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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

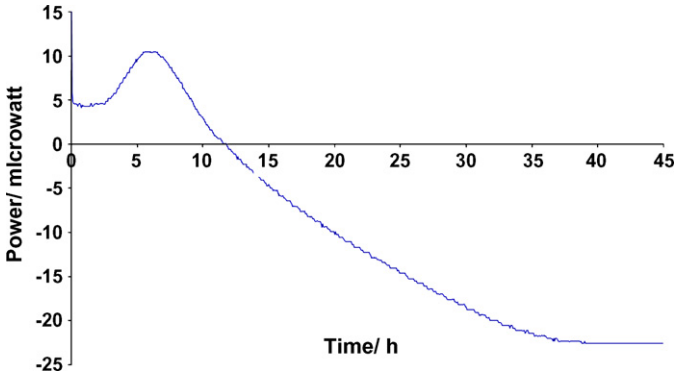

Fig. 1. Heat flow profile between a control (99% DCPD, 1% Mg stearate) and a test powder (98% DCPC, 1% Mg stearate and 1% GAHCL).

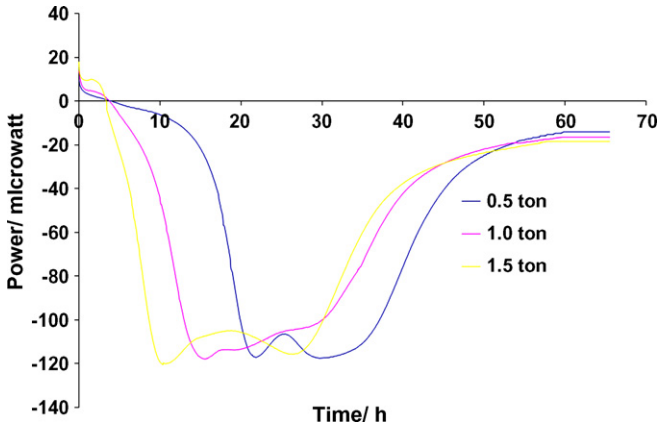

Fig. 2. Heat flow profiles of calcium phosphate dihydrate tablets containing traces of glutamic acid hydrochloride ($n = 3$), prepared under 0.5, 1 and 1.5 t compression forces.

heat flow is stable during the first 2.7 h, after which an exothermic reaction is detected. The heat flow reaches a maximum of 10.5 μW after 6.2 h. From this time onward, the total heat output decreases, reaching a steady state at 36 h. The maximum endothermic heat flow was −22 μW. It should be noted that the heat-flow curves of the individual powder components are flat lines with no net heat-flow (data not shown).

3.2. Water content of the powders after 45 h of incubation at 40 °C

Three samples of 1.2 g of control powder, GAHCL powder, and test powder were incubated at 40 °C for 45 h. The water content remaining in the powders was then assayed by the Karl Fischer titration. Table 1 shows the average water content of the samples and the standard deviation for each powder. The percent of water detected in both control and GAHCL powder after incubation was about 0.13%. This amount of water can be explained by moisture adsorption to the surface of any non-hygroscopic powder (0.1–0.2%). However, the presence of a trace amount of GAHCL in the test powder resulted in an increase in water content.

3.3. Heat-flow profile of tablets prepared using different compression forces

Fig. 2 shows the average thermal activity of the test tablets over the control tablet. Tablets of given composition were compressed at different compression forces. Although all tablets had similar heat flow patterns, the rates and timing were different. All the tablets showed a small exothermic flow, lasting for a short period of time (3.5 h), followed by a major endothermic heat flow which again overlapped with an exothermic reaction and finally reached a plateau. The second onset of an exothermic reaction seems to have an inverse proportional relationship with compression forces, which is best shown between the 0.5 and 1.5 t compression forces. The result shows that higher pressure causes a longer duration of the exothermic reaction. These reactions seem to be related to the compression forces used to prepare the tablets.

Table 1
Average water content of a control powder (99% DCPD, 1% Mg stearate), GAHCL powder (100% GAHCL) and a test powder (98% DCPC, 1% Mg stearate, 1% GAHCL), after incubation at 40 °C for 45 h

Test substance	Water content (mg g^{-1})
Control powder	1.28 ± 0.09
GAHCL alone	1.38 ± 0.19
Test powder	3.42 ± 0.22

3.4. Total heat exchange and t_{max}

The second column in Table 2 summarizes the average heat flow values for each experiment calculated from power-curves using the trapezoidal method. Each power–time curve was divided into small trapezoids, and then the area of these trapezoids were calculated and added together [20,21] which directly reflects the reaction's magnitude.

Statistical analysis showed that the three curves are significantly different from each other at $p < 0.01$. When the compression forces were plotted versus the average heat flow (graph not shown) a linear relationship was found with a correlation coefficient of 0.99.

The third column in Table 2 lists the average time required to reach t_{max}. Statistical analysis showed that the t_{max} values are statistically different from each other. An inverse linear relationship between t_{max} and compression forces with a correlation coefficient of 0.99 was observed (graph not shown).

Table 2
Average heat flow values in tablets compressed with different compression forces, observed t_{max} values and average heat exchanged during tablet relaxation using different compression forces at 0.5, 1, or 1.5 t

Compression force	Average heat exchange (J)	Average of t_{max} (h)	Heat exchanged during relaxation (mJ)
0.5 t exp	116 ± 3	21.5 ± 0.2	110 ± 0.003
1 t exp	127 ± 7	15.2 ± 1.0	190 ± 0.007
1.5 t exp	138 ± 3	10.6 ± 0.6	300 ± 0.013

$n = 3$.

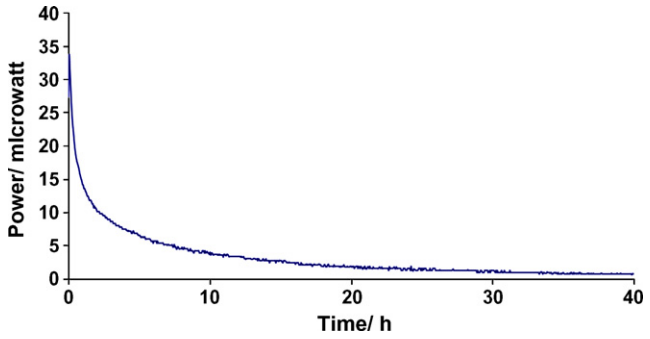

Fig. 3. Heat flow profile of the tablets prepared with anhydrous calcium phosphate and 1 t compression force.

3.5. Replacing calcium phosphate dihydrate with the anhydrous form

Replacing dihydrate with an anhydrous form of calcium phosphate resulted in a change in the heat flow profile, which is shown in Fig. 3. In this case, any endothermic reaction disappeared, and only the heat flow corresponding to exothermic reactions was observed.

3.6. Tablet relaxation

Fig. 4 shows the heat flow associated with the relaxation process is exothermic throughout the entire relaxation process. However, the compression forces used for tablet preparation had an influence on the amount of heat exchanged, i.e. higher the compression forces, the higher the heat flow. The fourth column in Table 2 summarizes the average heat exchange calculated from the heat flow profile. The higher the applied compression forces were, the greater was the heat exchange associated with tablet relaxation. ANOVA analysis proved that the curves are statistically different from each other. Plotting the heat exchanged during the first 6 h in the test tablets (mJ) versus heat associated with relaxation (mJ), within the same time interval, results in a linear relationship with a correlation coefficient of 0.99 (data not shown). This indicates a direct impact of the relaxation process on the solid state reactions in the tablets.

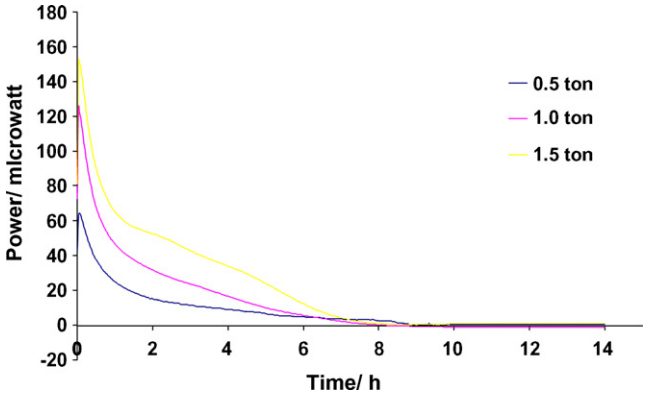

Fig. 4. Average thermal activity associated with tablet relaxation, after compression with 0.5, 1, and 1.5 t compression forces ($n = 3$).

4. Discussion

The first goal of the present study was to determine whether isothermal calorimetry is suitable to detect a possible incompatibility between trace amounts of an acidic ingredients and DCPD. The results show that a difference in thermal activity between a control and test powder was detected. The individual powders exhibit flat heat flow profiles (data not shown). The difference in the test powder can be attributed to the presence of GAHCL. The shape of the curve shown in Fig. 1 can only be explained by considering at least two types of reactions taking place. The first reaction is an exothermic neutralization reaction at the powder interfaces between acetic GAHCL particles and DCPD as alkaline reaction partners. As both of DDPC and GAHCL have certain amounts of moisture presented on their surface, it is possible that a neutralization reaction takes place slowly at the slightly humid interface of the particles. The occurrence of this exothermic reaction was confirmed when anhydrous calcium phosphate was exposed to GAHCL. In this case, the endothermic region was absent in the heat flow profile due to the lack of crystalline water in the anhydrous form (data not shown). An acid/base reaction produces free water and increases locally the moisture content in the powder. For DCPD it is known that a certain threshold of moisture is needed to trigger a loss of crystalline water. However, in the case of the powder mixture the lost of crystalline water (endothermic) seems to occur locally. As the two reactions have contradictory thermal properties, the heat flow recorded is the sum of the magnitude of both reactions. As shown in Fig. 1, after both reactions have taken place throughout the entire powder the total heat flow reaches a constant value. This constant heat flow might be associated with degradation reactions of GAHCL, but its origin is not known at this point.

To confirm the relationship between the endothermic reaction and loss of crystalline water, the amounts of water in the powders were determined using Karl Fisher titration. The results showed that only small amounts of water were associated with the individual powder components (control and GAHCL), which can be explained as surface-adsorbed water. On the other hand, an increase in water content was observed in the test powder, which can be attributed to an incomplete local loss of crystalline water from the DCPD in the presence of GAHCL. The incomplete reaction can be explained by the distribution of the moisture within the powder bed. As stated before, an elevated humidity is required to achieve a complete loss of crystalline water throughout the powder bed. The moisture produced by the neutralization reaction and the local loss of crystalline water might migrate into the surrounding powder bed. As a result, the relative humidity is not sufficiently high to self-induce reaction. Such an explanation was supported by the result obtained from a 1:1 powder mixture of GAHL and DCPD (data not shown), which resulted in an exothermic reaction followed by a huge endothermic reaction, exceeding the scale of the microcalorimeter. After completion of the reaction a slightly negative but constant heat flow similar to what is shown in Fig. 1 was observed. In the case of the 1:1 mixture the local humidity produced by the neutralization reaction became high enough to trigger the loss of crystalline

water throughout the entire powder bed. Such findings indicate that an instability reaction between two or more components in a mixture might be not detected instantly because of the minor amount of the substances which reacts with each other. However, the stability of the whole formula is affected.

The second goal of this study was to investigate the effect of different compression forces, used to prepare the tablets, on the incompatibility reactions. Fig. 2 shows the heat flows associated with the tablets prepared using 0.5, 1, 1.5 t compression forces. As shown, all the exothermic and endothermic reactions can be seen in all tablets. However, there was a significant increase in the total heat flow when the tablets were used in reference to the powder mixture. This effect might be due to two separate mechanisms. Firstly, it might be due to the limited water migration in a tablet compared to the loose particles in powder beds. The density inside of a tablet depends on the compression forces used in tablet preparation. A higher density of a tablet prepared with increasing compression forces might hinder the moisture migration. Therefore, humidity increases locally and triggers the loss of crystalline water, which in turn causes an increase in humidity in the surrounding powder particles. This humidity increase is now sufficiently high enough to trigger the loss of crystalline water throughout the surrounding powder particles and a chain reaction starts throughout the tablet. Another explanation might be that the energy put into the tablets by the compression forces is released by the relaxation process. The released energy might then catalyzes one or both of the solid state reactions. This is supported by the correlation between the amounts of energy released from the relaxation process and the extent of the solid state reaction in the first 6 h.

The occurrence of the second exothermic reaction in Fig. 2 might be due to moisture redistributions within the tablet or due to swelling processes induced by the increased free water content within the tablets. This is supported by the shape and duration of the observed signal. The swelling or moisture redistribution occurs faster in less packed tablets and takes more time in denser tablets as shown in Fig. 2. This is supported by the observation that the tablets begin to disintegrate from their surface after the loss of crystalline water.

It has been reported that it is not easy to monitor the relaxation energy using the available techniques, such as acoustic emission recorder [11]. Fig. 4 shows that isothermal calorimetry is able to detect tablet relaxation processes. The importance of relaxation rises from the fact that it is the main way to release excess energy from the compression process. An instant energy release is the major reason for tablet capping and lamination [22] whereas slow relaxation is known to be associated with modification in tablet characteristic during long-term storage such as changes in tablet hardness or tablet friability [10]. Our study showed the potential of isothermal calorimetry to monitor such processes. However, the results are not sufficient yet to prove that isothermal calorimetry can be used for modeling the relaxation process, but demonstrated that isothermal calorimetry can be used to study tablet relaxation processes.

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