Research Article

Theme: Role of Dissolution in QbD and Drug Product Life Cycle
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Isothermal Microcalorimetry as a Quality by Design Tool to Determine Optimal Blending Sequences

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Abstract. This study was designed to assess the value of isothermal microcalorimetry (ITMC) as a quality by design (QbD) tool to optimize blending conditions during tablet preparation. Powder mixtures that contain microcrystalline cellulose (MCC), dibasic calcium phosphate dihydrate (DCPD), and prednisone were prepared as 1:1:1 ratios using different blending sequences. ITMC was used to monitor the thermal activity of the powder mixtures before and after each blending process. Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) were performed on all final powder mixtures. Final powder mixtures were used to prepare tablets with 10 mg prednisone content, and dissolution tests were performed on all tablet formulations. Using ITMC, it was observed that the powder mixtures had different thermal activity depending on the blending sequences of the ingredients. All mixtures prepared by mixing prednisone with DCPD in the first stage were associated with relatively fast and significant heat exchange. In contrast, mixing prednisone with MCC in the first step resulted in slower heat exchange. Powder mixture with high thermal activity showed extra DSC peaks, and their dissolution was generally slower compared to the other tablets. Blending is considered as a critical parameter in tablet preparation. This study showed that ITMC is a simple and efficient tool to monitor solid-state reactions between excipients and prednisone depending on blending sequences. ITMC has the potential to be used in QbD approaches to optimize blending parameters for prednisone tablets.

KEY WORDS: isothermal microcalorimetry; powders blending; quality by design; tablets.

INTRODUCTION

Quality by design (QbD) is intended to build quality into a pharmaceutical product during its development and manufacturing cycle (1). This approach goes beyond any previous initiative and involves all aspects of a pharmaceutical product from the physicochemical properties of an active ingredient or excipients to the quality system, which has to be established to ensure that a product has the same quality over its life cycle (2). Therefore, QbD aims to move the formulation process away from empirical trial-and-error approaches and to orient the process into predictable and precisely controlled environments to ensure product quality within the life cycle (3).

In QbD, critical product attributes and critical process parameters have to be identified and controlled to ensure product quality (4). Blending of an active pharmaceutical ingredient is one critical process in tablet manufacturing which has to be precisely controlled to ensure content uniformity within a batch (5–7). In-process analytical methods based on near-infrared (8,9) or thermal methods using thermal conductivity or effusivity (10,11) may provide valuable information to determine blending end points. However, such methods may fail to give any information about interactions between excipients and the active ingredient during the blending process. Moreover, it lacks any information about how blending sequences might impact the drug product's performance over its entire shelf life (10).

Isothermal microcalorimetry (ITMC) is a universal analytical method to observe the thermal activity of any state of matter (12). These heat exchanges can originate from chemical instabilities or might be due to physical changes in the materials under investigation (13). Chemical changes can be detected using analytical methods like HPLC, whereas physical changes such as changes in the crystal structure or loss of water of crystallization are often more difficult to detect due to the nature of reaction and the low concentration of the involved ingredient (14). Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) may or may not be able to give conclusive results for the described

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reactions (15,16). Dissolution tests are used in stability studies to determine if an active ingredient had undergone any changes which might impact the performance of the drug product (17). These methods are important, but they require extensive sample preparation and can be time-consuming (13). Sample preparation for isothermal microcalorimetry is simple and fast (18). However, the drawback of this method, which is also a main advantage, is its universality (19). ITMC can only monitor the changes in thermal activity without explaining the reason for the observed heat flow. Therefore, combining ITMC with a second analytical test may allow the identification the nature of the reaction (20).

The present work gives an example of the use of ITMC as a QbD tool to optimize blending process for prednisone tablet preparation. Along with the active ingredient prednisone, the formulation contained two main excipients: microcrystalline cellulose (MCC) and calcium phosphate dihydrate (DCPD). All these techniques, ITMC, DSC, XRPD, and dissolution test, were used to assess the impact of blending sequences on the drug dissolution of tablets prepared.

EXPERIMENTAL

Materials and Methods

- DCPD (lot no. ST-2421090104) and magnesium stearate (lot no. ST-25987) were received from Street Chemical & Co (Montreal, Canada). USP-grade prednisone was purchased from Sigma, Canada. MCC (Tabulose® 102 lot no. 1601/01) was purchased from Balnver, Brazil, and crospovidone (Kollidon® CL) was purchased from BASF Aktiengesellschaft, Germany.
- A rotary tumbler (33 B, Lortone Inc. USA) was used for mixing the powder blends.
- The particle size was measured using the multi-angle sizing option of the ZetaPALS Zeta Potential Analyzer (Brookhaven Instrument Corporation).
- A single-punch manual compression machine (Fred S. Carver Inc., UK) and suitable tablet tooling were used to prepare standard biconvex tablets of 0.2-g weight and 65-mm diameter.
- Crimp-top vials of 4-ml volume were purchased from Machery & Nagel, Düren, Germany with polytetrafluoroethylene (PTFE) rubber seal and aluminum caps.
- An ITMC (TAM III®, TA instrument, Sweden), adjusted to 37°C, was used to monitor the thermal activity of the powder mixtures, with accuracy of $\pm 2 \times 10^{-4}$ K and sensitivity of 0.01 μ W.
- A VK 7020 dissolution system connected with a VK 8000 auto sampler (Vankel, USA) was used to perform dissolution tests. The dissolution samples were analyzed using an isocratic HPLC system consisting of SPD-10A UV detector, SIL-10A auto sampler, LC-10A pump (Shimadzu, Japan). This system was equipped with C18 Licosphere® 100 RP-18 column (Merk KGaA, Germany). The samples were eluted using a mobile phase consisting of 65:35 acetonitrile/water and the pump adjusted to 1-ml/min constant flow. The UV detector was adjusted to 254-nm wavelength.
- Solid-state reactions between different constituents were investigated by DSC (TA Instruments, USA, DSC 1000).

Procedures

Powder Mixture Preparation

Stepwise blending was used to prepare different equivalent powder mixtures consisting of 1:1:1 ratios of prednisone/MCC/DCPD. The sequence of blending, as well as the incubation time of prednisone with one of the excipients, MCC or DCPD, varied during the preparation of the eight different powder mixtures. The mixtures were prepared in pairs; each pair (here defined as A and B) only differ in the sequence of blending prednisone with DCPD or MCC as shown in Fig. 1.

Pair I consisted of two mixtures: IA and IB. Mixtures IA/IB were prepared by mixing 0.5 g of prednisone with 0.5 g of MCC or DCPD, respectively, for 30 min using a rotary tumbler. Complementary excipient (0.5 g), MCC or DCPD, was then added to the blends and tumbled for additional 30 min. Mixtures IA/IB were considered fresh mixtures as their preparation was incubation-free.

In pair II mixtures, prednisone was mixed with either MCC or DCPD and then incubated at 37°C for 1 month before the complementary excipient was added. 0.5 g of prednisone was mixed with 0.5 g of MCC (A) or DCPD (B) for 30 min. The mixtures were filled in crimp-top 4-ml vials; the vials were sealed with PTFE rubber seal and aluminum cap and inserted in the TAM III channels. The heat flow of the mixture was recorded over 1 month, then the vials were taken out and 0.5 g of the complimentary excipient DCPD or MCC was added respectively to the mixtures in the vials and blended again for 30 min.

Mixtures of pair III were also prepared by a two-step blending procedure similar to IIA/IIB mixtures. However, the last blending step was followed by a second cycle of incubation which lasted for 3 months, which is the time required for the monitored reaction to finish, as shown in Fig. 1. IVA/IVB mixtures were prepared in a different way as an extensive blending for 1 h was applied during preparation. As shown in Fig. 1b, 0.5 g of prednisone was blended extensively with either MCC or DCPD for 1 h. The resultant powder mixtures were left at room temperature for 2 h before the complimentary excipient, DCPD for (A) or MCC for (B), was added followed by a second cycle of extensive blending for 1 h. The final mixtures were then incubated in the ITMC at 37°C until the monitored reaction was finished.

Thermal Analysis

Isothermal Microcalorimetry. The thermal activity of the incubated powder mixtures under isothermal conditions at 37°C were recorded using a TAM III. Plain powders and (1:1) two-layer powder preparation were used as controls. The two-layer powders were prepared by adding the components, prednisone/DCPD or prednisone/MCC, to a 4-ml crimp vial to form two layers, one above the other. To ensure that the components of the two layers share minimum contact surface, no mixing was applied. The thermal activity of different two-layer powder preparations, with prednisone as the upper layer or the lower layer, was examined.

Differential Scanning Calorimetry. DSC was performed on all eight different powder blends. Approximately 10 mg of each mixture was weighed into aluminum pans. The pans were sealed and heated from 50°C to 300°C at 10°C min⁻¹ heating rate. An empty sealed pan was used as a reference.

Fig. 1. Blending sequence of eight different powder blends consisting of equivalent content of 1:1:1 ratios of prednisone/MCC/DCPD. **a** Blending sequences of I, II, and III powder mixtures. **b** Blending sequences of powder mixtures IV

XRPD

Samples were analyzed using a Shimadzu XRD-6000 X-ray powder diffractometer equipped with a Bragg–Brentano optical setup. Cu K α radiation was used with a long, fine-focus X-ray tube. The tube voltage and amperage were set to 40 kV and 30 mA, respectively. The divergence and scattering slits were set at 0.5°, and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. Samples were scanned at 0.02 2 θ /s from 10° to 110° 2 θ . Scans of each sample were run in triplicate. All powder samples were front-filled using a circular area aluminum holder. A silicon standard was analyzed to check the instrument alignment each time before sample measurements.

Tablet Preparation

The mixtures IA/B–IVA/B were used to manufacture tablets of an average weight of 200 mg with nominal 10 mg prednisone content. Mg stearate as lubricant and croscopolvidone as disintegrating agent were added to the powder mixtures forming concentrations of 3% and 5% of the total tablet weight, respectively. The mixtures were mixed for 30 min and then compressed using 1-ton compression force for 30 s. The tablets were named according to the mixture used in the preparation. Dissolution tests were performed using 12 tablets of each tablet formulation.

Dissolution Tests

The dissolution test was performed according to the dissolution test conditions as described in the USP 31 mono-

graph for prednisone tablet with the following modification: the medium was 500 ml of degassed water at 37°C and 50 rpm. One-milliliter samples were taken at 10, 15, 20, 30, 45, and 60 min with no medium replacement. The dissolution media samples were directly injected into a Licosphere® 100 RP-18 HPLC column. The mobile phase was 65:35 acetonitrile/water and the flow rate was 1 ml/min. The run time was 3 min and the prednisone peak had a retention time of about 2 min. A calibration curve between 3.75% and 120% of the expected prednisone content was used to determine the prednisone content in the samples.

Statistical Analysis

As F_1 and F_2 factors are considered as simple and effective ways to compare different dissolution profiles in terms of similarity and dissimilarity (21), this approach was used in the current study to compare the dissolution behavior of the different prednisone tablets.

RESULTS

Particle Size Measurements

An average particle size of 1.68 ± 0.03 μ m was determined for the prednisone powder; the reported result is an average of five different tests.

Thermal Activity Monitored by ITMC

Plain powders of prednisone, MCC, and DCPD were associated with almost no thermal activity, as shown in Fig. 2a

Fig. 2. **a** Thermal activity of prednisone, MCC, and DCPD as plain powders. **b** Thermal activity of two-layer (1:1) powder preparations: 1 MCC/prednisone (prednisone is the lower layer). 2 Prednisone/MCC (prednisone is the upper layer). 3 DCPD/prednisone (prednisone is the lower layer). 4 Prednisone/DCPD (prednisone is upper layer). **c** Thermal activity of 1:1 mixtures of prednisone and MCC (mix a) and prednisone and DCPD (mix b). The thermal activity of both mixtures is different. **d** Thermal activity of powder mixtures (IIIA) and (IIIB) during the second cycle of incubation. **e** Thermal activity of powder mixtures (IVA) and (IVB)

Similar to what observed for the plain powders, the two-layer preparations of prednisone and MCC showed no thermal activity, indicating that these mixtures were reaction-free. Two-layer preparations of prednisone and DCPD showed a very small tendency to have an endothermic thermal activity starting about 11 days after incubation. The order in which prednisone was placed (upper or lower layer) had no effect on the thermal activity (Fig. 2b).

The 1:1 prednisone/MCC mixture showed almost no thermal activity, similar to that seen in the two-layer preparations. In contrast, mixing prednisone with DCPD for 30 min (pair IIB) resulted in a sharp, endothermic peak after approximately 8 days of incubation (Fig. 2c).

As seen in Fig. 2d, both IIIA/IIIB powder blends show an endothermic reaction. However, these endothermic reactions followed different kinetics. IIIB mixture showed a sharper peak, and the reaction has a faster rate as it took 18 days to reach the maximum. The reaction in mixture IIIA was slower when compared with mixture IIIB as it took about 25 days to reach the maximum endothermic heat flow.

Differential Scanning Calorimetry

Prednisone and DCPD showed sharp melting peaks at 123.4°C and 239.7°C, respectively. MCC showed a no distinguishable peak within the range of 50–300°C (Fig. 3).

When prednisone was mixed with DCPD, the DSC showed a shift in the DCPD melting peak, from 123.4°C to 192.7°C. This shift was observed in all mixtures having prednisone and DCPD together regardless of the blending sequences (Fig. 3).

IIB/IIIB mixtures showed extra peaks at the range between 216°C and 222°C, which was not observed in any other mixtures (Fig. 3). DSC runs of IA, IB, IIA, IIIA, IVA, and IVB were similar (data not shown for IVA/IVB mixtures).

The DCS graphs of IVA/IVB mixtures show identical results to IA/IB mixtures (data not shown).

Dissolution Test

Mixtures IA and IB showed a similar dissolution behavior with a maximum prednisone level of around 74%.

Fig. 3. DSC tests of different powder mixtures between 50°C and 300°C at 10°C min⁻¹ heating rate

The calculated F_2 value was 80 indicates similarity in the dissolution pattern, as shown in Fig. 4, IA/B.

In contrast to what was observed for IA/IB tablets, a significant difference in the dissolution behavior was observed between IIA and IIB tablets. The calculated dissimilarity F_1 factor was 41.2; the release failed the similarity analysis too with a F_2 of 33.2, indicating that both tablets did not follow the same dissolution patterns (Fig. 4). As shown in Fig. 4, tablets of

mixture IIB exhibit lower releasing pattern compared to mixture IIA. Moreover, the dissolution behavior of tablets IIA was similar to what was observed for the mixture IA tablets. The F_2 value calculated for the tablet IA and IIA was 81.3.

The dissolution behavior of the tablets IIIA and IIIB were further influenced by the blending sequences (Fig. 4). The release patterns of tablets IIIA and IIIB were dissimilar, as indicated by F_1 (31.5) and F_2 (35.2) values.

Fig. 4. Dissolution test of IA/IB, IIA/IIB, IIIA/IIIB, and IVA/IVB tablets. Each point represents the average of 12 tests $\pm$ SD of the mean

XRPD

Figure 5 shows a comparison of the evolution of XRPD spectra for different powder mixtures. By carefully analyzing the evolution of the peaks, no significant peak position changes were observed. This suggests that blending sequences did not result in any polymorph transformation of the initial crystal structure.

DISCUSSION

A substantial change in the thermal activity was observed between prednisone/DCPD two-layer preparations (Fig. 2b) and the 1:1 ratio blended mixtures (Fig. 2c). The prednisone/DCPD two-layer preparation showed a latent solid-state reaction occurring, which was represented by the slow endothermic heat flow (Fig. 2b). This reaction is mostly limited by the small surface shared between prednisone and DCPD particles. However, mixing prednisone with DCPD for 30 min provided enough contact surfaces shared between the two materials, boosting the solid-state reaction to a visible peak. Mixing did not affect the prednisone/MCC preparations as the thermal activity of the two-layer and mixed preparation of prednisone and MCC were identical (Fig. 2b, c), exhibiting no heat flow. Therefore, the solid-state reaction existed only between prednisone and DCPD, but not between prednisone and MCC. Since one excipient triggered a solid-state reaction and the other did not, our interest was to investigate how the blending sequences might affect the observed solid-state reaction and ultimately the release profile of prednisone/DCPD/MCC powder blends and tablets.

In an industrial scale, larger amounts of material are mixed in different sized blenders. Thus, the amount of friction and the heat resulted during the blending process might not be comparable with the gram scale that was used during this study. Therefore, the study was designed to include an extra time of incubation during powder preparation to compensate for such effects (Fig. 1). This incubation was carried out in the ITMC channels in an isothermal environment at 37°C. The powder mixtures were incubated until the ITMC recorded zero heat exchange, indicating the end of any reactions.

Even though IA/IB mixtures were prepared using different blending sequences (Fig. 1), DSC and dissolution tests showed similar results (Fig. 3). This can be explained by the

Fig. 5. XRPD tests of IA/IB, IIA/IIB, IIIA/IIIB, and IVA/IVB powder mixtures

lack of heat and presumably time required to initiate a solid-state reaction between prednisone and DCPD. In other mixtures, a longer incubation was used to see the effect of that reaction.

In an industrial scale, similar mixtures to IA/IB may happen after brief mixing process. This might be preferable to eliminate any solid-state reaction; however, brief mixing will lead to uneven distribution of prednisone in the final mixture that may react upon storage. Although IA/IB mixtures were prepared without incubation, both mixtures produced a shift in DCPD melting point from 123.4°C to 192.7°C, similar to all other mixtures (Fig. 3). Compared with other tablets, IA/IB showed higher dissolution rates (Fig. 4, IA/B). This indicated that the reaction responsible for the shifting DCPD melting point has no effect on the dissolution behavior of the tablets.

The appearance of the new peak at 222°C in the DSC of IIB mixture (Fig. 3) confirmed the observation made by ITMC about having an extra thermal activity in the prednisone/DCPD powder mixture. The peak at 222°C did not appear in the DCS of the IIA in which prednisone was mixed and incubated in the first stage with MCC. Comparing the dissolution profiles of IIA and IIB tablets revealed a significant difference between the tablets with a dissimilarity factor of 41.2 and failing similarity with a F_2 of 33.2 (Fig. 4, IIA/B). This proves that the extra thermal activity detected by ITMC in IIB mixture was associated with different prednisone dissolution behavior.

The difference in the thermal activity between IIIA and IIIB mixtures further emphasized the effect of the blending sequences on the solid-state reaction. Although both mixtures showed endothermic thermal activity, the one associated with mixture IIIA was faster compared to IIIB (IIIA $T_{\max}$ =24 days, IIIB $T_{\max}$ =19 days) and had a larger amount of heat exchanged (223 mJ for IIIA and 456 mJ for IIIB, respectively). IIIB mixture preparation was initiated from a reacted IIB mixture, and MCC was not added until the thermal activity associated with prednisone/DCPD mixture was almost zero, indicating the end of the solid-state reaction. Therefore, it was expected that IIIB will not exhibit any extra thermal activity after adding MCC and mixing it for 30 min. The ITMC results showed the opposite, indicating that adding and mixing an inert material, like MCC, to an already reacted mixture will provoke the reaction again. This is most probably due to blending which will provide a new interactive surface between the two materials.

This can be explained by the fact that blending might create new surfaces between the reacted materials. On the other hand, the slow reaction associated with IIIA mixture indicates that mixing and incubating prednisone with MCC before adding DCPD had a protective effect on the prednisone/DCPD reaction (Fig. 2d), presumably by the coating effect of MCC on the prednisone particles. DSC of the IIIB mixture showed the appearance of a new peak, indicating a similar reaction to what was seen in the IIB mixture (Fig. 3). The absence of the extra peak in the DSC of the IIIA mixtures indicates that an additional reaction is going on in IIIB mixture, but not in IIIA mixture.

As ITMC is a universal tool with the ability to monitor the total heat exchange, it shows the total heat exchange over time without differentiating between different reactions happening simultaneously, or forming any new products. This

suggests that the blending sequences of IIB and IIIB mixtures, in which DCPD was added and mixed with prednisone then incubated, might provoke a new reaction to happen and resulted in the appearance of the new peaks in the DSC.

The behavior of IVA/IVB mixtures was surprising. The extensive blending of prednisone with one material for a longer time before and after adding the complementary excipient resulted in two mixtures with identical thermal heat flow and similar dissolution rates regardless of the sequence of excipient blending. ITMC showed a very slow heat exchange (Fig. 2f) and no extra peaks on the DSC runs (data not shown); the DSC was identical to what seen in IA/IB mixtures (data not shown). The absence of the new peaks in the DSC runs of IVA/IVB indicates that the extra reactions associated with mixtures IIB/IIIB was not happening with IVA/IVB mixtures. Both IVA/IVB showed similar dissolution behavior as $F_2=73.8$ (Fig. 4, IVA/B). Although both the IVA/IVB tablets showed a lower release pattern compared to mixture I A/IB, the difference was not significant as indicated by borderline F_2 values: 55 and 52 for IVA and IVB, respectively.

CONCLUSION

This study proved that blending sequences can have a profound effect on the dissolution of prednisone tablets of the same formula. Therefore, the blending process should be considered as a critical process parameter to assure similarity in drug release of the finished product. Having one or more active ingredients with one or more main excipients will result in high numbers of possibilities concerning the blending sequences. Making tablets from different powder mixtures, which have the same content but blended in different ways, and performing dissolution tests on all of the formulated tablets is time-consuming. Our results showed that powder mixtures that were blended differently but had the same thermal activity showed the same dissolution behavior. Moreover, the larger the difference in thermal activity detected by ITMC, the higher is the difference observed in the dissolution behavior of the tablets. Therefore, ITMC has the potential to be used as a screening tool in QbD to identify critical process parameters in the blending of prednisone with excipients.

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