearrangement of solid particle sliding over each other. After the heat and the pressure are removed, solidification occurs and results in solid bonds formation between particles in compressed tablet (Swarbrick and Boylan, 1996).

The effect of sintering on compact powder has known to cause microstructure changes as the sample of ibuprofen was compressed at force of 215kgf/cm^2 (21kN/m^2) and heated at 70°C for 24h. Coalescence of deformed particles occurred on the surfaces of the compact within microscopic observation (Swarbrick and Boylan, 1996). Sintering was also reported for compressed erythromycin stearate at various compression forces (Setyawan *et al.*, 2011). It was seen on scanning electron micrographs that particles of erythromycin stearate loss its surface boundary even at low force of 4.9 kN and fuse with the adjacent at higher force.

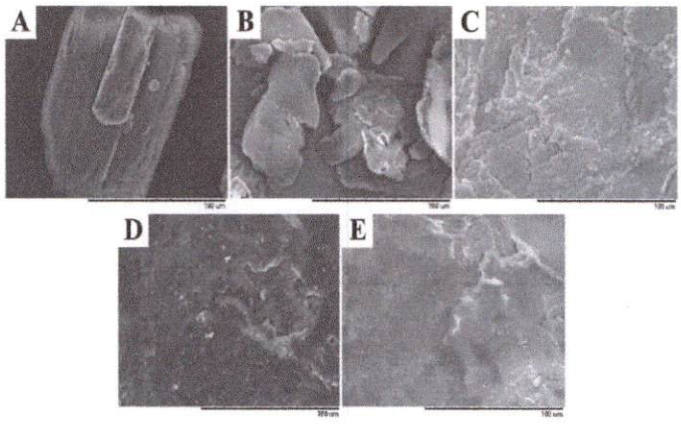

Figure 6. Scanning electron micrographs of A. Ibuprofen, B. Stearic acid, C. Compressed ibuprofen at 19.9kN, D. Compressed stearic acid at 19.9kN, and E. Compressed 4:6 weight ratio binary mixture of ibuprofen-stearic at 19.9kN.

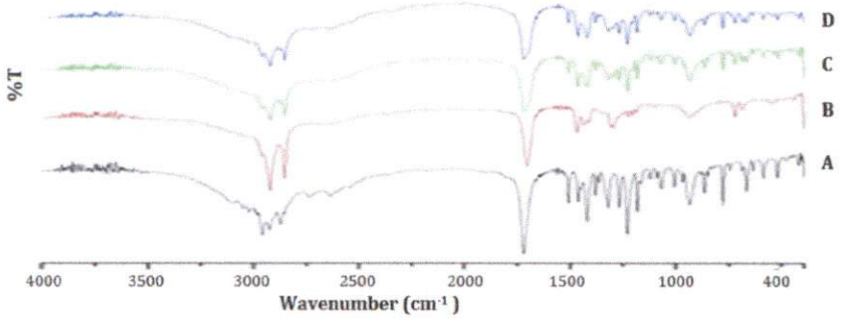

Figure 7. FT-IR spectra of A. Ibuprofen, B. Stearic acid, C. Binary mixture of 4:6 weight ratio, and D. Compressed binary mixture of 4:6 weight ratio at 19.9 kN

Fourier transform infrared spectroscopy study

Figure 7 shows FT-IR spectra of pure components and its binary mixture of 4:6 weight ratio. Ibuprofen gives sharp specific peak of C=O group at 1720cm^{-1} and broad peak at OH group's region. Stearic acid yields sharp peak at 1703cm^{-1} for C=O group and two sharp peaks at 2917 and 2848cm^{-1}. Compressed and uncompressed binary mixture depicts no significant difference of peak transmission as it's seen to be superimposed to each other. New hydrogen bond involving OH and C=O group can be detected if change in intensity and peak take place (Putra *et al.*, 2012). Thereupon, it can be concluded that upon compression ibuprofen and stearic acid binary mixture undergoes simple eutectic.

CONCLUSION

Physical interaction of eutectic formation between ibuprofen and stearic acid had been characterization. The physical interaction is formed under compression force, which is supported by mechanical properties and thermal analysis of the compressed binary mixture that shows higher compactibility than the pure components and new single endothermic peak at 54,1°C, respectively. Physical interaction due to compression is also confirmed by increasing X-ray diffraction peak intensity at high compression f orce, sintering phenomenon, and not involving new hydrogen bonding based on FT-IR study. Due to eutectic interaction can occur by compression and gives different physical characteristics, it's essential to

pay more attention on formula and technology involved in tablet manufacturing.

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