

## Characterizing Particle Disintegration Formulation to Tablet Dissolution

### Introduction

USP tablet dissolution testing is recognized as a standard analytical test used in the pharmaceutical industry. However, the information gathered during the USP test is often not sufficient to establish the root cause of dissolution inconsistency.

As the role of dissolution testing moves towards screening formulation development and enabling quality by design (QbD), a more mechanistic understanding is required to determine why tablets release API with varying kinetics. A series of industrial case studies are presented where the application of *in situ* particle monitoring technology,

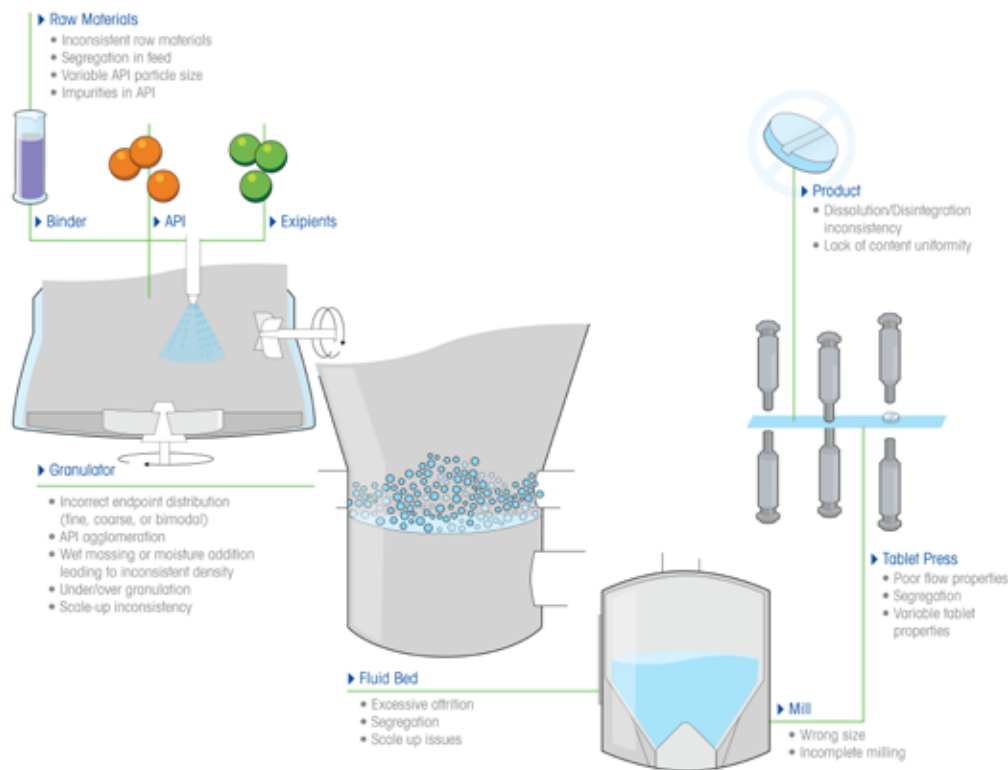
METTLER TOLEDO FBRM® (Figure 1), is demonstrated to track a series of tablet disintegration and dissolution profiles while measuring the particle distribution in real time at full concentration with no sampling necessary.

By understanding the mechanism for particle disintegration and dissolution, users can correlate release inconsistencies to the upstream source of variability, i.e. changes in raw materials, granulation inconsistency, segregation during transfer and storage, varying impurity profile of API or tableting irregularities (Figure 2).



Figure 1.

Figure 2 – Where do Particles Play a Role?



# Characterizing Particle Disintegration

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### Disintegration Study 1: BSC Class I<sup>1</sup>

In this study dissolution kinetics for an immediate release BCS Class I drug compound was studied. In theory the limiting factor for this highly soluble compound is the tablet disintegration.

Figure 4 shows a case when API solubilisation and tablet disintegration rates yield similar kinetics (at pH 1).

The counts per second FBRM<sup>®</sup> trend (blue) tracks the rate of tablet and granule disintegration.

This follows a similar path as the % API released as measured by fiber optic dissolution testing probe. In this case the drug dissolution profile is limited by the tablet disintegration.

Figure 5 shows a case where API solubilisation and tablet disintegration rates have varying kinetics (at pH 6.8).

The disintegration kinetics measured using FBRM<sup>®</sup> are similar to Figure 4 – however the API release rate is much slower. This indicates that the solubilisation of the API is the rate limiting step at this point in the design space.

### Disintegration Study 2: BSC Class II<sup>1</sup>

During the development of an immediate release BCS Class II drug compound, prolonged in vitro dissolution release times were observed for certain tablet lots.

Examples of 'good' and 'bad' tablets were prepared and monitored by FBRM<sup>®</sup> and fiber optic dissolution testing. Figure 6 shows dissolution and disintegration kinetics for a good and bad batch of tablets. FBRM<sup>®</sup> trends indicate that the bad tablets are initially broken up into larger particles that do not readily disintegrate. This disintegration mechanism correlates with a significantly slower drug release profile. The bad tablets are more brittle and are broken into larger particles.

By investigating the root cause of the disintegration problem and reformulating the tablets with a new filler, drug release inconsistency was eliminated (Figure 7).

### Disintegration Study 3a: Compression Force<sup>2</sup>

The impact of tablet compression force on dissolution is studied.

Figure 8 shows that a higher compression force results in a slower API release rate.

The mechanism of this is revealed by studying the FBRM<sup>®</sup> data (Figure 9). Tablets manufactured at high

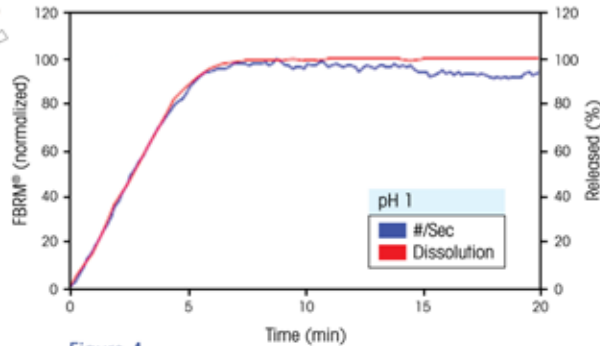
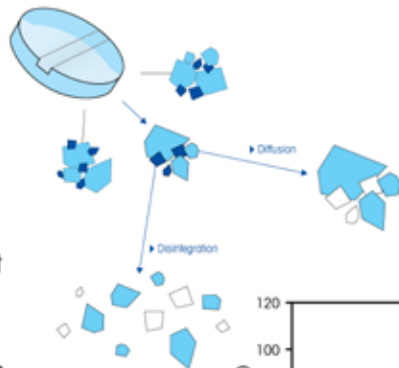


Figure 4.

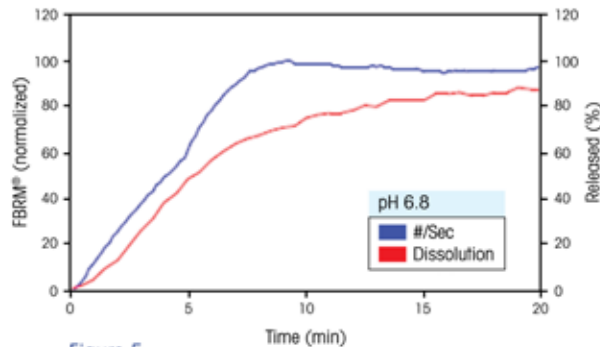


Figure 5.

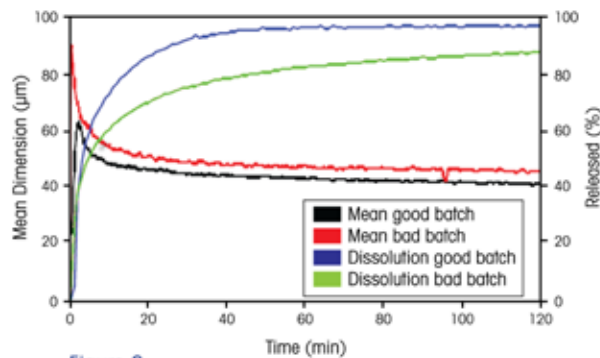


Figure 6.

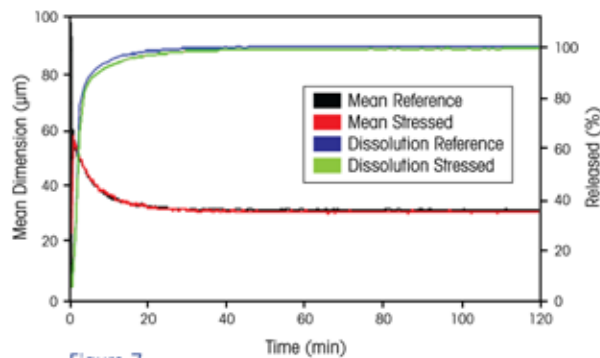


Figure 7.

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compression force break up into larger particles during dissolution – resulting in a slow release rate. It is likely that the higher compression force during tableting leads to plastic deformation and aggregation of the granules.

### Disintegration Study 3b: Compression Force<sup>3</sup>

In example 3b the opposite is observed. Figure 10 shows dissolution data gathered for a different process. In this case a higher compression force results in a faster and more complete dissolution rate.

Again the mechanism is revealed by studying FBRM® data. In Figure 11 the *in situ* particle distribution at the end of dissolution is clearly smaller at the higher compression force. It is likely that during compression there is more granule fracture and breakage at the higher compression force.

### Disintegration Study 4: Liquid Level and Tableting<sup>4</sup>

Disintegration studies were performed using tablets as well as the final granule blend (pre-tableting) in an effort to understand the impact that the tableting process has on the granules. Granules and tablets were developed using high and low water levels in the granulator. An insoluble media was chosen to study disintegration without dissolution.

In Figure 12 and 13 the disintegration profiles for tablets and the final granule blend were compared. In Figure 12 the formulation utilized low water levels. In Figure 13 the formulation utilized high water levels.

With low water levels (Figure 12), it is evident that the granule dimension at the end of the disintegration process is larger in the tablet than in the blend. This indicates that during tableting there is an increase in granule size most likely due to fragmentation or plastic deformation.

With high water levels (Figure 13), the mean is much larger however the granules at the end of the disintegration process have the same dimension in the final blend and the tablet. This indicates that high water level produces larger granules, but these granules show negligible fragmentation or plastic deformation during tableting.

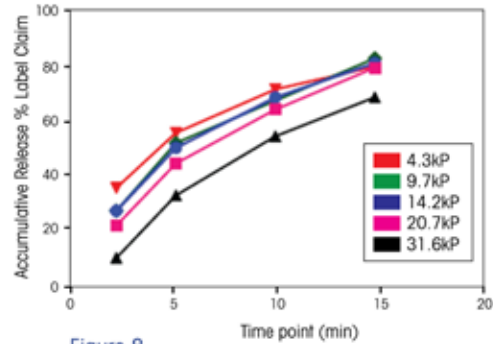


Figure 8.

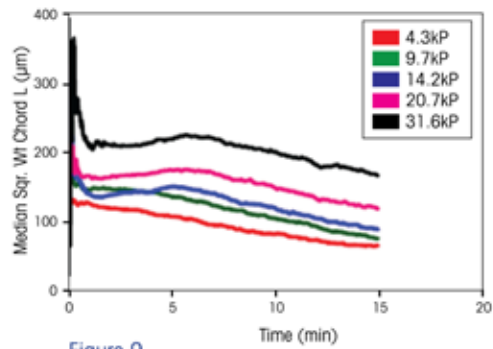


Figure 9.

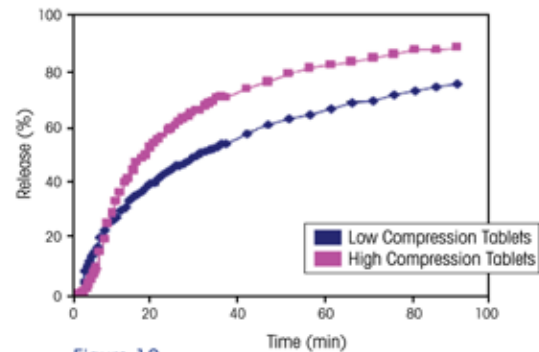


Figure 10.

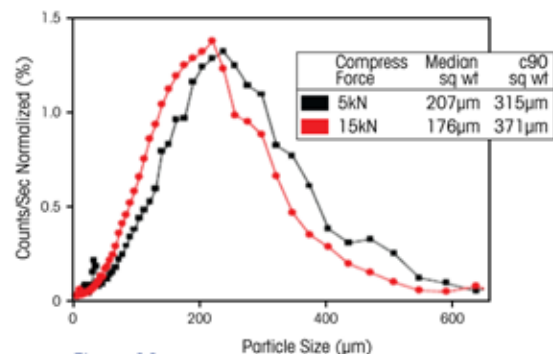


Figure 11.

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## Formulation to Tablet Dissolution

### Conclusions:

- *In situ* particle disintegration kinetics correlate to the dissolution profiles yet they offer added understanding to the root cause of tablet dissolution inconsistencies. Lot-to-lot variation is evident when examining the dissolution profile and tablet disintegration.
- By characterizing particle disintegration mechanisms with *in situ* FBRM® technology users can correlate upstream process variables to dissolution kinetics. This information can be used to quickly screen upstream granulation and tableting conditions to achieve a repeatable targeted dissolution release profile.
- FBRM® can speed process development by providing immediate understanding that allows formulators to make better decisions faster saving up to months of development time, targeting consistent final products, and ensuring formulators have answers for regulatory questions

### Acknowledgements/References

1. Jonas Johansson, AstraZeneca, Sweden  
<http://www.aapspharmaceutica.com/meetings/files/63/Johansson.pdf>
2. Kyle Bui Vertex Pharmaceuticals  
<http://www.aapspharmaceutica.com/meetings/files/126/bui.pdf>
3. Zane Arp, GlaxoSmithKline, AAPS, November 2007
4. Michael Cheng, Amgen, AAPS, November 2007
5. Moheb Nasr, CDER, FDA  
<http://www.fda.gov/cder/Offices/ONDQA/presentations/051024-MMN-Dissolution.pdf>
6. Des O'Grady, Benjamin Smith, Ian Haley, METTLER TOLEDO
7. Jeff Seely, Distek

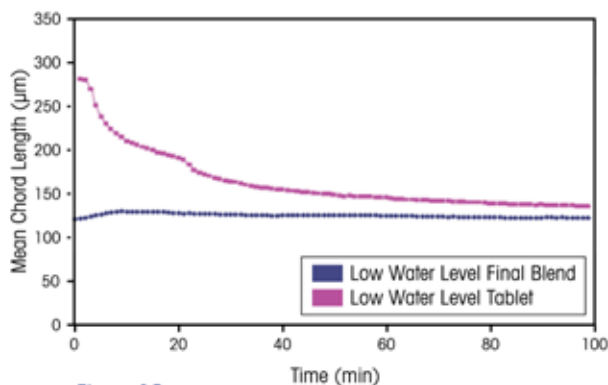


Figure 12.

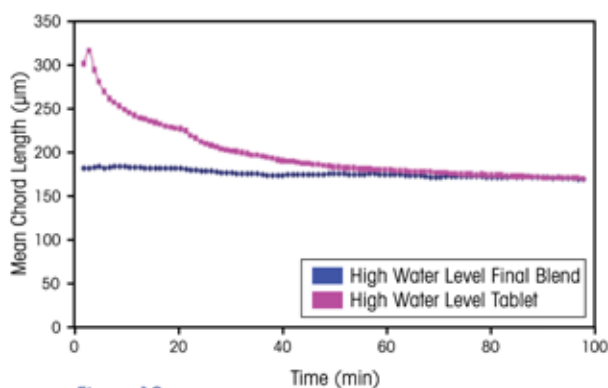


Figure 13.



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