

Not just polymorphism: The particle size as API CQA for drug product development

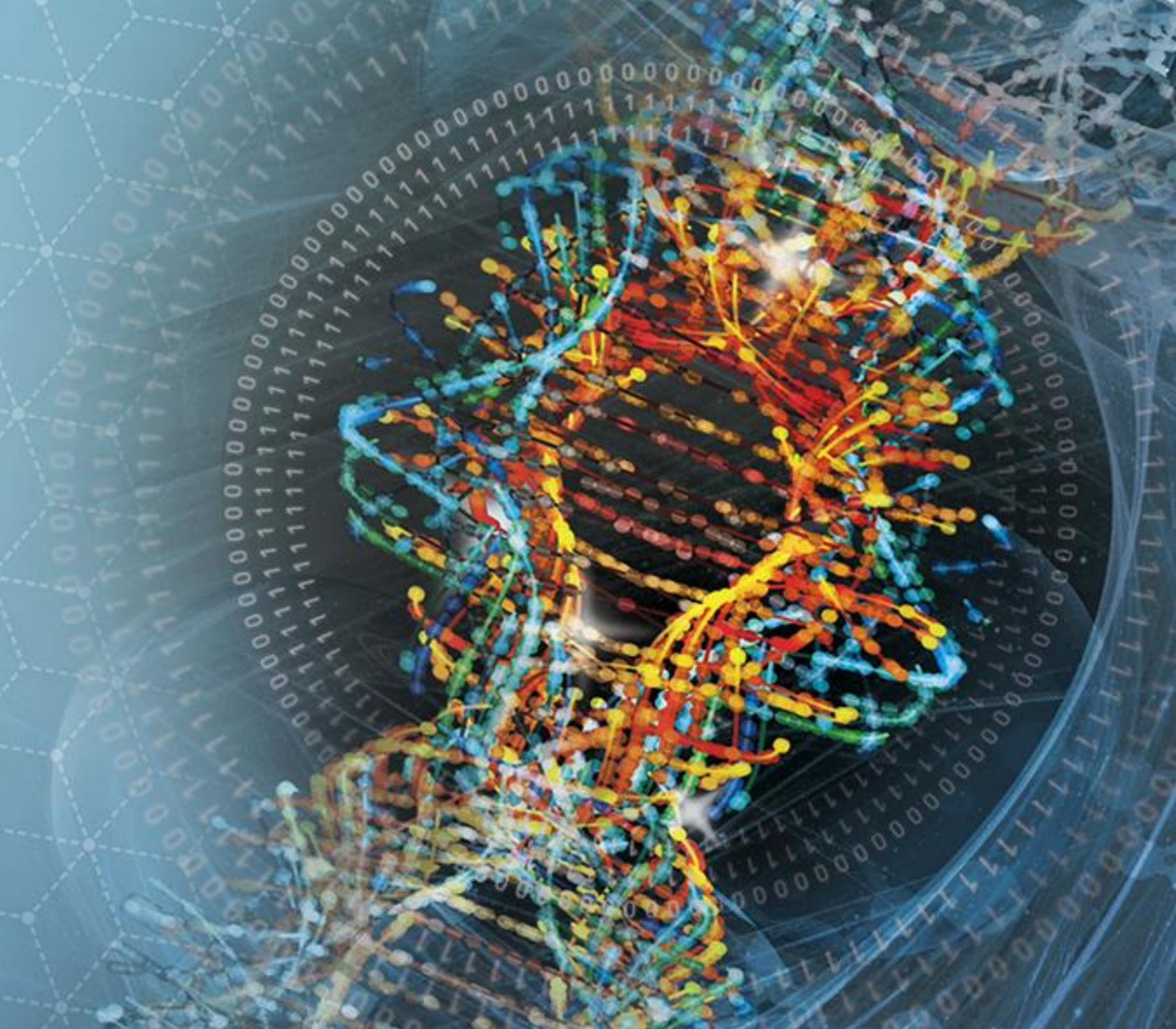
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PURPOSE

The solid state characteristics of an Active Pharmaceutical Ingredient (API) have great impact on the Drug Product (DP) performances and its formulation development approach. It is well established that the control of the **API form** (due to polymorphism) is more than critical due to the great influence of the form on the properties of the final DP with ethical, therapeutic, commercial and economic implications. Furthermore, another API Critical Quality Attribute (**CQA**) that has to be controlled in order to ensure the success of a given formulation strategy in terms of manufacturability (blend homogeneity, flow ability and API segregation) is the Particle Size Distribution (PSD).

In this case study, the **API PSD is controlled using different approaches:**

- **Mechanical reduction** by Fitzmill Hammer Mill
- **Crystallization method (seed response curve)**

METHOD(S)

A Fitzmill Hammer Mill (Fitzpatrick®) was equipped with a mesh of 297 μm aperture. API batch underwent a double processing step: the first passage was carried out at 5000 rpm while the second one at 8000 rpm.

This milled API batch was used to prepare blends at 2 API loads (low and high % w/w), which were filled in HPMC capsule with Zanasi 6E (IMA) automatic capsule filling machine to have a DP at two different strengths.

Alternatively, the existing final crystallization procedure (solvent/ antisolvent with seeding), already in place for the polymorphic control, was further investigated using two different types of seed at different loadings. All experiments were carried out in 50 mL Mettler Toledo EasyMax reactor equipped with a 4-blade impeller, internal temperature control and FBRM (Focused Beam Reflectance Measurement) probe for in-situ particles monitoring.

PSD data was generated using a Sympatec HELOS HF instrumentation. Ad-Hoc HPLC method was developed and validated for the API in the drug product.

RESULT(S)

The first API batch available for the formulation prototype production and selection showed a $D(v,0.9)$ (aka x90) around **350 μm** . Double passage in the **FitzMill** resulted in API with a $D(v,0.9)$ around **140 μm** . This was compatible with the chosen excipients, especially with the mannitol grade (e.g. Pearlitol 200 SD) given that has a mean diameter of 180 μm .

Both blends produced with this milled API were **homogeneous** (RSD < 2.0%) and with an acceptable **flowability** (see Table 1). Capsules obtained after automatic filling showed **stable weight uniformity, API content uniformity** and **good assay** (see Table 1). These results confirmed that a particle size of about $D(v,0.9)$ < 150 μm was a suitable target quality attribute for the API.

Meanwhile, the existing API crystallization procedure was further investigated to understand the impact of seed attributes / loading on the final API PSD.

Two different seed types were utilized (**daughter seed** with $D(v,0.9)$ around 460 μm and a **micronized seed** with $D(v,0.9)$ around 14 μm produced with a Jet Mill) at **different seed loads**. A clear dependence on the seed size and load was demonstrated as shown in the Figure 1 and 2 below.

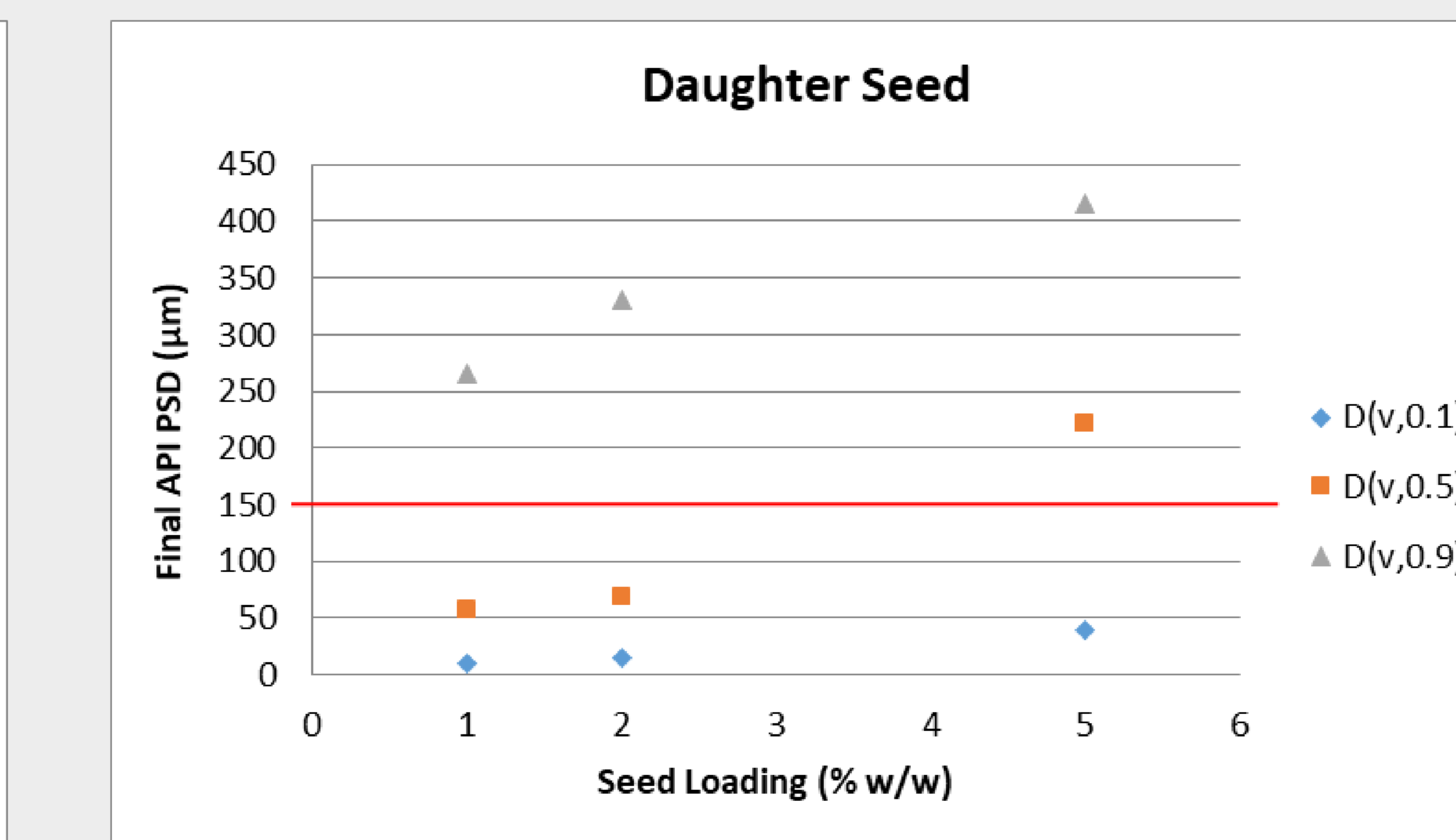
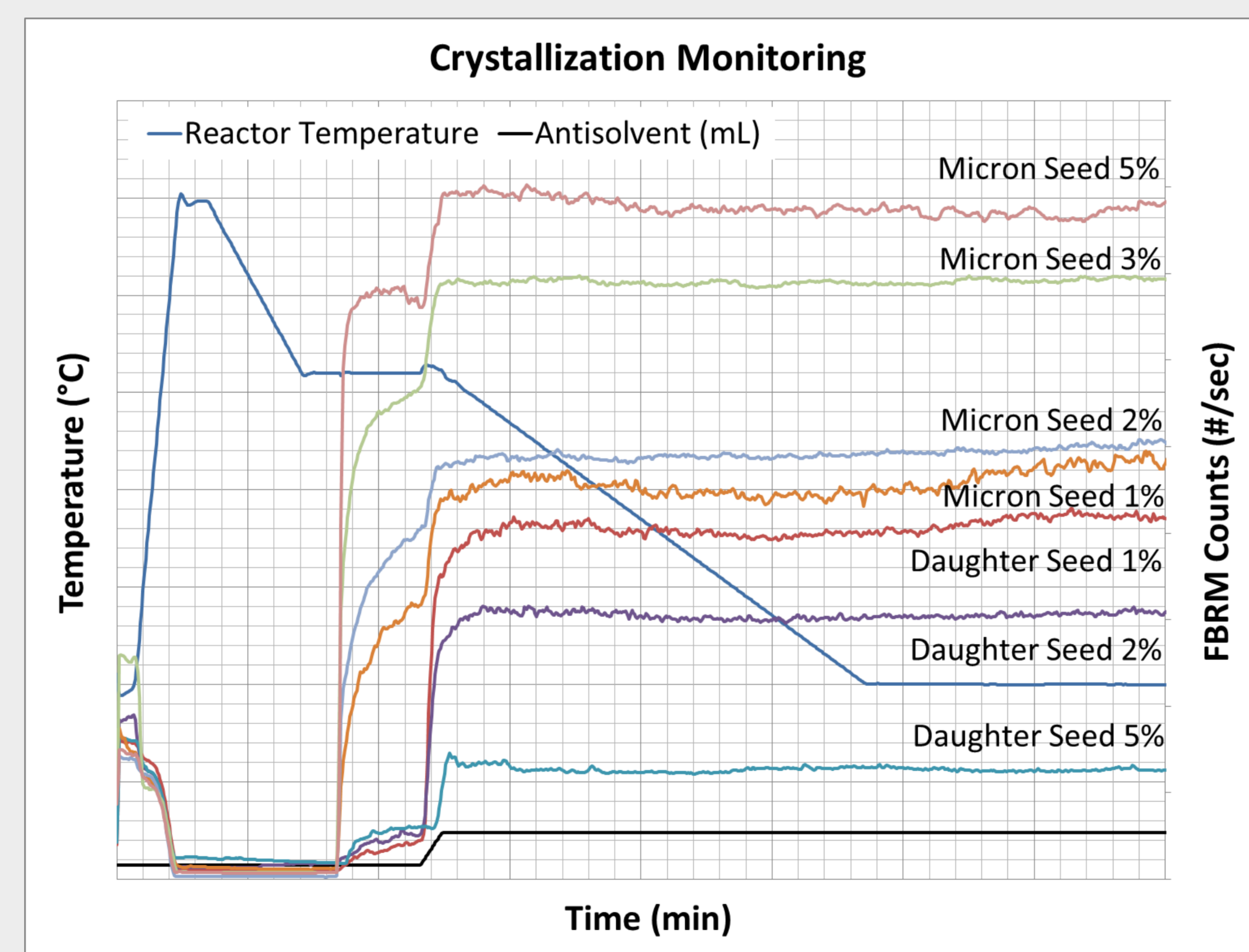


Figure 1: Seed Response Curves with FBRM

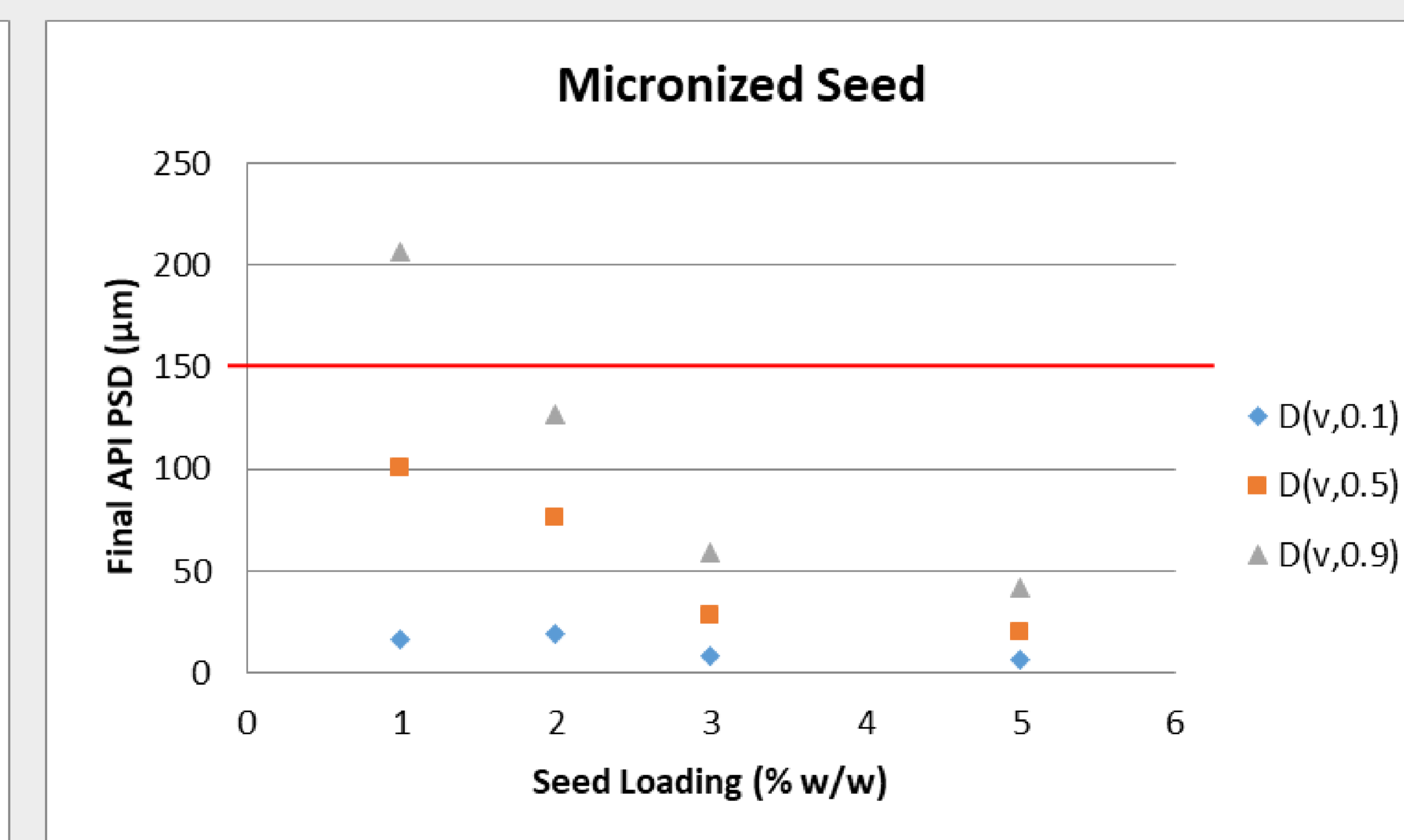


Figure 2: Seed Response Curves – PSD Data (target $D(v, 0.9)$ value highlighted by a red line)

The use of micronized seed reduced the PSD of re-crystallized material. It was shown that the PSD control of re-crystallized material to the target dimensions ($D(v,0.9)$ (aka x90) around 150 μm) can be obtained by means of micronized seeds at relevant loading (at least 2% w/w), with a robust process which delivered consistently the PSD in the desired range.

CONCLUSION(S)

PSD is an **API CQA** to be taken into account for successful formulation development approach, especially for blend in capsule formulations.

This case demonstrated how a controlled particle size of the API, in light of the chosen excipients, was important to guarantee blend homogeneity, acceptable mechanical characteristics for the encapsulation (i.e. flowability) and final DP quality, avoiding problems such as segregation during the manufacturing process.

The **effective control** of this CQA (PSD) was reached via **mechanical milling** of the input API before formulation. Moreover, in order to avoid extra steps before DP manufacturing, an alternative route to control API PSD was obtained via **crystallization**, demonstrating the **influence of the seed size and load** on the final API PSD and the ability to control particle size without the need for post isolation milling.

Blend	Content Uniformity: % Claim (average of 6 replicates)	RSD %	Hausner Ratio
Low % w/w	99.5	1.5	1.31
High % w/w	96.4	1.1	1.32
Capsules	Content Uniformity: % Claim (average of 10 replicates)	RSD %	Assay (% Label Claim)
Low % w/w	97.3	1.4	97.7
High % w/w	102.3	1.8	100.1

Table 1: Analytical Data

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