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The effect of compression forces on the stability of dibasic calcium phosphate dihydrate tablets in the presence of glutamic acid hydrochloride monitored by isothermal calorimetry

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Abstract

Dibasic calcium phosphate dihydrate (DCPD) has been widely used as tablet diluent in both wet granulation and direct compression. Although DCPD is considered as a stable and inert diluent, it has been reported that certain acetic drugs and humidity/temperature conditions can evoke the loss of crystalline water. This study investigates the ability of isothermal calorimetry to detect any incompatibility reaction between glutamic acid hydrochloride (GAHCL), as an acidic model drug, and DCPD. The study identified an exothermic and endothermic reaction between GAHCL and DCPD which are influenced by compression forces. A correlation between the tablet relaxation energy and the magnitude of the solid state reaction between GAHCL and DCPD was established.

Keywords: Dibasic calcium phosphate dihydrate; Incompatibility; Compression forces; Tablet relaxation; Isothermal microcalorimetry; Solid state reaction

1. Introduction

Although various techniques are available to investigate instability reactions, isothermal calorimetry has become a well established method in preformulation and stability testing of tablets [1] and is able to provide the formulator with sufficient information to select suitable excipients compatible with the active ingredient [2]. Isothermal calorimetry has a number of advantages over techniques such as HPLC and DSC. Isothermal calorimetry can detect extremely low thermal activity accompanied with any reaction. Furthermore, it is able to conduct non-destructive tests under controlled storage conditions [3], and is compatible with all physical forms; solid, liquid, gas, or any combination of the three, with no need for special sample preparation [4]. HPLC, on the other hand, is only able to detect processes accompanied with a chemical modification of one or more substance. It is therefore suitable only for monitoring chemical instability or incompatibility, but not necessarily for physical changes such as polymorphic transformations or vapor sorption [5]. In contrast, as each physical or chemical process is associated with thermal activities, isothermal calorimetry is more universal and is capable of detecting any form of physicochemical changes in a dosage form, including loss of water of crystallization [6]. However, the main draw back of this technique is the unspecificity of the measurement, which makes the interpretation of data more difficult, i.e. the recorded thermal activity represents not only one reaction, but all reactions taking place simultaneously [7]. A keen design of the experiment is crucial to assure the relation between the recorded power output and the reaction intended to monitor. [1].

Compressed tablets are the most commonly used dosage form and are mostly prepared by compressing a mixture of powder or granules inside a confined space using different compression forces. Therefore, the compaction process is an important factor that determines the success of tablet formulation in general. Furthermore, it is well known that compression forces, applied during tablet formulations, have a direct impact on tablet characteristics such as appearance, tablet disintegration, dissolution

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properties, physical strength and relaxation [8,9]. Relaxation of compressed dosage forms is one of the physical changes that cannot be detected by HPLC or DSC; however it might have substantial effects on important features such as thickness, hardness, friability, disintegration and dissolution profile [10]. It might also have an impact on the physical stability of dosage forms, in particular during long-term storage [9]. Tablet relaxation is mostly thermally controlled and accompanied with energy exchange with the surrounding environment [11].

Dibasic calcium phosphate dihydrate (DCPD) has been widely used as tablet diluent in both wet granulation and direct compression. It might also be used as calcium source in supplements [12]. Although DCPD is considered a stable and inert diluent, the loss of crystalline water might be a potential source of instability. It has been reported that certain conditions of humidity and temperature evoke the loss and redistribution of water of crystallization [13]. This might change the surface properties of DCPD particles. Alkaline nature of surfaces might induce a neutralizing reaction with surrounding acidic materials [14]. The loss of crystalline water with acetic substances such as aspirin [15] and inodmethacine [16] is well known. It is linked with tablet ageing signs such as blotching and substantial weight loss [17]. Furthermore, the conversion of calcium phosphate from the dihydrate to the anhydrous form might cause errors in stability tests due to water evaporation at elevated temperatures [18].

Glutamic acid is one of the conditionally essential amino acids, which is orally administered in some multivitamin formulations. It might be used in the form of glutamic acid hydrochloride (GAHCL) [19]. GAHCL was chosen in this study as an acidic model drug to study the solid state compatibility between GAHCL and DCPD.

The focus of this study was to investigate the ability of isothermal calorimetry to detect any solid state reactions between GAHCL and DCPD, and to study the influence of compression forces on the solid state compatibility including the impact of tablet relaxation.

2. Experimental

2.1. Materials and methods

DCPD (lot#ST-2421090104), Mg stearate (lot#ST-25987) and GAHCL lot (#ST-25018) were a gift from Street Chemicals & Co. Montreal.

Crimp-top vials of 2.5 ml volume were purchased from Machery & Nagel, Düren, Germany with PTFE rubber seal and aluminum caps.

A single-punch manual compression machine (Fred S. Carver Inc.) and suitable tablet tooling were used to prepare standard convex tablets of 0.3 g weight and 65 mm diameter.

A Thermal Activity Monitor (TAM) model 2277 (Thermometric AB, Sweden) was used to measure the thermal activity at 40 ^{O}C.

The TAM was equipped with DI-710 data acquisition unit (DATAQ instrument, Ohio) connected to a computer system with WinDaq (data acquisition software) installed. After being collected, data were converted to Excel format for further data processing.

A Cou-Lo Compact Karl Fischer titrator was used for determination of water content.

The following reagents were used for the analysis: Hydranal® solvent, Hydranal®-standard sodium tartrate and Hydranal® composite 5. All reagents were purchased from Sigma–Aldrich.

2.2. Procedures

2.2.1. Powder preparation

Batches of 10 g of the *control* powder, which was GAHCL free, were prepared by screening with 10-mesh sieve. 0.1 g of Mg stearate was added to 9.9 g of DCPD. The mixture was then mixed manually for 2 min. To prepare the *test* powders, the pervious formula was modified by replacing 0.1 g of DCPD with 0.1 g of GAHCL. Hence, the test powder consists of 98% DCPD, 1% Mg stearate and 1% GAHCL. These batches were used for tablet preparation. Anhydrous dibasic calcium phosphate was prepared from the DCPD by drying at 105 °C and under vacuum (−70 kPa) for 12 h.

Control and test tablets were prepared with increasing compression forces from 0.5 and 1–1.5 t.

To exclude any errors emerging from differences between control and test samples during preparation, all tablets were prepared at the same time, and four tablets of 1.2 g average weight were sealed into the vials.

2.2.2. Relaxation experiments

To measure the heat exchange linked to tablet relaxation, the thermal activity of freshly compressed control tablets was compared with old relaxed tablets stored in well-closed plastic containers for 24 h at room temperature and in a dry place.

The closed vials were cleaned with Kimiwipes and inserted into the equilibrium position for 25 min and then lowered into the measuring position with data acquisition being started. Each experiment was performed in triplicate.

The endpoint of an experiment was defined when there was no change in the thermal activity for 5 h. The average heat output of each experiment was calculated and the final results plotted as power–time curves. Two main parameters were used for evaluation: t_{max} (h) and total heat exchange (J), where t_{max} is the time required to reach the maximum difference in thermal activity between the control and test sample. The total heat exchange was extracted from the power–time profile by integrating the profile using trapezoidal method [20,21]. Statistical analysis was performed using single-factor ANOVA test with a significance level of 0.01.

3. Results

3.1. Thermal activity of powders

Fig. 1 shows the difference in heat flow between a test powder and a control powder. The graph shows two processes of opposite direction: an exothermic followed by an endothermic. The