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Development of an X-ray Diffraction Method for the Quantification of API recrystallized from Amorphous API in a Low Dose Dry Powder Formulation used for Inhalation

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PURPOSE

Typically, in the development of dry powder inhaler (DPI) formulations the use of a stable crystalline form of the active pharmaceutical ingredient (API) is desired. However, often in order to produce crystalline particles of suitable size for inhalation, micronization processes will be required, resulting in surface amorphous material which may affect the efficacy of the product. If required, additional conditioning/processing steps may then be applied to the API (or to ensure drug product stability under use) without requiring any additional solid state characterization of the API in the drug product.

Increasingly, formulations are now being developed with non-crystalline engineered API particles. These amorphous APIs are thermodynamically unstable and may be prone to recrystallization over time or upon exposure to humidity, with such recrystallization having potentially dramatic effects on the efficacy and performance of the product.

ICH Q6A[1] details that if the efficacy can be affected by a change in form of the API, then acceptance criteria must be determined for the polymorph content for the API. Identifying crystalline content in the drug substances in isolation is relatively straight forward using techniques such as X-ray diffraction as described in USP941[2]. However, they are not so straight forward for analyzing drug products (formulations) that contain additional excipients.

For the purposes of this study we have developed a model DPI formulation containing amorphous API that is also known to be able to convert to crystalline under the correct conditions. The formulation consisted of 0.4% API and 99.6% lactose monohydrate.

With such an amorphous formulation it is necessary to monitor and establish acceptance criteria for polymorph conversion within the drug product. Established X-ray diffraction (XRD) methods of quantification, for example Rietveld refinement, or the Ruland method, were not suitable here given the very low concentration of API in the formulation and the overlapping of diffraction peaks from the API and the highly crystalline lactose monohydrate carrier. The very low API concentration and small sample size also makes the use of spectroscopic methods (such as Raman spectroscopy) unsuitable. Raman mapping may improve the potential for identifying the API form in the formulation but the low sample size and very long analysis times make this an unsuitable method for QC release purposes.

Despite the difficulties mentioned, one diffraction peak at ~14.9° 2theta gave sufficient separation from the lactose diffraction peaks, enabling a powder XRD method to be developed and validated for the quantification of crystalline API in the formulation.

METHODS

Preparation of Crystalline Spiked Blends
In order to be able to quantify the degree of crystalline API in our model, drug formulation spiked samples containing a total of 0.4% API/99.6% lactose monohydrate were prepared. Spiked samples containing mixtures of amorphous and crystalline API in the following ratios were prepared. 0%, 1%, 2%, 5% 10%, 20%, 50% and 100% crystalline API (w/w). Note both the crystalline and amorphous API used were of similar sized particles suitable for inhalation.

Initially spiked blends were prepared using a simulated manufacturing process with a formulated batch size of 200g per blends as per table 1.

Table 1: Spiked blend formulation compositions.

Crystalline API		Amorphous API		Lactose	TOTAL
Conc (%)	THEORETICAL AMOUNT (g)	Conc (%)	THEORETICAL AMOUNT (g)	THEORETICAL AMOUNT (g)	
0	0.0000	100	0.7840	199.2	200.00
1	0.0082	99	0.7762	199.2	200.00
2	0.0163	98	0.7683	199.2	200.00
5	0.0408	95	0.7448	199.2	200.00
10	0.0815	90	0.7056	199.2	200.00
20	0.1631	80	0.6272	199.2	200.00
50	0.4077	50	0.3920	199.2	200.00
100	0.8154	0	0.0000	199.2	200.00

As part of the mixing process an initial pre blend was prepared by mixing the same amount of lactose as API in a vial and intimately mixed using a Turbula mixer for 25 min at 23 rpm. The pre-blend was then added to a process mixing bowl with the remaining lactose and Blended at 500 rpm for 15 minutes. All blending was performed in a controlled environment of below 30% relative humidity and between 15° C and 25° C in order to avoid any recrystallization of the amorphous API in during the blending process. However, upon analysis, issues with content uniformity were determined and thought to relate to adherence of the crystalline API to the walls of the blending vessels.

Therefore, in order to overcome the issues of content uniformity additional blends of the same ratios were prepared by directly weighing the constituents into a weighing boat with by gentle stirring before XRD Analysis. Blend masses of between 50mg total and 500mg and different analysis times between 1 hour and 6 hours per analyses were evaluated during the method development.

While the success with smaller sample sizes and four-hour collection times were observed, the compromise on 500mg sample size and 1 hour analysis time was considered most appropriate for the purpose of the method.

Experiment Parameters
XRD analysis was performed using a Panalytical X'Pert Pro instrument, with a copper radiation source and X-Celerator detector. 500mg of sample was placed directly into the sample holder and flat level surface was produced by gentle application of a glass slide to avoid any recrystallization of amorphous API. XRD Analysis was performed with the conditions as detailed: Start Position [° 2θ]: 14.7084, End Position [° 2θ]: 15.0824; Step Size [° 2θ]: 0.0170, Scan Step Time [s]: 3001.6450, Spinning: Yes

Data Analysis
Data analysis was performed using the HighScore software, with the maximum peak height determined at ~14.9° 2theta.

CONCLUSIONS

By using a conventional laboratory powder X-ray diffractometer we have been able to demonstrate by the data generated for this model study that a relatively simple method for the detection and quantification of very low levels of recrystallization API can be developed and validated as required by ICH Q2 (R1) guidelines [3]. This has been achieved despite the challenges presented from the very low overall API content (0.4%), the highly crystalline lactose carrier (99.6%) and only a very small region suitable for detection to work in. This methodology will be a useful tool to support the development of low-dose DPI formulations to characterize the physical form of the API

RESULTS

Figure 1 shows the initial overlaid diffractograms obtained at ~14.9° 2theta using 50mg sample size and 4 hours analysis time. This clearly demonstrates the suitability of the technique to identify very low levels of crystalline API content within the formulation.

However, as mentioned previously, the 4-hour analysis times were deemed unsuitable as a routine method of analysis. Hence the switch to greater sample size and reduced collection time. The mean response for is given in Figure 2 and clearly demonstrates a linearity of response from the mean of six replicates of each spiked blend.

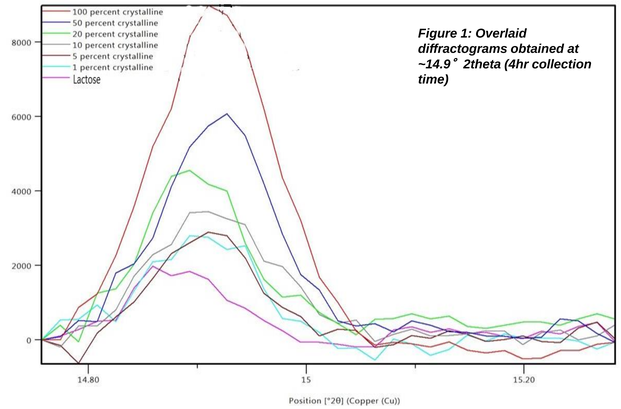

Figure 1: Overlaid diffractograms obtained at ~14.9° 2theta (4hr collection time)

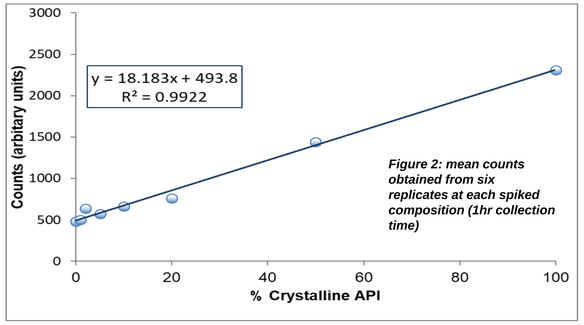

Figure 2: mean counts obtained from six replicates at each spiked composition (1hr collection time)

REFERENCES

[1] ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.
[2] USP 941 Characterization of crystalline and partially crystalline solids by X-ray Powder Diffraction.
[3] ICH Q2 (R1) Validation of Analytical Procedures: