RESEARCH ARTICLE

Thermal Analysis in the Pre-formulation of Amorphous Solid Dispersion for Poorly Water-soluble Drugs

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ABSTRACT

This study is unique in studying the thermogravimetric analysis (TGA) of poorly water-soluble drugs before their formulation. Three selected drugs atorvastatin, albendazole and diclofenac were mixed with three different polymers hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP) and soluplus (SOL). The pure drugs and physical mixtures were subjected to solvent evaporation and milling techniques to obtain solid dispersions. All, as received and TGA analyzed solid dispersion mixtures to evaluate their thermal behavior at a temperature that ranged from 0–300°C.

The results showed that the addition of polymer either in physical mixtures or solid dispersions of the drugs has resulted in either increase or decrease of the thermal stability of the drugs depending on the method of preparation and the type of the polymer and the nature of the drug.

Keywords: Amorphous solid dispersion, Thermal behavior, Thermal stability, Thermogravimetric analysis.

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INTRODUCTION

Thermogravimetric analysis (TGA) is a thermal technique for detecting compatibilities between active medicinal ingredients and excipients.[1] This method is often used to investigate pharmacological compounds' thermal degradation to determine their thermal stability. TGA, on the other hand, does not offer information on non-mass-change reactions, including polymorphic transformations and double-decomposition processes.[2] Furthermore, unless the temperature range of the reaction has previously been defined and there are no interfering reactions, it is worthless to identify a drug or a combination of compounds. The TGA is a quantitative technique in the case of identifiable chemicals, and it is typically used to measure a drug in a combination. Regardless, TGA traces are routinely registered simultaneously with differential thermal analysis (DTA) or differential scanning calorimetry (DSC) scans to obtain additional information about thermal events that have been associated with mass loss (e.g., degradation) and those that have not (e.g., melting or crystallization).[3-5]

Given that amorphous forms are more reactive than their crystalline counterparts, it's not unexpected that amorphous forms are more sensitive to heat deterioration.[6-8] However, evaluating the deterioration of an amorphous form is necessarily challenging. Amorphous forms are prone to recrystallization, but crystalline forms do not deteriorate considerably until they melt.[9,10] TGA is a widely used method for assessing deterioration. TGA is used to measure mass changes by either heating the sample throughout a temperature range at a set rate (non-isothermal technique) or heating the sample at a specified temperature for a given period (isothermal method).[11] Mass is lost when solvent/water is lost and volatile degradation products are generated. In a study of current research using TGA to assess polymer or crystalline drug compatibility for HME processing, it was discovered that 100% of the investigations (n = 30) employed non-isothermal heating (10°C/min being the most prevalent heating rate).[12]

Atorvastatin (ATR), diclofenac (DCL) and albendazole (ALB) all have low aqueous solubility and characterized as class II drugs according to biopharmaceutical classification system (BSC) resulting in poor absorption from the gastrointestinal tract (GIT) and hence low oral bioavailability and consequently present a challenge in formulating a suitable dosage form.[13-15]

The study described herein has several objectives. First, TGA to assess thermal degradation of crystalline APIs (and amorphous APIs, when possible) and common polymers used in solvent evaporation and milling processing.

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MATERIALS AND METHODS

Materials

Atorvastatin was supplied from pioneer pharmaceutical company (Iraq), diclofenac from Sama Al-faihaa pharmaceutical company (Iraq) and albendazole from Wadi Al-Rafedain pharmaceutical company (Iraq). Hydroxypropyl methylcellulose (HPMC) and Polyvinylpyrrolidone (PVP) were purchased from Hi-Media Laboratories (India) and soluplus was supplied by BASF pharmaceutical industries. All other chemicals were purchased from the market, and all are of analytical grade.

Preparation of Solid Dispersion Formulas

Amorphous solid dispersions (ASD) of ATR and DCL were prepared by the solvent evaporation method, at which the required amount of drug and carrier (polymer) in a (1:3) ratio is weighed and blended in a porcelain dish. Then, the mixture was dissolved in the least amount of solvent possible and stirred (Dragon Lab- USA) at 600 rpm for 15 minutes at room temperature. After complete dissolving, solvent removal was carried out under reduced pressure for 20 minutes at 70°C using a rotary vacuum evaporator.[16] The ASD of ALB have been prepared by milling method using mortar by co-grinding the required amount of drug with the carrier (polymer) in a (1:3) ratio.[17] The obtained ASD were pulverized in a mortar and sieved, then stored in a desiccator to be utilized for further characterizations.

Preparation of Physical Mixtures (PM)

PM's of the corresponding ASDs were prepared by mixing the drug and the carrier (polymer) in a (1:3) ration in a mortar until a homogeneous mixture is obtained (for 10 minutes) at room temperature.[18]

Thermogravimetric Analysis (TGA)

The weight change of ASD powder samples as a function of temperature was determined using a TGA-50 Shimadzu thermogravimetric analyzer (Tokyo- Japan). About 4–6 mg of sample was placed in a ceramic sample cup and heated up to 400°C at a rate of 5°C/min. The sample chamber was continuously purged with nitrogen gas at a flow rate of 20 mL/min during the analysis. Triplicate measurements were conducted for each batch and results were averaged. The ASD water content was estimated by calculating the percent loss in weight between 20 and 400°C.[19]

RESULTS AND DISCUSSION

Atorvastatin

Atorvastatin TGA analysis results are shown in Figure (1). The major weight loss of atorvastatin began at around 110°C at which it lost approximately 4.5% of its weight in one stage due to loss of water which is in agreement with theoretical value of a trihydrate[20] which indicates that the trihydrate form of the drug has been converted to anhydrous form.[21] At 180°C, the minor loss of atorvastatin mass might be explained to the drug's breakdown after melting.[22,23] The major weight loss of atorvastatin pure began at around 200°C. According to the TGA curve, less than 70% of atorvastatin remained at 300 and at 400°C only 30% of the drugs has remained. There are slight changes obtained from solvent evaporating the drug alone as the TGA data shows that the degradation has started also at 200 and at 300°C only 60% of the drug remained and at 400°C only 32% of the drugs has remained. Physical mixtures of the drug with the three polymers resulted in delay in the onset of the major degradation process as the process started

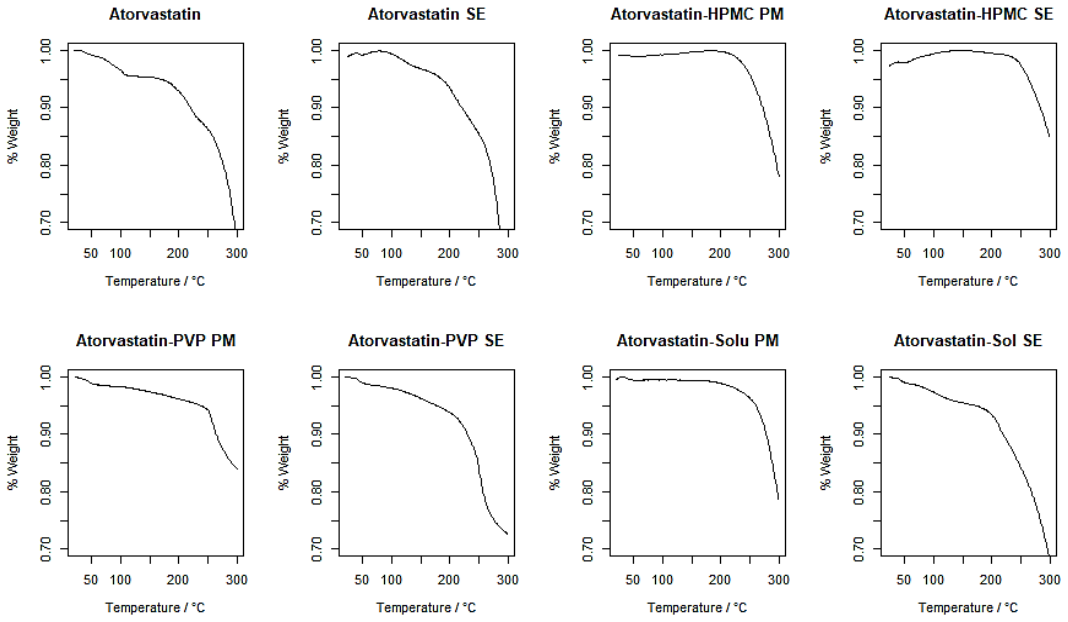

Figure 1: The DSC thermogram of the atorvastatin as received, physical mixtures of the drugs with polymers and amorphous solid dispersion of the drugs with polymers.

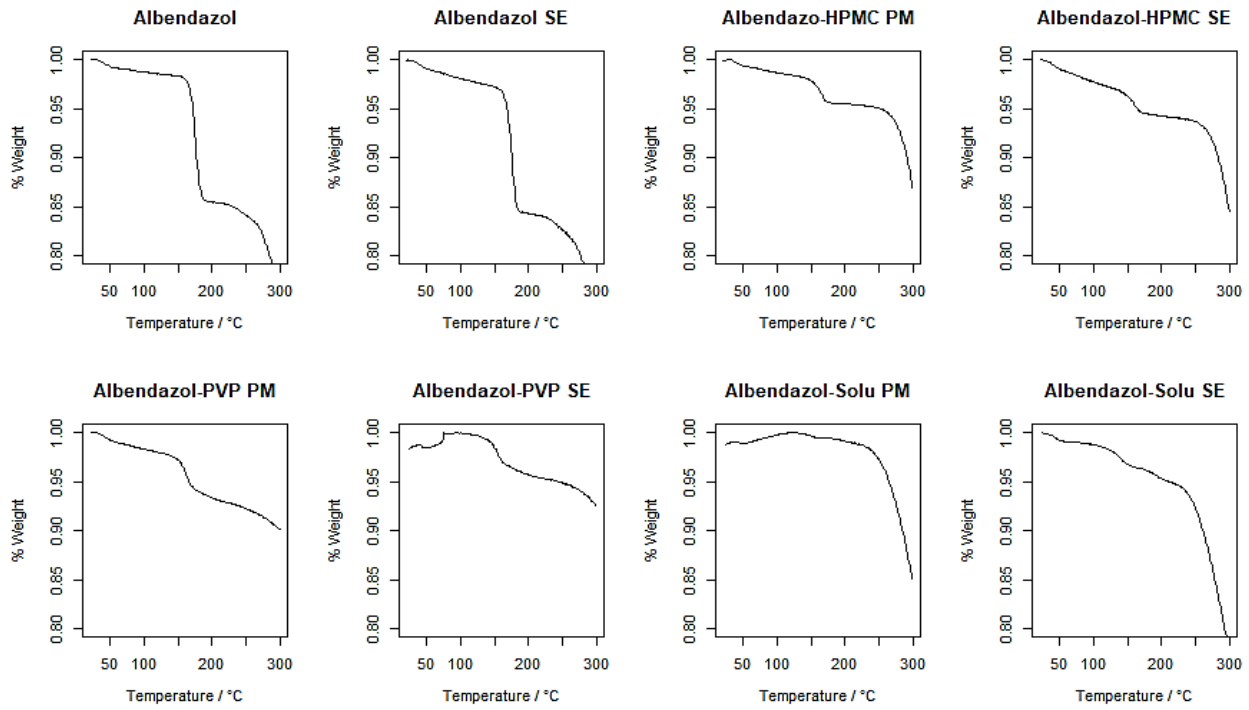

Figure 2: The DSC thermogram of the albendazole as received, physical mixtures of the drugs with polymers and amorphous solid dispersion of the drugs with polymers.

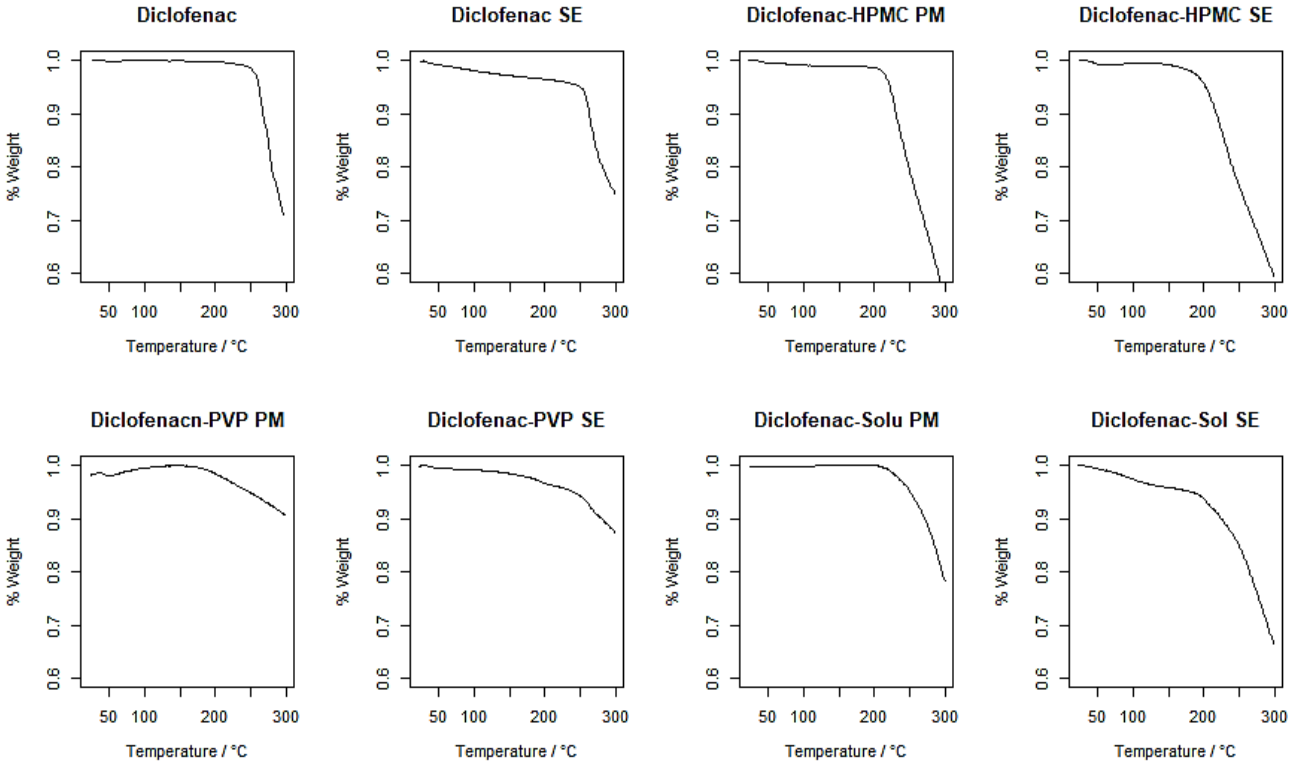

Figure 3: The DSC thermogram of the diclofenac as received, physical mixtures of the drugs with polymers and amorphous solid dispersion of the drugs with polymers.

at around 240, 250 and 265°C and the remaining % is 17, 60 and 34% for atorvastatin-HPMC, PVP and soluplus physical mixtures, respectively as shown in Figure (1). Solid dispersion formulas show similar results to physical mixtures with slight changes. However, the degradation of atorvastatin-soluplus ASD happened at lower temperatures (220°C) compared with atorvastatin-HPMC and PVP ASDs, indicating that this formula is less stable than HPMC and PVP solid dispersion upon heating. The PVP shows the lowest weight loss among all formulas; this can be attributed to the hygroscopic nature of the polymer and, likewise, many polymers is reported not to melt.[24]

Albendazole

Albendazole TGA analysis results are shown in Figure (2). The weight loss of Albendazole occurred in two steps, the first has begun at around 160°C at which it lost approximately 2% of its weight due to loss of moisture and the second step at around 197°C which represents the major mass loss of albendazole after being melted.[25,26] According to the TGA curve, less than 80% of albendazole remained at 300°C and at 400°C only 30% of the drugs has remained. Milling of albendazole shows slight changes except the milled formula has been degraded entirely at 392°C. Physical mixture and solid dispersion formulas of the drug with the three different polymers has no effect on the first step of degradation, while they resulted in delay in the onset of the major degradation process as the process started at around 280°C and higher as shown in Figure (2) indicating increased stability of the formulas compared to the pure drug alone. The results of the TGA suggest that albendazole formulations with the polymers has thermal properties of higher thermal stability than albendazole alone.

DICLOFENAC

Diclofenac TGA analysis results are shown in Figure (3). The degradation of diclofenac occurred at around 285 °C at which the percent fall dramatically after the melt of the drug[27] and solvent evaporation of the drug alone shows no changes on TGA curve. Diclofenac-HPMC physical mixture and solid dispersion show a slight decrease in the onset of diclofenac degradation. Despite diclofenac-soluplus physical mixture shows the same results to the drug alone but the solid dispersion of it shows a decrease to 200°C at which the degradation begun. Whereas the diclofenac-PVP physical mixture and solid dispersion shows a delay in the onset of degradation to about 275°C. The results of the TGA suggest that diclofenac formulation with the PVP has thermal properties of higher thermal stability than diclofenac alone or diclofenac with other polymers.

CONCLUSION

The using of TGA in analysis of the selected drugs is important procedure for characterization. By this method of analysis, the selection of best method for preparation of solid dispersion can be helpful and the selection of best drug-polymer mix will be easier than without TGA characterization. This will help in the preformulation study prior manufacturing of the pharmaceutical active ingredient.

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