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## Challenges and considerations of automated agglomeration detection method development with image analysis in dissolution testing

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### SUMMARY

Dissolution testing is widely used during all stages of drug development. The potential to develop an imaging analysis method to automatically detect agglomerations during dissolution testing has recently been explored. The stages of the method development were manual observation of pre-recorded videos from the dissolution testing, choice of parameters for agglomerate identification and 2-stage method validation (internal and external). This work presents the two main challenges faced during the agglomeration identification method (AIM) development a) attaining an optimal number of particle detections in a video frame and b) discerning different objects (e.g., air bubbles, single particles and agglomerates) based on their specifications.

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### INTRODUCTION

Although traditional dissolution testing shows drug mass dissolved over time, it does not explain what happens in the test cell during dissolution. Application of shadowgraph imaging (SGI)<sup>1</sup> analysis can give extra visual information about particle morphology and motion in the flow-through apparatus (FTA) test cell. Agglomerate formation could potentially affect bioavailability of the drug through altering the dissolution rate in vivo. An agglomerate identification method (AIM) was recently developed to automatically detect and raise an alert when agglomerates are detected using SGI during dissolution testing in the USP 4 FTA.<sup>2</sup> The purpose of this work is to discuss the challenges and considerations encountered during AIM development.

### MATERIALS AND METHODS

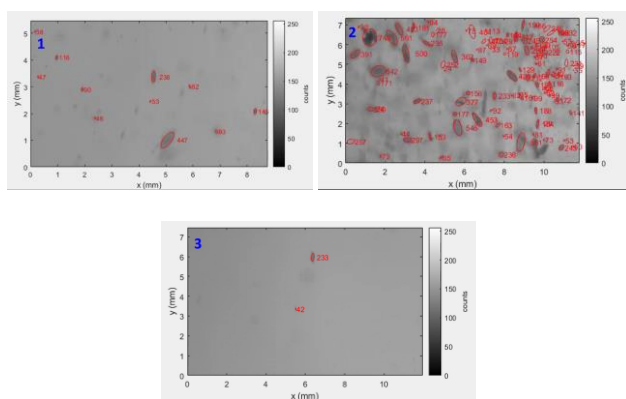
Dissolution testing was performed on a model drug (ibuprofen) in a single-cell FTA (CE1) (Sotax AG) for

2 h at 37 °C using a 22.6 mm diameter cell, closed-loop configuration and 200 mL reservoir. SGI involved recording and sizing of particles detected in a 11 x 7 mm<sup>2</sup> imaging window in the cylindrical section of the cell. The SGI set-up consisted of a high-speed CMOS Grasshopper 3 (FLIR / Point Grey Research) GS3-U3-23S6C-C camera and LED light source. 15 s videos at 10 frames/s were recorded during the dissolution test.

Matlab software (MathWorks) was used for video post-processing. AIM development involved manual agglomerate detection and creation of a reference image dataset, followed by steps to identify and validate the optimal image parameter combination for automatic agglomerate detection. Parameters of interest included the particle diameter and solidity, which is a concavity measure (i.e., the image area divided by its convex hull area). Optimal image characteristics thus needed to be identified and incorporated in the AIM.

## RESULTS AND DISCUSSION




Two main challenges became apparent during AIM development – the number of detections per video (manual observation, Fig. 1) and how to discern a particle (A), an air bubble (B) and an agglomerate (C) (Table 1). A frame with 10-20 particles (Fig. 1.1) was found to be acceptable for manual agglomerate identification. Hundreds of particles per frame made it difficult to manually identify agglomerates due to particles overlapping (Fig. 1.2). Furthermore, it was possible for AIM to count two or more overlapping particles as one agglomerate, thus, giving false positive signals. On the other hand, detection error is more difficult to quantify when there are a limited number of particles per video (Fig. 1.3).



**Fig. 1.** An example of number of particles presents in a single frame during dissolution testing in FTA. Frames with 1) 10-20 particles, 2) many particles overlapping and difficult to count and 3) few particles.

As shown in Table 1A, particle sizes varied during dissolution testing (20-800  $\mu\text{m}$ ). They are characterized by high solidity ( $> 96\%$ ). Agglomerates (Table 1C) are often bigger than a single particle, with lower solidity ( $< 96\%$ ). Both objects can move in any direction in the test cell. Air bubbles (Table 1B) are perfect circles (2D image) with solidity close to 100%, usually characterized by dark edge and bright centre. They move faster than the particles and only upward through the cell. By incorporating these characteristics in the method, AIM detection range can be better determined, hence false signals were minimized to a range of 5-12%, during validation.

**Table 1.** Characterization of a single particle, air bubble and agglomerate detected by SGL.

Object	Type	Characteristics
A 	Single particle	<b>Size:</b> 20-800 $\mu\text{m}$ ; <b>Solidity:</b> $>96\%$ <b>Movement:</b> $\updownarrow$
B 	Air bubble	<b>Size:</b> 20-40 $\mu\text{m}$ ; <b>Solidity:</b> $\sim 100\%$ <b>Movement:</b> $\uparrow$
C 	Agglomerate	<b>Size:</b> $> 150 \mu\text{m}$ ; <b>Solidity:</b> $<96\%$ <b>Movement:</b> $\updownarrow$

## CONCLUSIONS

For both manual and automated analysis, considering the optimal number of detections per frame is an important parameter for AIM development. Specific particle characteristics should be identified to distinguish particles of interest from other particles/bubbles in the cell.

## ACKNOWLEDGEMENTS

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