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Characterization of Ibuprofen Solid Dispersion Part-I: DTA/TG Analysis

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In this paper, the formulation of solid dispersions of ibuprofen is suggested with skimmed milk to improve bioavailability. In order to determine the interaction between ibuprofen and skimmed milk, differential thermal analysis (DTA) and thermogravimetry (TG) studies were performed on the solid dispersion of ibuprofen as well as its individual components. Disappearance of the specific DTA peaks of the drug in DTA curve of the solid dispersion showed that the drug has interacted with the carrier. The DTA/TG curves of the solid dispersion indicated that the formation of an inclusion complex between ibuprofen and skimmed milk occurred.

Key Words: Ibuprofen, DTA/TG, Inclusion complex, Skimmed milk, Solid dispersion.

INTRODUCTION

Solid dispersions have been prepared to overcome bioavailability problems of the drug substances with aqueous insolubility[1-5]. Non-steroidal anti-inflammatory drugs (NSAID) such as ketoprofen, ibuprofen, tenoxicam, indomethacine, possess such problem[6]. It is well-known fact that most NSAIDs cause gastric irritancy[6]. Several approaches have been proposed to solve these two problems[7-9]. Preparation of solid dispersions with skimmed milk is one of the best approaches modulating gastric irritancy as well as improving the aqueous solubility of the plain drug[9,10]. In these systems, drug is expected to form an inclusion complex with the skimmed milk (SM) due to the surface active agent and amino acid content of SM[8,11,12]. Numerous techniques are available to identify the formation of such complex in solid dispersions[13-20]. Scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC) and differential thermal analysis and thermal gravimetry

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(DTA/TG) have been used to obtain information about the interaction between the carrier and the plain drug upon formation of the inclusion complex in solid dispersion[13-21].

Ibuprofen (2-[4-(2-methylpropyl)phenyl]propanoic acid) (Fig. 1) is a safe non-steroidal antiinflammatory drug being used for the treatment of a wide range of indications, including pain, fever, inflammation, arthritis, and dysmenorrhea[6]. Ibuprofen's main mechanism of action is known to be the inhibition of prostanoid biosynthesis *via* blockade of cyclo-oxygenase (COX). Ibuprofen has been found to inhibit both COX-1 and COX-2 isoforms[6,22].

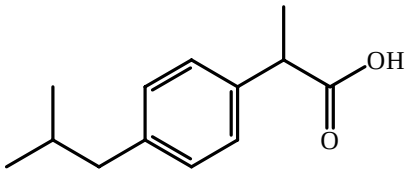

Fig. 1. Structure of ibuprofen (2-[4-(2-methylpropyl)phenyl]propanoic acid)

No characterization of the solid dispersion (SD) which was prepared with skimmed milk of Ibuprofen (Ib) is available in the literature. In this study, the solid dispersion of ibuprofen is prepared and characterized using differential thermal analysis and thermogravimetry techniques.

EXPERIMENTAL

Ibuprofen is a gift from Eczacibasi Pharmaceuticals Manufacturing Co., Turkey. Skimmed milk used in this study had fat less than 1 % and purchased from Miss Milk Products Co., Turkey. All other reagents and chemical substances were of analytical grade.

Preparation of skimmed milk powder: Skimmed milk (SM) was lyophilized until the humidity ratio was lowered to 3 %. Based on our preliminary studies, the duration of lyophilization process was chosen as 72 h to reduce humidity. In the end of lyophilization process, 25 mL of SM yielded *ca.* 2.625 g skimmed milk powder (SMP). This lyophilized skimmed milk powder was then sieved through 250 µm mesh and kept in a scintillation vial in a desiccator for further experiments.

Preparation of the solid dispersions of ibuprofen: Solid dispersions of ibuprofen were prepared employing the method of Topaloglu *et al.*[10]. 500 mg Ib was suspended in 50 mL of SM. Next, the obtained suspension was mixed upon continuous stirring in a water bath with constant temperature at 50°C for 0.5 h. It was freezed and lyophilized (Christ Freeze Dryers, Freeze Dryer Alpha 1-2LD, Germany) for 2 d. The yield of the solid dispersion of Ib was sieved through 250 µm mesh.

Thermal studies: A Shimadzu model DTG-60H simultaneous, DTA/TG thermal analysis system was used over the temperature range 298-1473 K. The samples (pure drug, SM and SD) were placed in platinium crucibles and α-Al_2O_3 was used as the reference material. Heating was performed under a nitrogen atmosphere and a flow rate of 60 mL/min. The sample size was limited to 8-10 mg and the heating rate was adjusted to 10 K/min in all cases.

RESULTS AND DISCUSSION

In order to improve the aqueous solubility of ibuprofen, solid dispersion was prepared with skimmed milk. In this system it is expected that an inclusion complex will be formed between skimmed milk and ibuprofen. Identification of such complex can be carried out by DTA/TG techniques. For this purpose, we analyzed DTA/TG curves of plain drug, skimmed milk powder and solid dispersion.

In the first part of this study, DTA/TG analysis of ibuprofen (2-[4-(2-methylpropyl)phenyl] propanoic acid) was conducted and the DTA/TG diagram shown in Fig. 2 was obtained. Thermal analysis diagram indicated that ibuprofen was pure in nature with one endothermic peak at 348 K corresponding to its melting point (reference melting point is 347-349 K)[23-25] and decomposed in one step at the range of 384-538 K. Total mass loss percentage was found to be 99.9 % at the temperature range of 273-538 K.

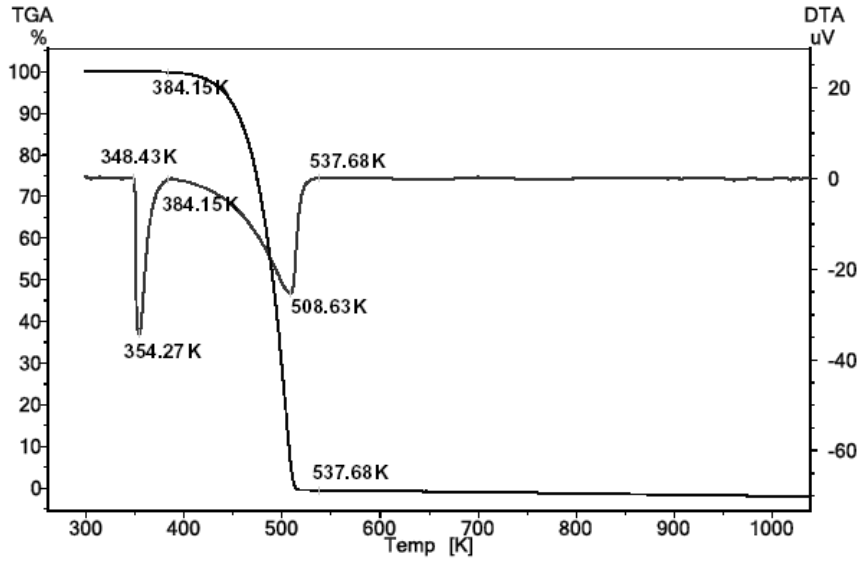

Fig. 2. DTA/TG thermogram of 2-[4-(2-methylpropyl)phenyl]propanoic acid

In the second part, skimmed milk powder was prepared using lyophilization process[9,10]. Then, thermal behaviour of skimmed milk powder was investigated by DTA/TG techniques. As shown in Fig. 3, SMP presents a complex DTA/TG diagram with numerous endothermic and exothermic effects. Such DTA/TG diagram obtained for skimmed milk powder is typical for the compounds that possess such complex organic structure[26]. Experimental mass loss percentage was 71.0 % at the temperature range of 273-1473 K.

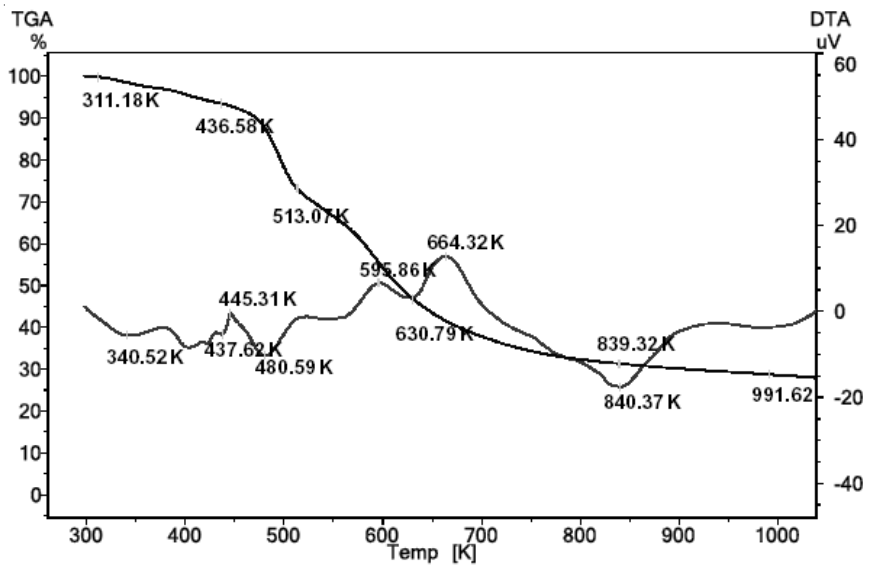

Fig. 3. DTA/TG thermogram of skimmed milk

In the last part of the study, simultaneous DTA/TG analysis was performed for solid dispersion of ibuprofen. Fig. 4 is the DTA/TG diagram of ibuprofen solid dispersion, indicating decomposition of solid dispersion at a wide range of temperature between 273-1473 K. The total mass loss percentage was determined as 71.4 %.

DTA/TG diagrams of the substances points out that mass loss percentage of skimmed milk powder and solid dispersion at the same temperature range are similar. However, mass loss percentage of solid dispersion is greater than that of skimmed milk powder. This difference may be due to the formation of inclusion complex. Another important outcome of thermal analysis is the evidence of a chemical interaction between skimmed milk powder and ibuprofen while forming solid dispersion. As apparent from Fig. 2, pure ibuprofen begins melting at 348 K and then, gives a sharp endothermic melting point peak at 354 K. However, no melting peak of

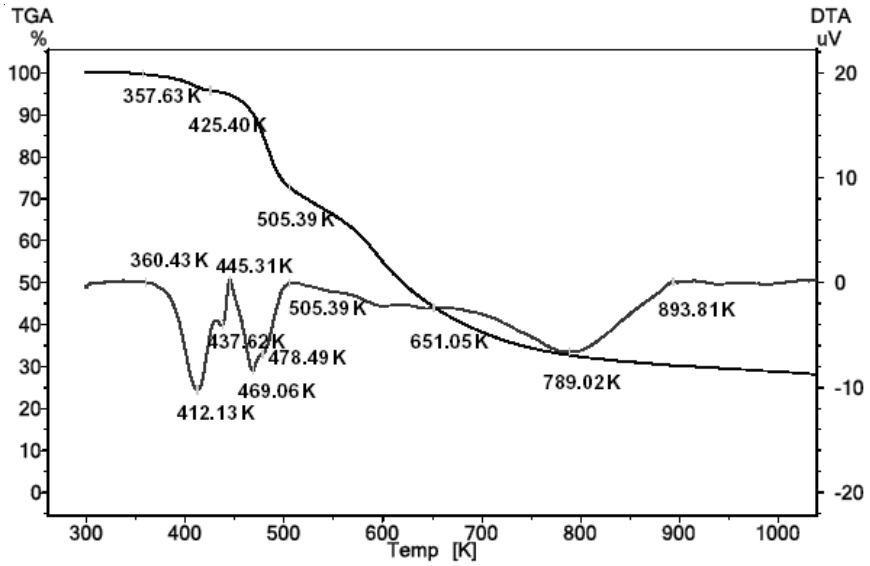

Fig. 4. DTA/TG diagram of ibuprofen solid dispersion

ibuprofen was observed in the thermal analysis diagram (Fig. 4) of solid dispersion at this temperature range. Based on the data, it can be concluded that ibuprofen has chemically interacted with skimmed milk to form inclusion complex in solid dispersion.

Conclusion

Solid dispersion of ibuprofen was prepared with skimmed milk to improve bioavailability and reduce gastric irritancy. Thermal behaviour of ibuprofen, skimmed milk powder and solid dispersion were analyzed by differential thermal analysis and thermogravimetry techniques. Comparison of DTA/TG diagrams indicates that a chemical interaction takes place between skimmed milk and ibuprofen while forming the inclusion complex for solid dispersion.

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