Wet Granulation Investigated in Real-Time Using Synchrotron-Based Dynamic Microtomography

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INTRODUCTION

Wet granulation is the most widespread method of pharmaceutical granulation [1]. Although the external mechanisms during granule formation has been studied extensively, it is much more difficult to study how the internal structures evolve [2-3]. The granule's opaque appearance prevents direct observations, and the granulation process is also on the order of seconds which requires ultrafast data acquisition [4-5]. Understanding how the internal structures form can help predict the final granule properties (i.e., porosity) which ultimately influence the dissolution, strength, and pharmaceutical products performance [6]. The synchrotron-based dynamic microtomography (μCT) technique can provide non-destructive and sub-second data acquisition [7-8]. This technique was used to investigate wet granulation and has the potential to bring new insights into evolving microstructures [9-10].

MATERIALS and METHODS

Lactose monohydrate (LMH) was used as a representative material for demonstrating the dynamic-μCT technique. The powders were loaded into a container and placed onto a rotation stage. The undisturbed powders were rotated at a constant speed of 360 deg/sec. The droplet dispenser system was turned on and slowly released a 2.5 μL water droplet 1.5 cm above the powders. The high-speed camera was turned on and the droplet was monitored closely. The camera was turned off at 20 sec after the droplet was released. Dynamic-μCT captured this process in-situ at a rate of one CT every 0.5 sec.

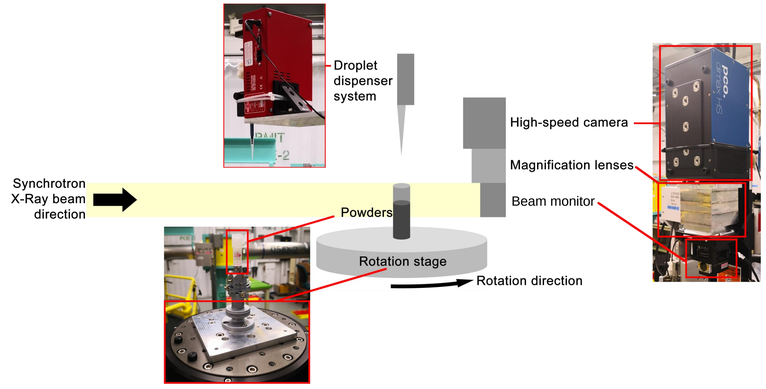

Fig. 1. Schematic of the experimental setup for performing dynamic-μCT on *in-situ* wet granulation.

RESULTS

Dynamic-μCT is a three-dimensional (3D) technique. Volume rendering of the granule and evolving interior microstructure are shown in Fig. 2. It is possible to show individual pores and networks of pores as they change and grow over time. The average pore from 3 sec to 20 sec during the granulation process increased from 2.8 to 6.8 mm^3. The porosity of the granule was observed to have increased from 1.9 to 8.8 % over the same time period.

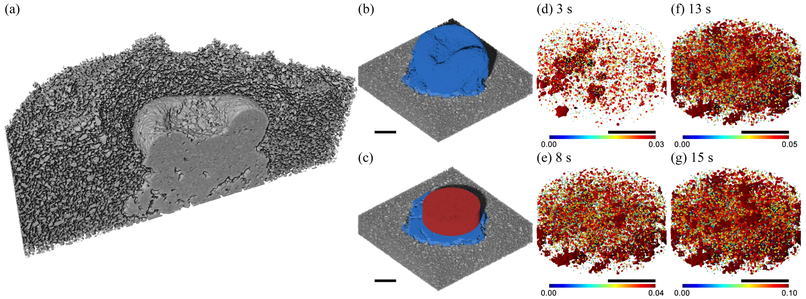

Fig. 2. (a) 3D renders of the granule exterior and interior. (b)-(c) The granule segmented from the powder bed and a representative volume extracted from the granule. (d)-(g) Individual pores of the extracted volume over time in mm^3. Every scale bar represents 1 mm.

Dynamic-μCT can non-destructively visualize the evolution of pores inside the granules in real-time. In cases where the powders were not uniformly distributed, aggregates could affect how the granule forms. This aspect of aggregates was known but was not be visualized until dynamic-μCT. The evolution of pores in a regular and an irregular granule are shown in Fig. 3.

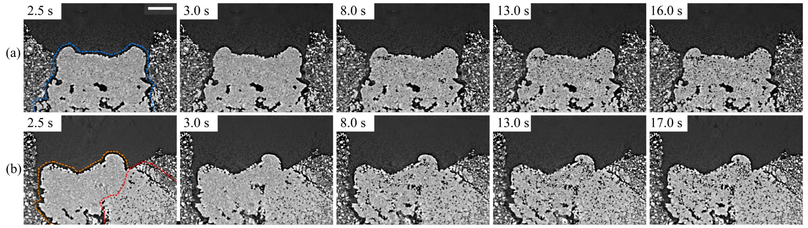

Fig.3. (a) A regularly formed granule, outlined in blue, by impact of a single drop of the liquid binder onto dry powders. (b) An irregularly formed granule, outlined in orange, due to the presence of a large aggregate, outlined in red, The scale bar represents 1 mm. The full progression can be viewed as supplementary movies.

The rate of change in porosity of the regular granule appears linear with R^2 = 0.93. In the irregularly shaped granule, the aggregate portion exhibited a small but linear rate of change with R^2 = 0.96. The siphoning effect of the aggregate increased the rate of pores evolving in the remainder of the granule for the first six seconds and becomes linear afterwards with R^2 = 0.97.

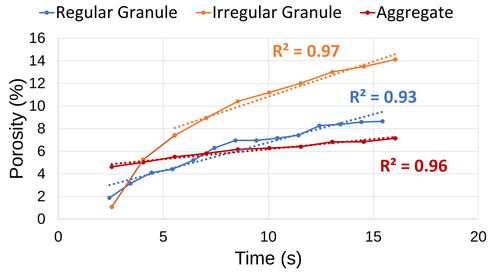

Fig.4. The changing porosity of a regularly shaped granule, an irregularly shaped granule and its associate aggregate.

DISCUSSION

The rate of change of porosity in the granule was found to be faster in the first 5-6 sec before becoming more linear. Dynamic-μCT can be used to investigate those early moments of wet granulation. One of the most powerful aspects of dynamic-μCT is the capability of choosing very specific time intervals for analysis. This can be conducted on a millisecond scale and as such, the state of the granule structure in between the early time points can not only be visualized, but also quantified with the methods shown in Fig. 2.

Supplementary movies created with dynamic-μCT

CONCLUSION

1. Dynamic-μCT is a powerful technique to non-destructively capture evolving microstructures on a sub-second scale.
2. Successfully applying dynamic-μCT to a single material is critical towards more realistic pharmaceutical formulations undergoing wet granulation.
3. This study is a key towards understanding the factors that influence granule porosity which in turn, influences pharmaceutical performance.
4. There is good potential for dynamic-μCT to be applied to not only pharmaceutical research, but also other fast occurring phenomenon in chemical engineering.

REFERENCES

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ACKNOWLEDGEMENTS

University of Saskatchewan, Canadian Light Source, Centre canadien de rayonnement synchrotron, NSERC CRSNG