A Real-time Study of Disintegration and Dissolution in Solid Oral Dosage Forms with Focused Beam Reflectance Measurement (FBRM) Technology

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Background

- To study the effect of disintegration mechanism on the drug release of solid oral dosage forms using Focused beam reflectance measurement (FBRM) technology.
- FBRM measures particle distribution in real-time, providing valuable information for formulation development.
- Breaking up of granules upon capsule/tablet disintegration into smaller particles is an important step for drug release.
- Here we have utilized FBRM technology for investigating drug release behavior from capsule and tablet formulations with different sizes of API.
- We also utilized a fiber optic dissolution testing system to correlate the dissolution profiles to the differences in particle size distribution between formulations.

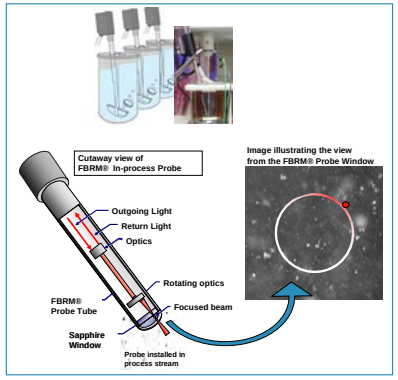

Figure 1. FBRM Technology and Working of the FBRM probe

FBRM Method of Measurement

Inserted directly into the process, FBRM probe contains internal optics that focus a tight beam of rotating laser light at the probe window. When light hits a particle, the duration of the backscatter is measured and converted into a chord length. Tens of thousands of particles are measured/second generating a chord length distribution in real time.

Methods

- Three experimental formulations of the same API (50mg), Form. A, Form. B and Form. C was each added to 900 ml of dissolution medium.
- Form. A and Form. B are capsule formulations with unmilled and milled API & excipients, respectively. Form. C is a tablet with milled API & excipients (Table 1).
- Dissolution test was carried out at 150 rpm.
- Changes in the particle distribution were continuously monitored using the FBRM probe, inserted in the dissolution vessel over 70 minutes.
- Dissolution samples were collected manually every 10 minutes for 70 minutes to obtain % drug release using HPLC.
- Fiber optic dissolution testing system was also utilized to determine the dissolution profiles of the 3 formulations (n = 2), especially during earlier time points in the experiment.
- Data was acquired every minute for 70 minutes, experimental setup was similar to the conventional dissolution experiment. App 2, 150 rpm@ 37°C.

Table 1. Formulations used in the study

Formulation	Particle size of API
Formulation A – Capsule	Large, Unmilled API
Formulation B – Capsule	Small, Milled API
Formulation C - Tablet	Small, Milled API

Results

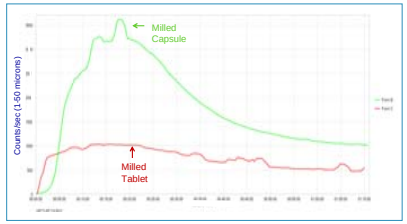

Figure 2. Comparison of fine particle counts between capsule (Form B) and tablet (Form C) formulations containing milled API

Results

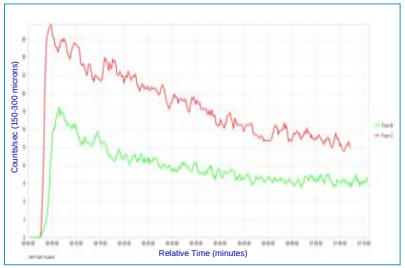

Figure 3. Comparison of coarse particle counts between capsule (Form B) and tablet (Form C) formulations containing milled API

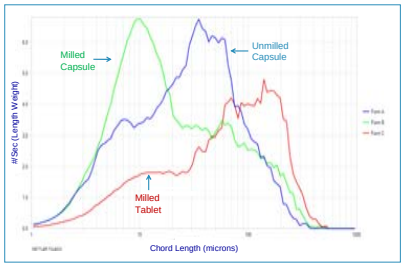

Figure 4.Comparison of particle distribution between Formulations A, B and C after 15 minutes.

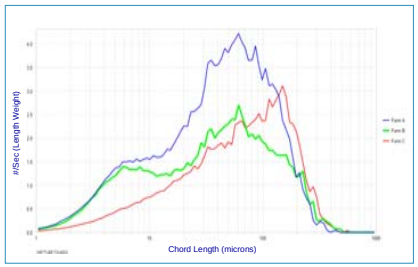

Figure 5. Comparison of particle distribution between Formulations A, B, and C after 60 minutes.

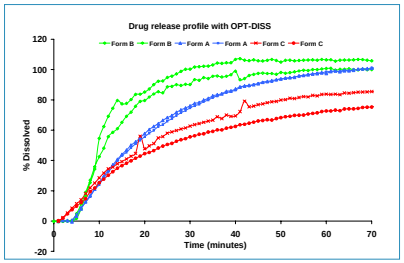

Figure 6. % Drug release from capsule and tablet formulation over 70 minutes, obtained via fiber optic dissolution method

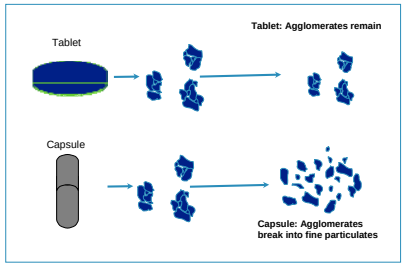

Figure 7. Possible disintegration mechanism differences between capsule and tablet formulations

- Fig. 2 shows that the milled tablet (Form C) disintegrates immediately whereas there is a delay for the milled capsule (Form B). This correlates with drug release kinetics (Fig. 6) which show the milled tablet releasing API instantly while there is a delay for the milled capsule; likely due to delayed shell opening
- Fig. 2 also shows that the milled capsule breaks apart into a much larger number of fine particles. Since fine particles have a larger surface area-to-volume ratio one expects the dissolution rate to be faster; this is confirmed by the drug release kinetics in Fig. 6.
- Milled tablet breaks apart into a much larger number of coarse particles within which API will be trapped reducing the overall extent of drug release (Figure 3).
- Figs. 4&5 show FBRM distributions for each formulation at 15mins and 60mins respectively. Initially the milled capsule breaks apart into a larger number of fines compared to the milled tablet – with the unmilled capsule between the two. After 60mins the distributions are more similar as the fine API particles have dissolved and insoluble excipients remain
- OPT-DISS determination of drug release profiles for all three formulation indicates that the extent of drug release is far higher for the milled capsule (~100%) than for the milled tablet (~80%) by 60 minutes.
- A probable mechanism for the difference in the disintegration and dissolution profiles is shown in Fig. 7. FBRM demonstrated that the differences in disintegration patterns for capsules and tablets altered the performance of the formulation and resulted in differing drug release profiles.

Conclusions

- Differences in particle disintegration mechanisms, revealed by FBRM, clearly correlated to the different % drug release rates for each formulation.
- FBRM can quickly identify the root cause of dissolution variability and assess the impact of different formulation conditions (tablet vs. capsule) and raw materials (milled vs. unmilled API) on dissolution performance.
- FBRM provides beneficial supplemental information to identify the root cause of low drug release, maximizing the process output, and provide for a better QbD approach.

References

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2. Investigation of an atypical observation of harder tablets having a Faster Dissolution Rate, Zane Arp et al., GlaxoSmithKline, AAPS November 2007

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