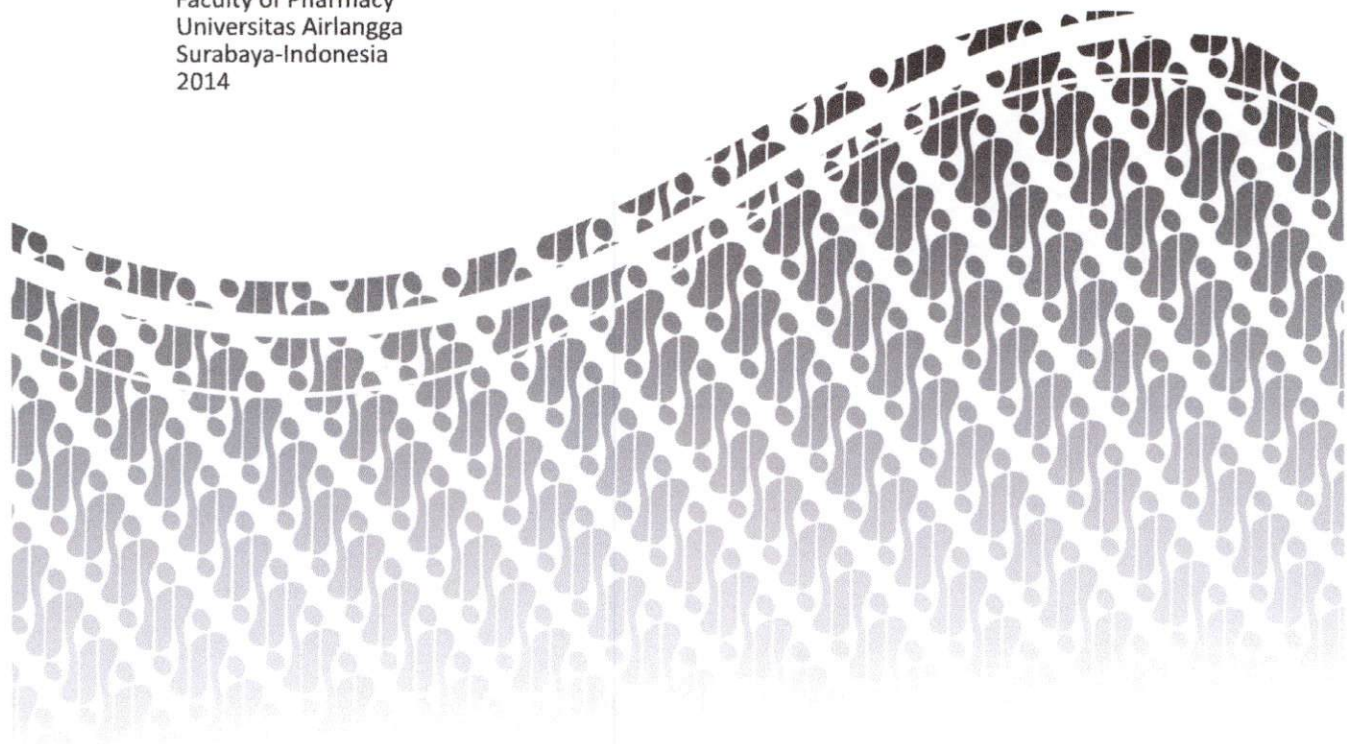


Proceeding

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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PHYSICAL INTERACTION STUDY OF IBUPROFEN-STEARIC ACID BINARY MIXTURE

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INTRODUCTION

Ibuprofen is a non steroid anti-inflammatory drug (NSAID) derived from propionic acid [3]. It has low aqueous solubility but high permeability so it is classified into BCS (Biopharmaceutical Classification System) Class II [6]. High cohesivity and adhesivity cause ibuprofen has bad powder flow and also contributes to its high tendency for sticking to the punch. Granulation step is necessary in ibuprofen tableted dosage form manufacturing due bad compaction behaviour [9]. Thus, addition of appropriate excipients is hardly avoidable in order to improve powder properties in ibuprofen tableted dosage form formulation.

Pharmaceutical dosage form manufacturing always involves heat and mechanical energy during the process [10]. This energy could induce interaction between drug and excipient molecules [10] as well as eutectic formation. Eutectics are intimate crystalline mixture of one compound in another and it has unique property in its lower melting temperature than that pure compound. Generally, eutectic interaction does not impact the pharmacological activity, but may contribute in alteration of the pharmaceutical properties. Unintentional eutectic formation in tableted dosage form development have been reported to lead to unwanted changes in the physical and/or chemical characteristics of the tablets [2].

Ibuprofen is a kind of drug that forms eutectic with some kind of excipients as reported in many studies [7, 11, 1]. It has been identified by DSC analysis that ibuprofen forms eutectic with stearic acid [7], one of most frequently used lubricant [4]. Therefore, further physical characterization was conducted in this study for better understanding of eutectic formation in ibuprofen-stearic acid binary system.

MATERIALS AND METHODS

Materials

Ibuprofen was purchased from Shasun Chemicals and Drugs Ltd., India. Stearic acid was obtained from Hense Chemicals Manufacture Ltd., China.

Binary mixture was prepared by weighing each compound separately and mixing them gently in a mortar at ambient temperature. Weight ratio of 4:6 of ibuprofen and stearic respectively was used for each binary system. Eutectic formation of binary mixture was induced by heating the prepared binary mixture upon water-bath at temperature about 70°C.

Methods

Hot Stage Microscopy

Hot stage microscopy was performed under polarizing microscope observation equipped with heating apparatus. The higher melting compound, which is ibuprofen, was melted first on a microscope slide to occupy about half the area under cover slip. After the first compound had cooled and solidified, the second compound, stearic acid with lower melting temperature, was placed at very edge of cover slip, near the first compound. The sample was heated until stearic acid completely melted to contact with solidified ibuprofen. Then, the sample was allowed to cool. After the sample had solidified, the contact area of two compounds was observed whilst the temperature was gradually raised.

X-ray Powder Diffraction

X-ray powder diffraction data were obtained using a Phillips Xpert X-ray diffractometer, Netherland, with CuK α radiation (1,54Å), at 40 kV and 30 mA, and passing through a nickel filter with divergence slit (0,25°). Samples were scanned over 2 θ range of 5-50° with



step size of 0,017°.

Scanning Electron Microscopy

Scanning electron-micrographs of crystal of pure compounds and binary mixture were collected by a Hitachi TM3000, Japan. Observation was conducted by magnification of 1000. Samples were fixed on aluminium stub with conductive double-sided adhesive tape and coated with gold in a low vacuum atmosphere.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectra were obtained using a Shimadzu 8400s FTIR spectrometer, Japan. Samples of ~2 mg were mixed with 300 mg potassium bromide and then compressed in a hydraulic press to form transparent disc. Each sample was analysed from 4000 to 400 cm⁻¹.

RESULTS AND DISCUSSION

Hot stage microscopy was performed to identify the type of physical interaction between two compounds. It is a simple technique to understand phase behaviour in binary system upon heating. Under polarizing microscope, only crystalline phases will be visible because they direct the polarized light and, in other hand, liquid phases allow the light to pass through unchanged so no light reaches microscope [5]. Crystalline phases will be seen full of colours with different intensity which is affected by fragment orientation, thickness, and polarized light absorbed or pass through crystalline fragment [13]. When crystalline phases melt to form liquid phases, it will be quickly seen and recognized as a black line or region [5].

Figure 1 shows the behaviour of ibuprofen and stearic acid under hot stage microscopy observation. Area of A.1 and B.1 is re-crystallized phase of ibuprofen, A.2 and B.2 is re-crystallized phase of stearic acid, A.3 and B.3 is contact area of two compounds. It's clearly seen that contact area of two compounds is melted first than the pure compound when temperature increases (Figure 1 B), leaving single blank line between crystalline phases. This single eutectic formation indicates conglomerate crystallization [5].

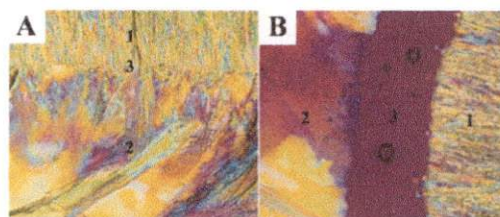


Figure 1 The mixed fusion behavior of ibuprofen and stearic acid, A. Contact area is formed, and B. Contact area is melted first.

Eutectic formation between two compounds also shown thermal analysis study we conducted (result not shown). Diagram phase obtained from DTA analysis of various weight ratio binary mixture in our study shows similarity pattern compared to previous study by Lerdkanchanaporn et al. (2001).

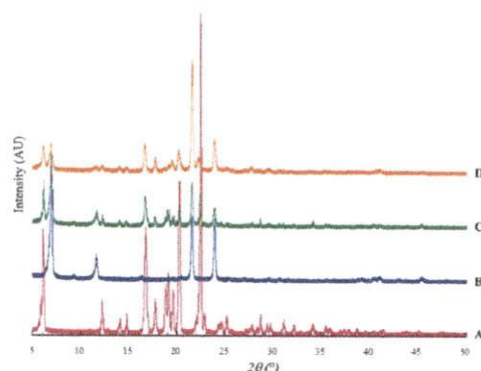


Figure 2 X-ray diffractograms of A. Ibuprofen, B. Stearic acid, C. Binary mixture in 4:6 weight ratio, and D. Eutectic-formed binary mixture in 4:6 weight ratio.

The crystalline nature of binary mixture of ibuprofen and stearic acid was examined by X-ray powder diffraction of binary mixture and eutectic-formed binary mixture as well as each pure compound.

Ibuprofen showed numerous strong diffraction peaks in 2θ of 6.07°, 12.18°, 16.71°, 17.71°, 18.83°, 19.59°, 20.32°, 22.45°. Stearic acid showed few strong diffraction peaks in 2θ of 6.94°, 11.62°, 21.49°, and 23.91°. These pure compound peaks superimpose each other as it

shown in X-ray diffractogram of binary mixture in 4:6 weight ratio (Figure 2 C). Eutectic-formed binary mixture showed similar X-ray diffraction pattern with binary mixture and it also shown superimposition diffraction peaks of the pure compound. This phenomenon indicates eutectic formation between ibuprofen and stearic acid do not result new crystalline phase but conglomeration two crystalline in solid state. Difference of peak intensity showed shifting on degree of crystallinity [13].

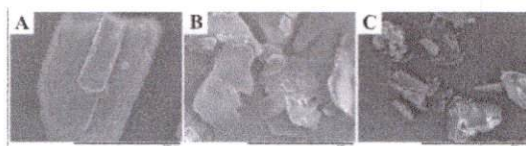


Figure 3 SEM photographs of A. Ibuprofen crystals, B. Stearic acid crystals, and C. Eutectic-formed binary mixture in 4:6 weight ratio.

The outer appearance of pure compound crystal can be distinguished each other as it can be seen in Figure 3. The typical outer appearance of ibuprofen no longer can be seen in photograph of eutectic-formed binary mixture whilst the layered-outer appearance of stearic acid still exists. Stearic acid is well-known to be a "boundary" type lubricant [12], so it may form thin film on ibuprofen crystal surface. Therefore, this stearic acid behavior may takes role in disappearance of ibuprofen crystal on eutectic-formed binary mixture photograph. Hydrogen bonding interaction of ibuprofen and stearic acid in their binary mixture and eutectic-formed binary mixture shown by FTIR spectra (Figure 4). It is characterized by shifting of carbonyl and hydroxyl functional groups vibration which can form hydrogen bond amongst themselves [8]. From this hydrogen bonding interaction, we can conclude that ibuprofen interacts physically with stearic acid to form conglomerate mixture.

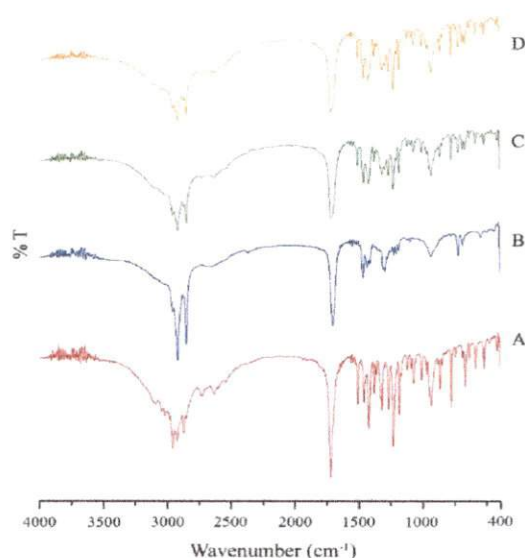


Figure 4 FTIR spectra of A. Ibuprofen, B. Stearic acid, C. Binary mixture in 4:6 weight ratio, and D. Eutectic-formed binary mixture in 4:6 weight ratio.

CONCLUSION

Identification of physical interaction with hot stage microscopy showed eutectic formation of ibuprofen and stearic acid leads to conglomerate crystallization. It is supported by X-ray powder diffraction that is diffraction peak superimposition characterizes conglomeration phenomena. Eutectic formation also leads to disappearance of ibuprofen crystal amongst stearic acid existence. Moreover, hydrogen bonding interaction is present in eutectic formation of two compounds. The study presented here allows a better understanding of the drug/excipient phase behavior in binary system.

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