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Study of Differential Scanning Calorimetry of complex of Magnesium Sulfate with Aspirin, Paracetamol and Naproxen

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Abstract

Differential scanning calorimetry is a thermo-analytical technique whereby the difference in heat flow between a sample and reference is measured as a function of temperature. Samples were prepared from co-evaporated dispersion of magnesium sulfate with aspirin**,** paracetamol and naproxen in different ratios. DSC thermogram of aspirin showed sharp melting endotherm at 142.61°C which corresponded to its melting with normalized energy of -143.17J/g and the endotherm peaks at 52.13°C, 97.08°C (main peak), 112.68°C and 159.89°C were represented by magnesium sulfate heptahydrate. The thermogram of aspirin and magnesium sulfate at a ratio of 2:1 showed the melting endotherm at 125.92°C with normalized energy – 87.30 J/g. The DSC thermogram of sample (2:1 ratio) at 125.92°C is not present in the thermogram of aspirin and magnesium sulfate that represented the identity of a different product and it indicated the presence of complexation between aspirin and magnesium. On the other hand, DSC thermogram of paracetamol showed sharp melting endotherm at 170.76°C which corresponded to its melting with normalized energy of -173.19J/g. The thermogram of paracetamol and magnesium sulfate at 1:1 molar ratio showed the melting endotherms at 96.46°C and 170.73°C, while at molar ratio 1:2 the melting endotherm were seen at 98.42°C and 171.07°C and at molar ratio 2:1 the melting endotherms were evident at 98.82°C and 171.53°C. DSC thermogram of naproxen showed sharp melting endotherm at 156.52°C which corresponded to its melting with normalized energy of -98.39J/g. The thermograms of naproxen and magnesium sulfate at a molar ratio 1:1, 1:2 and 2:1 showed the melting endotherms at 90.17°C and 156.90°C, at 94.57°C and 157.02°C and at 91.84°C and 157.32°C, respectively.We found that the DSC thermogram of all samples at different ratios of paracetamol and magnesium sulfate, and naproxen and magnesium sulfate showed the melting endotherm at that temperature similar to the endotherm of paracetamol, naproxen and magnesium sulfate separately, but the thermogram of aspirin and magnesium showed sharp change indicating complexation.

Key words: DSC, NSAIDs, Magnesium sulfate, Aspirin**,** Paracetamol, Naproxen**.**

Introduction

The study on interaction and complexation of drug molecules with other drugs and various metal ions is an important field of research in the chemical, biochemical, medicinal and pharmacological point of views. Complexation of drugs with metal ions remarkably influences the bioavailability and other pharmacokinetic properties of drugs in our body. The proposed curative properties of Cu-based non-steroidal anti-inflammatory drugs (NSAIDs) have led to the development of numerous Cu(II) complexes of NSAIDs with enhanced anti-inflammatory activity and reduced gastrointestinal (GI) toxicity as compared to their uncomplexed parent drug (Weder *et al*., 2002). Our body possesses a large number of metal ions for operating normal physiological activities and we also intake a number of metals as drug, dietary factor, drinks and we also come in close contact with different drugs. In case of pharmaceutical formulation many metallic compounds may be used as APIs as well as excepients.

The biological activities of the drug-metal complexes may affect stability and usual activities of drugs through changing pharmacokinetic and pharmacodinamic properties. There are many organometalic compounds which have remarkable pharmacological effects and are also used as active ingredients. Magnesium is present in three different states in most biological system: freely coordinated to water, associated with anions and bound to

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proteins. On average, the human body contains approximately 1 mol (24 g) of magnesium. Magnesium-drug complexes have been studied for use as new drug molecule and some of these complexes showed excellent therapeutic activities (Gielen and Tiekink, 2005). The proposed curative properties of Mg-based nonsteroidal anti-inflammatory drugs (NSAIDs) might lead to the development of some Mg-based complexes of NSAIDs with enhanced anti-inflammatory activity and reduced gastrointestinal toxicity as compared to the parent drug. For this reason, the study of complexation of aspirin, paracetamol and naproxen with metal ions is an interesting field of research.

The use of stepwise isothermal high sensitivity differential scanning calorimetry (HSDSC) as a novel means of detecting excipient incompatibility is described using mixtures of aspirin with magnesium stearate and stearic acid as model systems (Sylvia, 2000). Aspirin, magnesium stearate and stearic acid individually and as mixtures were studied in scanning mode using conventional DSC. Compacts of magnesium stearate and aspirin were also studied, with considerably more pronounced thermal events taking place compared to the powder mixtures. It was concluded from these studies that while the study has highlighted certain limitations of the approach, stepwise isothermal DSC represents a potentially highly useful means of detecting excipient incompatibilities.

The aim of the present study is to construct phase diagram of magnesium sulfate with aspirin, paracetamol and naproxen from their DSC data at different molar ratios and to infer about the complexation between magnesium and drug molecules.

Materials and Methods

Aspirin and Paracetamol were collected from *Square* Pharmaceuticals Ltd.,Bangladesh; Naproxen was collected from SK+F Pharmaceuticals Ltd., Bangladesh; Magnesium sulfate heptahydrate (E.Merk, India, Ltd.), Methanol (Merk, Germany), Demineralized water were supplied from our laboratory and other reagents were of analytical grade and purchased from local market.

Co-evaporated dispersion method: The inclusion complex of magnesium sulfate heptahydrate with aspirin, paracetamol and naproxen at molar ratios 1:1, 2:1 and 1:2 were prepared by dissolving the drug in methanol and the magnesium salt was dissolved in demineralized water separately. The salt solution was then added to the drug solution and stirred to attain the equilibriums. The resulting solutions were evaporated to dryness by a water bath at below 60°C (Nitin *et al*., 2009; Bhanubhai *et al.*, 2006).

Preparation of microscopic slide: Small quantity of complex samples at different ratios as well as aspirin, paracetamol, naproxen and magnesium sulfate were separately spreaded over microscope slides and observed under electronic microscope 'OLYMPUS, CKX41', Japan and the physical state of the samples were recorded.

Thermal analysis of complex: Thermal analysis is a branch of material science where the properties of materials are studied as they change with temperature. Differential scanning calorimetry is a thermo analytical technique whereby the difference in heat flow between a sample and reference are measured as a function of temperature. Here, the sample and reference were maintained at the same temperature throughout the study. Experiment was carried out by using Differential scanning calorimeter, DSC-60 WS, Shimadzu, Japan, equipped with computer and appropriate software program. Experiment was performed under nitrogen gas at a flow rate of 20 ml/ min and increase in heat by 10°C/ min. The weights of the samples were in the range of 2-5 mg. The temperature range of DSC runs was 30°C to 200°C (Al-Suwayeh *et al*., 2009). The DSC thermograms were recorded for samples sealed in aluminum pans and indium was used as standard for calibrating the instrument. The peak temperature of melting of each sample and the heat of fusion were determined from the DSC traces by thermal analysis program.

Then Phase diagram of magnesium sulfate with aspirin, paracetamol and naproxen were constructed from their DSC data of binary mixtures in various molar ratios.

Results and Discussion

Microscopic analysis: Aspirin, paracetamol, naproxen, magnesium sulfate and the prepared samples of magnesium sulfate with aspirin, paracetamol and naproxen at molar ratios of 1:1, 2:1 and 1:2 were observed physically to see the physical state of samples. Small amount of sample on microscopic slide was placed under the electronic microscope and the nature/ shape of the particle of the sample were observed. The results are given in Figures 1 - 4.

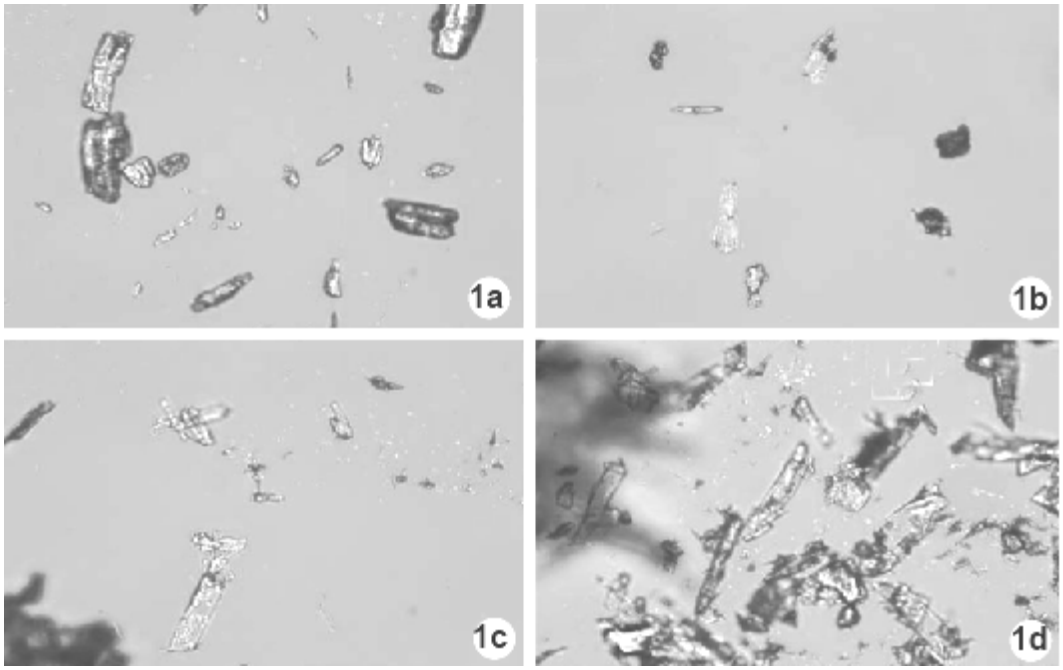

Figure 1. Microscopic view of- a. Aspirin, b. Aspirin and $MgSO_4$ (1:1), c. Aspirin and $MgSO_4$ (1:2) and d. Aspirin and $MgSO_4$ (2:1)

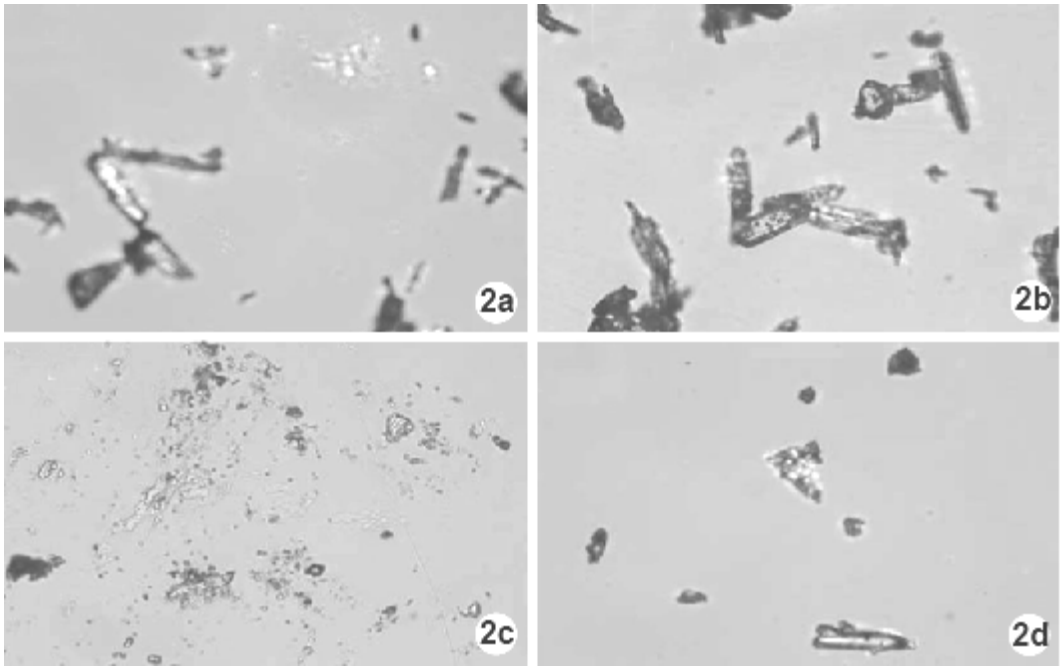

Figure 2. Microscopic view of- a. Paracetamol, b. Paracetamol and $MgSO_4$ (1:1), c. Paracetamol and $MgSO_4$ (1:2) and d. Paracetamol and $MgSO_4$ (2:1)

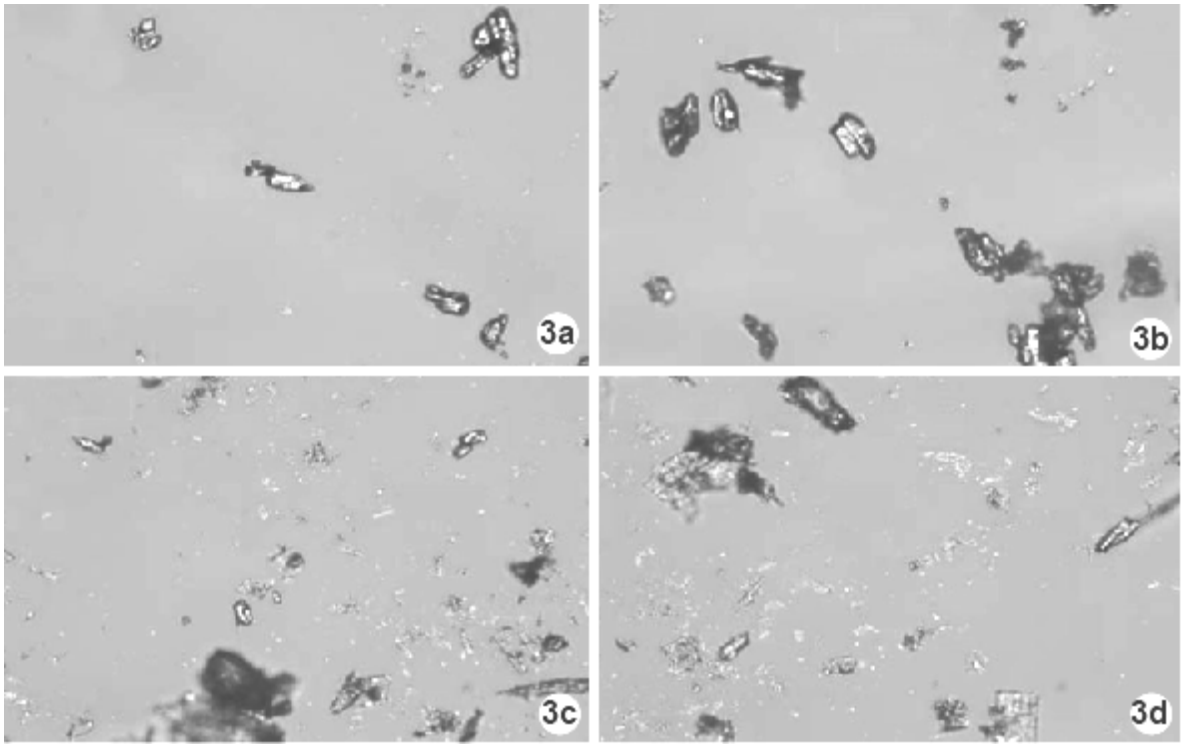

Figure 3. Microscopic view of- a. Naproxen, b. Naproxen and $MgSO_4$ (1:1), c. Naproxen and $MgSO_4$ (1:2) and d. Naproxen and $MgSO_4$ (2:1)

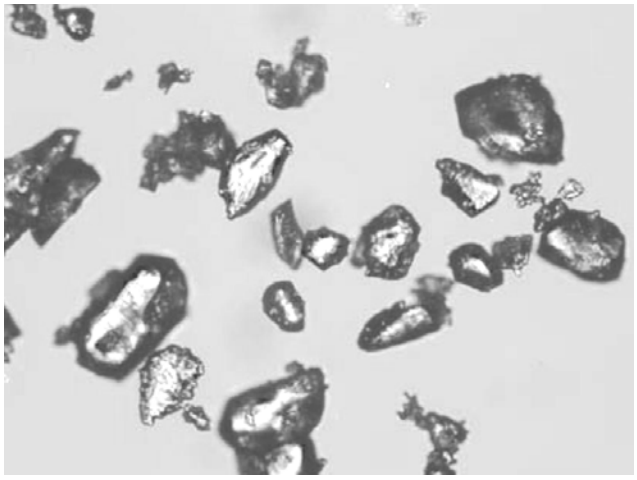

Figure 4. Microscopic view of Magnesium sulfate heptahydrate.

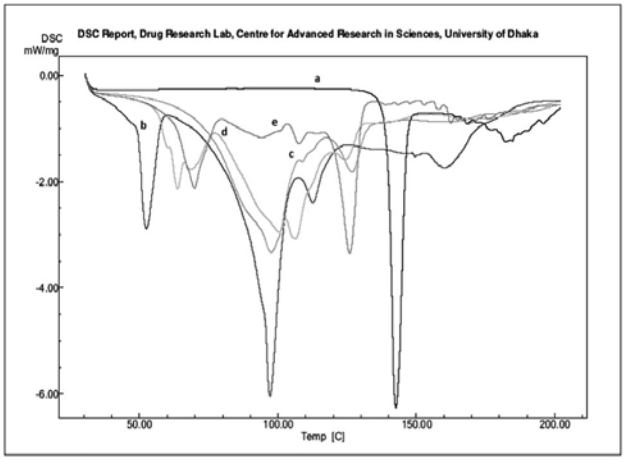

Figure 5. DSC thermogram- a. Aspirin, b. Magnesium sulfate heptahydrate, c. Aspirin and $MgSO_4$ (1:1), d. Aspirin and $MgSO_4$ (1:2) and e. Aspirin and $MgSO_4$ (2: 1).

Thermal analysis of samples: DSC thermogram of aspirin, paracetamol, naproxen and magnesium sulfate and the complex samples of magnesium sulfate with aspirin, paracetamol and naproxen at molar ratios 1:1, 2:1 and 1:2 are shown in Figures 5-7.

DSC thermogram of aspirin showed sharp melting endotherm at 142.61°C which corresponded to its melting with normalized energy of -143.17J/g. The thermogram of aspirin and magnesium sulfate at 1:1 ratio showed the melting endotherm at 97.57°C (main peak) and at 126.75°C. The mixture of aspirin and magnesium sulfate at 1:2 ratio showed the melting endotherm at 100.37°C (main peak) and at 124.25°C. The thermogram of aspirin and magnesium sulfate at 2:1 ratio displyed the melting endotherm at 125.92°C. The endotherm peak at 52.13°C,

97.08°C (main peak), 112.68°C and 159.89°C were represented by magnesium sulfate heptahydrate and some of these peaks were present in the samples (aspirin and magnesium sulfate at 1:1 and 1:2 ratio). The DSC thermogram of aspirin and magnesium sulphate at ratios 1:1, 1:2 and 2:1 revealed endotherm peaks at 126.75°C, 124.25°C and 125.92°C that represented the identity of a different product than that of aspirin and magnesium sulphate and it indicated the presence of complexation by the co-evaporation method.

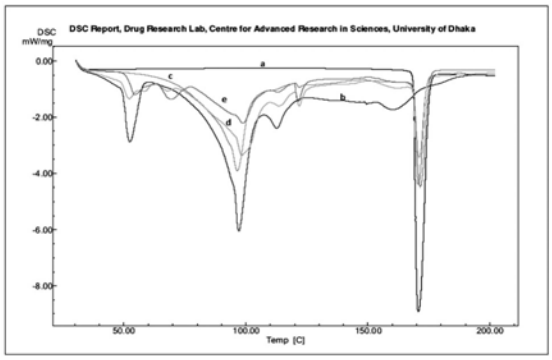

Figure 6. DSC thermogram- a. Paracetamol, b. Magnesium sulfate heptahydrate, c. Paracetamol and $MgSO_4$ (1:1), d. Paracetamol and $MgSO_4$ (1:2) and e. Paracetamol and $MgSO_4$ (2:1).

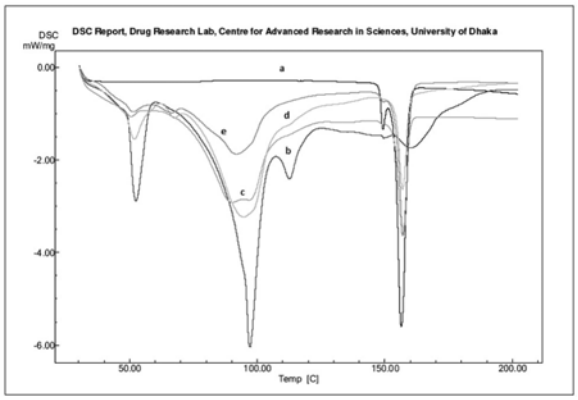

Figure 7. DSC thermogram - a. Naproxen, b. Magnesium sulfate heptahydrate, c. Naproxen and $MgSO_4$ (1:1), d. Naproxen and $MgSO_4$ (1:2) and e. Naproxen and $MgSO_4$ (2:1)

DSC thermogram of paracetamol showed sharp melting endotherm at 170.76°C which corresponded to its melting with normalized energy of -173.19J/g. The thermogram of paracetamol and magnesium sulfate at 1:1 ratio demonstrated the melting endotherm at 96.46°C and 170.73°C. Paracetamol and magnesium sulfate at molar ratio 1:2 showed the melting endotherm at 98.42°C and 171.07°C. The thermogram of paracetamol and magnesium sulfate at a ratio 2:1 exhibited the melting endotherm at 98.82°C and 171.53°C. We found that the DSC thermogram of all samples at different ratios of paracetamol and magnesium sulfate showed the melting endotherm at that temperature similar to the endotherm of paracetamol and magnesium sulfate separately.

On the other hand DSC thermogram of naproxen showed sharp melting endotherm at 156.52°C which corresponded to its melting with normalized energy of -98.39J/g. The thermogram of naproxen and magnesium sulfate at a ratio 1:1 revealed the melting endotherm at 90.17°C and a sharp peak at 156.90°C. The naproxen and magnesium sulfate at a ratio 1:2 showed the melting endotherm at 94.57°C and 157.02°C. The thermogram of naproxen and magnesium sulfate at a ratio of 2:1 displayed the melting endotherm at 91.84°C and 157.32°C. We also found that the DSC thermogram of all samples at different ratios of naproxen and magnesium sulfate showed the melting endotherm at that temperature similar to the endotherm of naproxen and magnesium sulfate separately.

Conclusion

DSC is a reliable method for the study and detection of complexation between drug- drug and drug- metals. We observed a clear indication of complexation between aspirin and magnesium but no indication of complexation was observed between naproxen-magnesium and paracetamol-magnesium.

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