Powder Technology 366 (2020) 12–21

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Powder bed packing and API content homogeneity of granules in single drop granule formation

Tianxiang Gao [a], Arun S.S. Singaravelu [a], Sarang Oka [b], Rohit Ramachandran [b], František Štěpánek [c], Nikhilesh Chawla [a], Heather N. Emady [a,*]

[a] School for Engineering of Matter, Transport and Energy, Arizona State University, Tempe, AZ, United States
[b] Department of Chemical & Biochemical Engineering, Rutgers, The State University of New Jersey, United States
[c] Department of Chemical Engineering, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic

ARTICLE INFO

Article history:
Received 5 December 2019
Received in revised form 6 February 2020
Accepted 13 February 2020
Available online 14 February 2020

Keywords:
Single drop wet granulation
Content uniformity
Granule formation mechanism
Powder packing structure

ABSTRACT

Single drop granule formation on a static powder bed of pharmaceutical mixtures was studied to investigate the effects of hydrophobicity and primary particle size distribution on the powder bed packing structure and the content homogeneity of active pharmaceutical ingredient (API) in granules formed. The granule formation mechanisms, drop penetration time, granule morphology and internal structure have been previously investigated in a mixture of coarse microcrystalline cellulose (MCC) and fine acetaminophen (APAP). When the APAP amount increased (decreasing particle size and increasing hydrophobicity), drop penetration time increased, formation mechanisms transitioned from Spreading to Tunneling, the granules became smaller in size, and the internal porosity of the granules decreased (Gao et al., 2018). In the current study, single drop granulation on mixtures of MCC and APAP with different particle sizes were investigated for formation mechanisms and granule morphology. Additionally, the powder bed packing structure was characterized by X-ray micro-CT and the API content uniformity was measured by UV–vis spectrometry. It was found that in the mixture made from coarse MCC and fine APAP, the internal structure became heterogeneous and there were dense aggregate regions in both the powder bed and granules from 25% APAP proportion, where the transition from Spreading to Tunneling occurs. The content uniformities of granules from fine powder beds are much more compromised (indicating a discrepancy between the actual value and theoretical value) than those from coarse powder beds. This content discrepancy becomes much larger when the APAP proportion in the powder bed is higher (above 50%). This was previously observed by other researchers (Nguyen et al., 2010) and was attributed to the preferential wetting of the ingredients. It is believed that the primary particle size of the powder bed is more significant than the hydrophobicity in affecting the formation mechanism, granule internal structure, and content uniformity.

1. Introduction

Wet granulation is a particle size enlargement process where powders are mixed with a liquid binder to ensure particle growth. This is an important process in many applications such as spray coating and drying, pharmaceutical tableting, detergent manufacturing and mining. Traditional wet granulation is carried out in diverse types of equipment where three rate processes occur: wetting and nucleation, consolidation and growth, and breakage and attrition [3]. The wetting and nucleation regime is of significant interest, specifically when it is in the drop controlled nucleation regime where one drop forms one granule, enabling the isolation of this critical first step of granulation [4,5]. Single drop granulation has been used to study the drop penetration time [6–8], the granule formation mechanism [1,4,9,10], and granule properties such as morphology, surface and internal structure [11–14].

In addition to the aforementioned granule properties, the content homogeneity is also of significant importance in wet granulation. The content homogeneity of the granules has been studied in single drop or high shear and continuous granulation [2,15–20] to investigate the effects of both the formulation properties as well as the granulation process parameters. Among them, the hydrophobicity and the primary particle size of the active ingredient are considered crucial factors that influence the content uniformity distribution across the granule size classes.

Nguyen et al. [2] investigated the effect of hydrophobicity on drug uniformity of a salicylic acid and lactose mixture in high shear granulation. As is the case with the binder of PolyVinylPyrrolidone (PVP) solution, where the wettability between powder and binder is good, the drug distribution is homogeneous across all granule size fractions. In contrast, when water was used as binder, the granule compositions

* Corresponding author.
E-mail address: Heather.Emady@asu.edu (H.N. Emady).

https://doi.org/10.1016/j.powtec.2020.02.039
0032-5910/

were compromised (the actual API amounts were lower than theoretically expected). The intermediate granule size fractions were deficient of drug content, while the finest and coarsest size fractions were enriched with drug content. This can be attributed to the preferential wetting of the hydrophilic ingredients that causes the overall preferential granulation of components. Similarly, Oka et al. [17] investigated the effects of improper mixing and preferential wetting of two particulate components (MCC, APAP) on content uniformity in high shear granulation. Both the powder mixture before the granulation and the granules formed after granulation were sampled. It was found that during the dry mixing stage, the top layer of the powder bed was sub-potent of the API compared with the theoretical value, indicating a potential cause of non-uniformity. For content uniformity in granules, fine granules were super-potent with API, while the coarse ones were sub-potent. A fraction of APAP remained ungranulated, likely due to the fact that MCC has a lower contact angle and thus a higher wettability with water compared with APAP, thus creating large disparity across all granule sizes. To further analyze the origin of the non-uniformity, further work was carried out by Oka et al. [16] by comparing the product content uniformity of single drop granulation and high shear granulation. They found that for a low API load percentage range (3–20%), the main cause of content non-uniformity may not be the preferential wetting of one component with the binder, but rather a combination of particle segregation during the dry mixing stage and the different kinetics of the granulation rate processes.

Recently, we investigated drop penetration time, granule formation mechanism, as well as granule internal structure with a binary pharmaceutical powder mixture of MCC and APAP [1]. Two granule formation mechanisms occurred: Spreading and Tunneling. It was found that with the increase of API, which decreases the primary particle size and increases the hydrophobicity of the mixture, the penetration time increased, the granule formation mechanism transitioned from Spreading to Tunneling, granules became smaller in size, and the internal porosity decreased.

In this work, we extend our previous study and focus specifically on the effects of hydrophobicity and primary particle size distribution on the powder bed packing structure before single drop granulation (for comparison to powder segregation in the dry mixing stage of high shear granulation) and the content homogeneity of API in granules formed. UV–vis spectrometry is used to characterize the content of API and micro-CT is used to reconstruct the internal structure and determine the porosity of the dry powder packing. These results will be useful for the design and processing of binary or multicomponent powder mixtures with regards to the homogeneity of initial bed packing and produced granules.

2. Materials and methods

2.1. Materials

Acetaminophen (COMPAP® COARSE L, APAP, Mallinckrodt Inc., Raleigh, NC) was used as the API and microcrystalline cellulose (Avicel PH-101, FMC BioPolymer, Philadelphia, PA) was the excipient. DI water was used as liquid binder. All experiments were performed at room temperature (20–23 °C), with a relative humidity around 25%. The contact angles with water for MCC and APAP are taken from the literature [17]. The pure as-received MCC and APAP powders have coarse surface mean particle sizes (d_{32}) between 30 and 50 μm. To achieve a contrast design to compare the effects of particle size distribution and the contact angle of the two materials comprehensively, finer micronized particle sizes of both MCC and APAP were prepared with a jet mill (Model 00 JET-O-Mizer system, Fluid Energy). The particle size distribution (Malvern Morphologi G3SE) and the true particle density (Micrometrics Accupyc II 1340) were measured. The fine particle sizes for both materials were reduced down to between 10 and 20 μm. The primary particle properties are listed in Table 1.

Table 1
Physical properties of powder materials (averages with standard deviations for three replicates).

Materials	Coarse d_{32} (μm)	Fine d_{32} (μm)	True density (g/cm^3)
MCC	33.7 ± 9.6	15.9 ± 5.1	1.63 ± 0.03
APAP	46.2 ± 11.0	11.5 ± 2.7	1.29 ± 0.01

2.2. Experimental design

From our previous work [1], the effects of particle size and contact angle on single drop granulation of binary mixtures could not be separated. Hence, we attempt to address this in the current work by varying the primary particle size of each binary mixture component. This design results in three mixture types with batches made from different MCC/APAP proportions. We previously studied Coarse-MCC/Fine-APAP, while the new mixture types are Coarse-MCC/Coarse-APAP and Fine-MCC/Fine-APAP.

At least 2 replicates were prepared for each MCC/APAP proportion within each mixture type. The hydrophobicity of the powder bed can be estimated by the proportion of one component compared with the other. For instance, a powder bed with a higher proportion of MCC will be more hydrophilic, while one with more APAP will be more hydrophobic. A larger difference between MCC/APAP proportions can result in large differences in the hydrophobicity of the mixtures.

2.3. Single drop granulation

Mixtures of MCC/APAP were made by measuring the weight of the two components. Then each batch was well mixed with a Turbula Shaker Mixer at 46 rpm for 20 min. Different powder mixtures were sieved through a 2.00 mm sieve into a Petri dish (1.2 cm in height and 8.5 cm in diameter) and then levelled by a stainless-steel spatula to get a smooth surface. A 100 μL syringe was filled with liquid binder and held at 5 mm above the powder surface, and a single drop was released from the syringe manually. The granules were extracted by scooping them out individually with a spatula.

The granule formation mechanisms were investigated by capturing the formation process using a high-speed camera (Photron Fastcam-X 1024 PCI). The details regarding identifying the formation mechanisms from the captured image sequences can be found in previous work [1]. The crater diameter increase is the key parameter in distinguishing between the Spreading and Tunneling mechanisms.

The granule morphology was characterized using a prism setup [1]. For each batch, six granules were excavated with the spatula as replicates. A top and side view of each granule can be captured by the setup. The images were analyzed by ImageJ software (U.S. National Institutes of Health, Bethesda, Maryland, USA) to obtain granule size and shape parameters. These parameters include projected area equivalent diameter (d_a), maximum granule height (h_{max}), maximum diameter (d_{max}), and minimum diameter (d_{min}). The horizontal aspect ratio, H.A.R. (d_{max}/d_{min}) and vertical aspect ratio, V.A.R. (d_a/h_{max}), were calculated based on these measurements.

2.4. Content uniformity

A UV–vis spectrometry method was used for determining the API (APAP) content in the powder bed surface as well as in the granules formed. Ethanol was used as solvent for APAP since it can be dissolved in pure ethanol while MCC cannot. For the uniformity of the powder bed, powder mixtures from the petri dish were sampled at five randomly chosen positions and were carefully extracted by a spatula from the surface of the powder bed to a depth of about 5 mm, with the weight of each sample between 20 and 50 mg, based on the weight of the granules formed. The spatula was wiped clean before extracting subsequent samples to prevent any contamination from the previous sample. For the uniformity of the granules, an amount of pre-weighed granules (four to six granules, with each granule weighing from 20 to 60 mg) was measured for each trial, and a total of six trials were performed for each mixture proportion. Both the bed surface samples and granules were incubated in 10 mL ethanol overnight on a shaking platform and kept out of light (APAP is sensitive to UV light). 10 μL of the solution was extracted and added to 3 mL of pure ethanol in a cuvette. The absorbance was measured at a wavelength of 250 nm, with the extinction coefficient of the acetaminophen in ethanol of $\lambda_{250,EOH} =$ 12,896 L mol^{-1} * cm^{-1} (measured by calibration experiments). The measured APAP content was then compared with the theoretical value in each proportion to assess the content uniformity.

2.5. Powder bed structure

A mixture from Coarse-MCC/Fine-APAP with 30% APAP was selected for investigating the powder bed packing structure. It would be a time intensive process to scan the entire powder bed with a duplicate (in our case, a volume of 350 mm^3 would be scanned in approximately 15 h). Hence, sampling random areas was resorted to, and care was taken to avoid any artificial changes to the microstructure of the sample. To prepare the intact sample of powder bed packing, two 1.5 mL microcentrifuge tubes were cut from the tip end and then tapped onto two random areas that were relatively far apart within the petri dish. Following the method in Section 2.3 after filling the petri dish with the powder mixture, two tubes were filled with powder and then carefully moved from the petri dish and sent for micro-CT scans.

The powder bed packing structure was scanned through a micro-CT system (ZEISS Xradia 502 Versa, Carl Zeiss X-ray Microscopy Inc., Pleasanton, CA, US). A sealed transmission source emits X-rays through the sample seated on an ultra-high precision rotation stage, which was rotated within the entire range of 0–360° with a step angle of 0.11°, resulting in 3601 radiographs. The projected image then impinges on a scintillator, which converts X-rays to visible light, and is subsequently magnified by an optical objective lens before reaching the 2048 × 2048 pixel charge-coupled detector. In order to obtain images with sufficient contrast and resolution from which the structural constituents can be easily separated, the X- ray source settings (tube voltage and current), physical imaging setup parameters (like source to sample distance and sample to detector distance) and exposure time were adjusted for the powder bed sample while obtaining the optimal voxel size achievable. The X-ray projections were processed for noise reduction using a Gaussian filter, before being reconstructed using Xradia XM-Reconstructor software with a correction for beam hardening and centre of rotation.

Reconstructed data in the form of TIFF files were then imported into Avizo (Version 9.0, FEI Visualization Sciences Group) for further image processing. A diffusion-based smoothing filter (Non-Local means) followed by a sharpening filter (Unsharp masking) was used to reduce noise, reinforce the contrast at the edges, and make details appear sharper in the datasets. Then, segmentation (binarization) was performed for separating the pixels of the grayscale images into background and foreground, i.e., voids and particles. Although the same image processing steps were applied for the volume of the powder bed, individual tailoring of thresholding values was required. Two sub regions are chosen from two samples to measure their volumes. A similar micro-CT procedure was performed for the granules, as described in previous work [1].

3. Results and discussion

3.1. Granule formation mechanisms

To identify the granule formation mechanisms and the transition between them visually, the crater diameter increase from each single drop granulation was captured from the image sequence and analyzed by

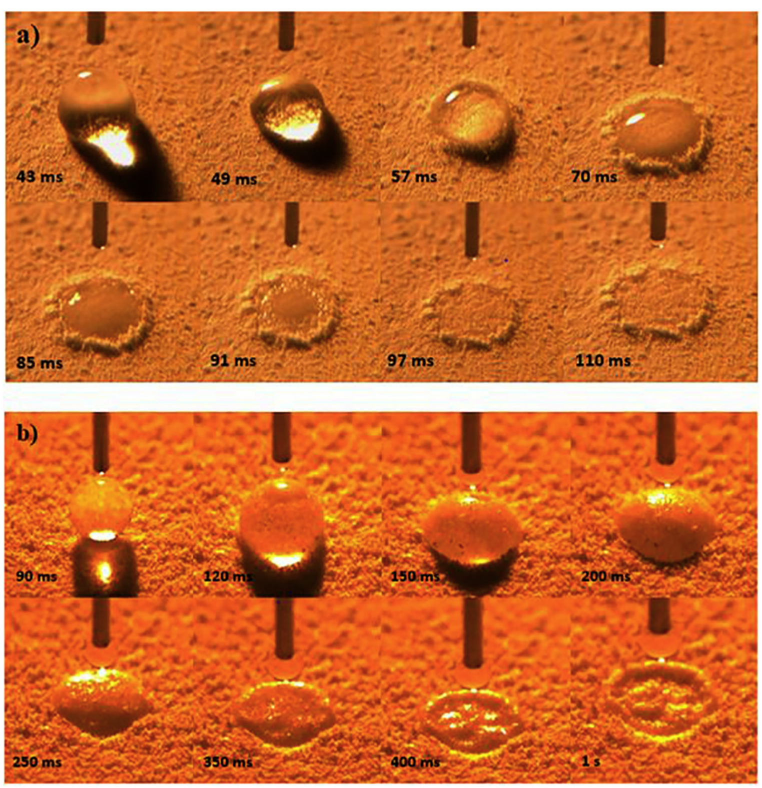


Fig. 1. High speed video image sequences of single drop granulation on Coarse-MCC/Coarse-APAP mixtures: a) 10% APAP, b) 90% APAP.

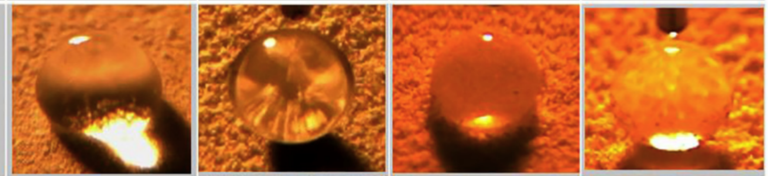
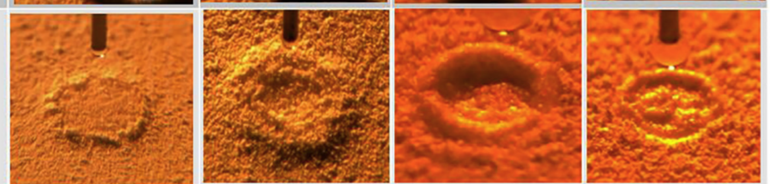
Coarse-MCC/Coarse-APAP	10 % (APAP)	30 %	70 %	90 %
Initial impact				
Final penetration				
Crater diameter increase (%)	36.1±8.3	36.7±8.9	35.8±5.4	38.1±6.3
Penetration time (ms)	67	155	300	910

Fig. 2. The crater diameter increases and penetration times of each batch from Coarse-MCC/Coarse-APAP mixtures.

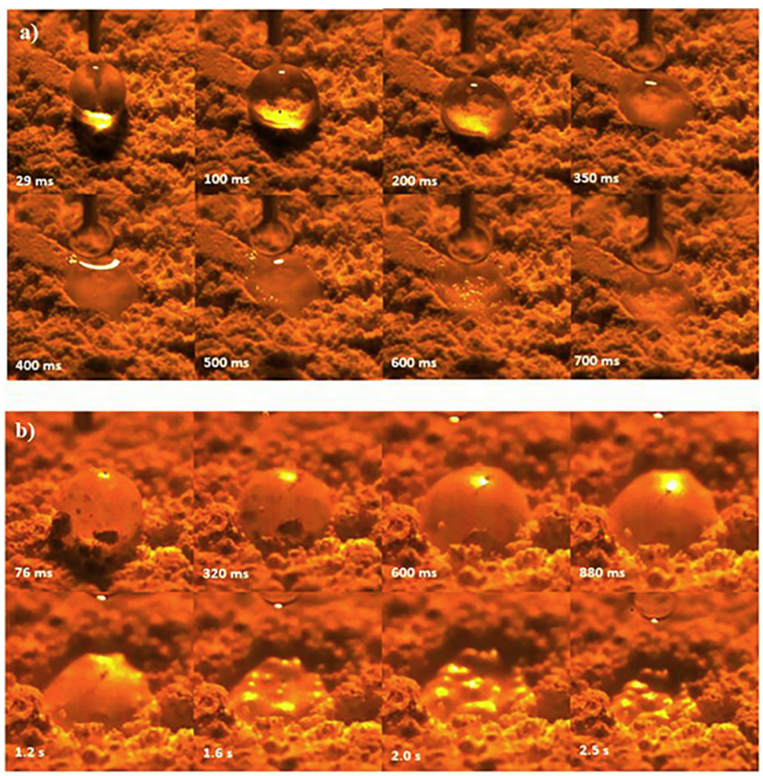


Fig. 3. High speed video image sequence of single drop granulation on the 90/10 Fine-MCC/Fine-APAP mixtures: a) 10% APAP, b) 90% APAP.

ImageJ [1]. By comparing the initial droplet footprint diameter with the diameter of the final crater formed after droplet penetration, the percentage increase was calculated and set as the value to distinguish each mechanism quantitatively. Since the results from Coarse-MCC/Fine-APAP have been discussed in previous work [1], the mixtures of Coarse-MCC/Coarse-APAP and Fine-MCC/Fine-APAP will be described in detail here. However, a comparison between all three types of mixtures will be made.

From previous work [1], it was found that the formation mechanism transitioned from Spreading to Tunneling with the increase of APAP proportion in mixtures of Coarse-MCC/Fine-APAP. The formation mechanisms for single drop granulation on mixtures of Coarse-MCC/Coarse-APAP are shown in the image sequences in Fig. 1. Different from Coarse-MCC/Fine-APAP, this mixture combination exhibits the Spreading mechanism for all MCC/APAP proportions. An initial hypothesis based on this is that increasing the overall particle size of the bed mixture results in the Spreading mechanism, regardless of the APAP proportion. To further investigate the details of the granule formation, the crater diameter increase from initial impact to final penetration was compared for each mixture proportion (see Fig. 2). The average crater

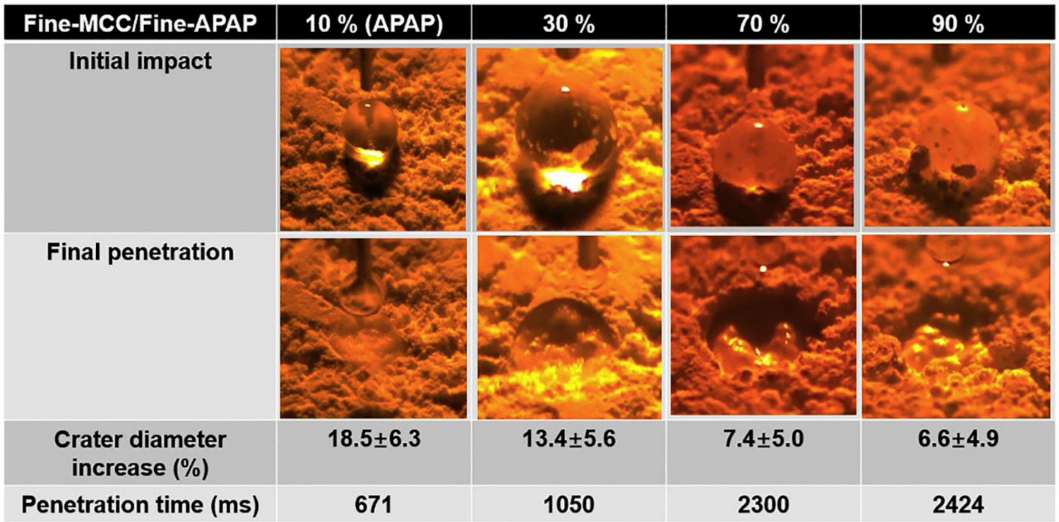


Fig. 4. The crater diameter increases and penetration times of each batch from Fine-MCC/Fine-APAP mixtures.

diameter increase ranges from 35.8% to 38.1%, which are all large enough to indicate the Spreading mechanism, based on the results from previous work, where Spreading occurred with a crater diameter increase larger than 20% [1]. Additionally, with higher APAP proportions (above 70%), marble formation also occurred (see Fig. 1b) [21,22], where the more hydrophobic powders climbed onto and covered the liquid droplet once it impacted the bed and finally formed a liquid marble [6,23]. The penetration time also increased with increasing APAP amount.

On the other hand, for the mixtures of Fine-MCC/Fine-APAP, the single drop granulation mechanism (see Fig. 3) turned out to be Tunneling for all proportions, which further substantiates our hypothesis about the significant effect of bed particle size on formation mechanism. Also, the penetration time for the droplet to completely penetrate through the powder bed increased, compared to the same proportions in the Coarse-MCC/Coarse-APAP mixtures. From the comparison of the crater diameter increase between the initial droplet and the finally formed crater (see Fig. 4), there is little change in the diameter (ranging from 6.6% to 18.5%). The crater diameter increase decreases with increasing APAP amount. With these mixtures, the droplet directly penetrated into the powder bed without spreading horizontally.

Through a comprehensive study of the formation mechanisms of single drop granulation on three different types of MCC/APAP mixtures (coarse/coarse, fine/fine, and coarse/fine), we can make some initial conclusions. In the mixtures of Coarse-MCC/Fine-APAP, it is known that with the increase of APAP, the drop penetration time increased and the formation mechanism transitioned from Spreading to Tunneling [1]. Here, both the particle size and the hydrophobicity of the bed changed, so these effects could not be distinguished. In mixtures made from coarse/coarse particles, droplets penetrate into the powder bed faster, with an obvious Spreading behaviour. On the other hand, it takes longer for the droplets to penetrate through the powder beds made from fine/fine particles, which exhibit a Tunneling behaviour. In the latter two mixture types, the APAP amount does not affect the formation mechanism. The only noticeable difference is that marble formation (an indication of hydrophobicity) occurred in both mixture types when the APAP amount increased in the mixture. As mentioned in Section 2.2, changing the APAP proportion in any mixture will lead to the change of the hydrophobicity of the powder bed. Thus, it seems that the overall particle size distribution of the powder mixture is more significant than the hydrophobicity in affecting the single drop formation mechanism.

3.2. Granule morphology

The size and morphology of the granules from Coarse-MCC/Coarse-APAP and Fine-MCC/Fine-APAP are shown in Figs. 5 and 6, respectively. The granules formed from beds of both coarse powders are all disk-shaped, with the V.A.R. ranging from 2.39 to 2.88, which is a typical Spreading indicator (where Spreading occurs for V.A.R.'s greater than 1.5 to 2.2, and Tunneling occurs for lower values) [1]. Both the size and shape are similar with all batches, regardless of APAP amount. On the other hand, the granules formed from beds made of both fine powders are much rounder. Here, with the increase of APAP amount, the sizes of the granules decrease slightly (from $d_a = 5.76$ mm to 3.96 mm). The V.A.R. values remain smaller, from 1.24 to 1.75 (with the increase of APAP proportion, V.A.R. values also decrease slightly from 1.75 to 1.24), which is a Tunneling indicator [1,4]. Moreover, the morphologies of some granules from fine/fine mixtures are more irregular, with protrusions around the surface, making them less smooth compared to granules from other mixture types.

The morphologies of the granules made from Coarse-MCC/Fine-APAP have been summarized in previous work [1]. The shapes changed from disk-shaped to round, and the granule sizes became smaller when the formation mechanisms transitioned from Spreading to Tunneling. By comparing the granules from three different mixture types, it seems that, as with the formation mechanisms, the particle size distributions of the powder mixtures significantly affect the granule morphology. When the overall particle size is large, the granules result from the Spreading mechanism and are relatively large and disk-shaped, with high V.A.R.'s. However, when the overall particle size is smaller, the granules are formed via Tunneling and are relatively small and round, with low V.A.R.'s. The amount of APAP did not significantly affect the granule morphology, except for a slight decrease in the granule size and V.A.R. with increasing APAP amount in fine/fine mixtures.

3.3. Content uniformity

Content uniformity discrepancies in the granules are expected based on the complexity of single drop granulation on the binary component system, and may be attributed to either the improper mixing of the original powder bed, or the preferential wetting of one ingredient over the other [16,17]. To investigate the potential origin of the content uniformity discrepancies, the content uniformity of both the granules and

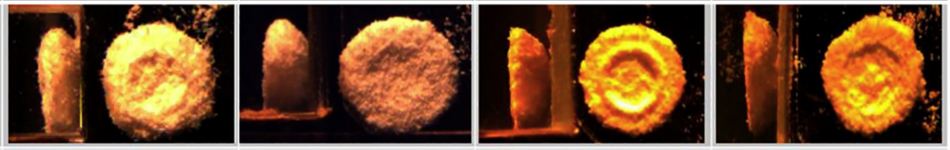
Coarse-MCC/Coarse-APAP	10 % (APAP)	30 %	70 %	90 %
Granules				
Formation mechanisms	Spreading	Spreading	Spreading	Spreading
Morphology parameters	Size (mm): d_a = 6.61±0.57 H_{max} = 2.32±0.28	d_a = 5.56±0.27 H_{max}= 2.44±0.23	d_a = 5.23±0.49 H_{max}= 2.21±0.29	d_a = 5.50±0.39 H_{max}= 2.21±0.22
	Shape: H.A.R.: 1.17±0.06 V.A.R.: 2.88±0.34	H.A.R.: 1.12±0.08 V.A.R.: 2.47±0.22	H.A.R.: 1.10±0.06 V.A.R.: 2.39±0.19	H.A.R.: 1.16±0.06 V.A.R.: 2.62±0.27

Fig. 5. The granule morphology from Coarse-MCC/Coarse-APAP mixtures.

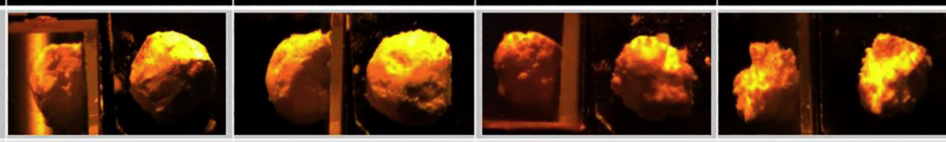
Fine-MCC/Fine-APAP	10 % (APAP)	30 %	70 %	90 %
Granules				
Formation mechanisms	Tunneling	Tunneling	Tunneling	Tunneling
Morphology parameters	Size (mm): d_a = 5.76±0.30 H_{max} = 3.30±0.21	d_a = 5.35±0.52 H_{max}= 3.54±0.29	d_a = 4.18±0.28 H_{max}= 3.36±0.41	d_a = 3.96±0.25 H_{max}= 3.23±0.34
	Shape: H.A.R.: 1.18±0.09 V.A.R.: 1.75±0.15	H.A.R.: 1.27±0.11 V.A.R.: 1.52±0.18	H.A.R.: 1.32±0.17 V.A.R.: 1.26±0.10	H.A.R.: 1.27±0.08 V.A.R.: 1.24±0.11

Fig. 6. The granule morphology from Fine-MCC/Fine-APAP mixtures.

the powder bed surface were tested. The results from three different mixture types are discussed individually and compared to each other to determine the causes of granule inhomogeneity.

For Coarse-MCC/Fine-APAP, mixtures were tested in 10% increments as a benchmark to determine the content uniformity trend. The comparison between the experimental and theoretical results are demonstrated in Fig. 7, where both the granule and bed surface uniformities with their standard deviations are shown. For the overall trend, it appears that with the increase of the APAP amount above 60%, both the content uniformities of the granules and the bed surface are compromised. The numerical values are provided in Table 2. The average deviation, V, of the actual content compared with the theoretical value is calculated as:

$$\mathbf{V} = \sqrt{\frac{\sum_{i}^{n} (\boldsymbol{x}_i - \hat{\boldsymbol{x}})^2}{\boldsymbol{n}-\mathbf{1}}} \tag{1}$$

where $\boldsymbol{x}_i$ is the actual measurement and $\hat{\boldsymbol{x}}$ is the theoretical value of APAP in each mixture. Specifically, the average deviation between the real APAP amount on the powder bed surface and in the granules becomes larger as the APAP amount increases (8.6%, 12.5%

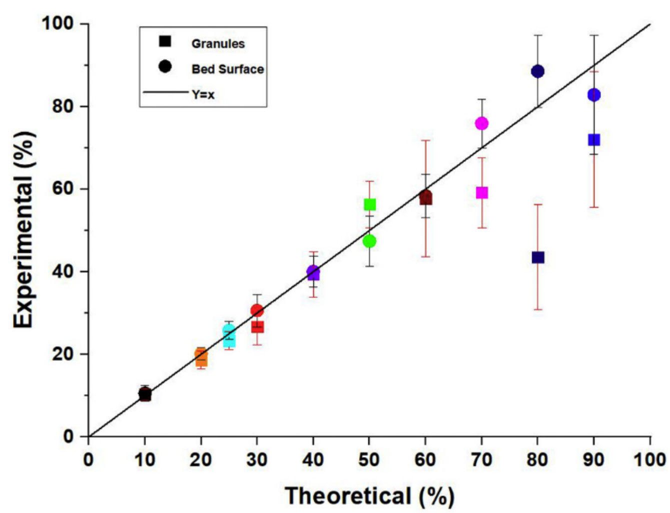


Fig. 7. Composition of granules and powder bed surface containing different proportions of APAP with MCC from Coarse-MCC/Fine-APAP mixtures.

Table 2
Measured APAP weight percentage for each proportion in powder bed surface and granules from Coarse-MCC/Fine-APAP mixtures (averages with standard deviations for three replicates for each mixture).

Coarse-MCC/Fine-APAP	10% (APAP)	20%	25%	30%	40%
Theoretical (% APAP)	10	20	25	30	40
Bed surface (% APAP)	10.6 ± 1.9	18.4 ± 2.7	25.7 ± 2.2	30.6 ± 3.9	40.0 ± 3.8
Average deviation in bed surface vs. theoretical (%)	1.9	1.6	2.3	3.9	5.4
Granules (% APAP)	10.3 ± 1.4	18.6 ± 2.2	23.3 ± 2.1	26.7 ± 4.4	39.3 ± 5.5
Average deviation in granules vs. theoretical (%)	1.5	2.6	2.7	4.8	5.4
Normalized API	0.97 ± 0.22	1.01 ± 0.19	0.91 ± 0.11	0.87 ± 0.18	0.98 ± 0.17
Coarse-MCC/Fine-APAP	50% (APAP)	60%	70%	80%	90%
Theoretical (% APAP)	50	60	70	80	90
Bed surface (% APAP)	47.4 ± 6.0	58.3 ± 14	75.9 ± 6.0	88.5 ± 8.7	82.8 ± 14.4
Average deviation in bed surface vs. theoretical (%)	6.6	5.5	8.6	12.5	16.4
Granules (% APAP)	56.3 ± 5.7	57.7 ± 14	59.1 ± 16.5	43.5 ± 22.0	72.0 ± 16.5
Average deviation in granules vs. theoretical (%)	8.8	12.9	14.1	36.3	25.1
Normalized API	1.19 ± 0.19	0.99 ± 0.34	0.78 ± 0.23	0.49 ± 0.25	0.87 ± 0.25

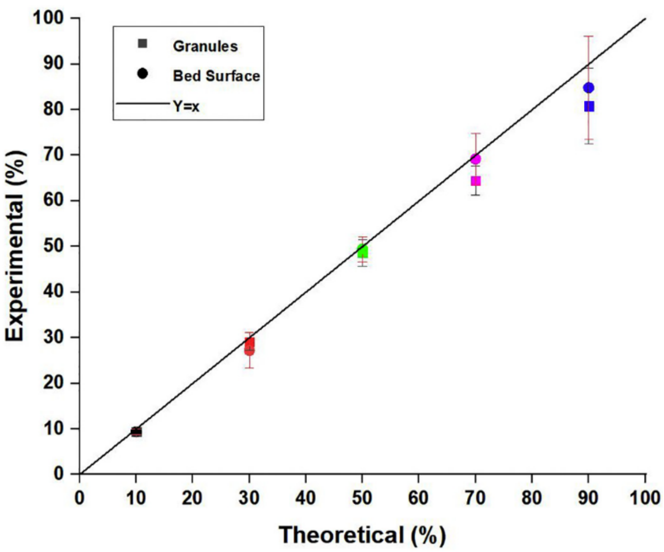


Fig. 8. Composition of granules and powder bed surface containing different proportions of APAP with MCC from Coarse-MCC/Coarse-APAP mixtures.

and 16.4% for 70%, 80% and 90% APAP in the bed surface; 14.1%, 36.3% and 25.1% for 70%, 80% and 90% APAP in the granules). Additionally, the standard error of each measurement also increases when the APAP amount is above 50%, indicating a potential heterogeneous behaviour of the powder mixing and granulation in higher APAP proportions.

By normalizing the API (APAP) content in the granule by that in the bed surface (demonstrated in Table 2), there is a noticeable difference between the content uniformity of the granules and the bed surface when the APAP proportion increases above 60%. The actual APAP amounts in the granules are all lower than in the bed surfaces. Thus, the granules incorporate less APAP than MCC during their formation. This indicates that preferential wetting of the more hydrophilic component (MCC) occurs in single drop granulation of binary mixtures with components of varying hydrophobicity, at least in the coarse/fine mixture type.

For Coarse-MCC/Coarse-APAP and Fine-MCC/Fine-APAP mixtures, five proportions are selected: 10%, 30%, 50%, 70% and 90% APAP.

In Coarse-MCC/Coarse-APAP mixtures, for lower APAP amounts (10% and 30%), the APAP contents in both the bed surface and the granules from experiments are very close to the theoretical values (see Fig. 8). When the APAP amount increases to 70% and 90%, there is a slight compromise in the content uniformities of the granules, which are also sub-potent (lower than the theoretical values). The numerical values are provided in Table 3. Compared to the results from Coarse-MCC/Fine-APAP mixtures, even though content uniformity is compromised in both cases, the compromised level in Coarse-MCC/Coarse-APAP is less significant for higher APAP proportions. For lower APAP proportions, the APAP compositions for both mixture types are close to the theoretical values. The average deviation vs. the theoretical values in Table 3 are all lower than those from Coarse-MCC/Fine-APAP mixtures. For lower APAP amounts (10% and 30%), since APAP only occupies a small portion of the whole mixture, changing from fine APAP to coarse did not greatly affect the overall particle size of the bed, so the effect of particle size on content uniformity is small. However, for higher APAP amounts, changing from fine APAP to coarse increases the overall particle size of the powder bed due to the higher APAP occupancy in the whole mixture (70% and 90%). Also, within the higher APAP ranges, larger discrepancies in the content uniformity occur. An initial hypothesis was made based on the comparison between Coarse-MCC/Coarse-APAP and Coarse-MCC/Fine-APAP mixtures: increasing the mixture bed particle size will result in a more uniform ingredient content.

In Fine-MCC/Fine-APAP mixtures, for the lowest APAP amount (10%), the content uniformities of both the bed surface and the granules from experiments are close to the theoretical values (see Fig. 9). With the increase of APAP amount, the content discrepancies compared with the same APAP proportion in the other two mixture types

Table 3
Measured APAP weight percentage for each proportion in powder bed surface and granules from Coarse-MCC/Coarse-APAP mixtures (averages with standard deviations for two replicates for each mixture).

Coarse-MCC/Coarse-APAP	10% (APAP)	30%	50%	70%	90%
Theoretical (% APAP)	10	30	50	70	90
Bed surface (% APAP)	9.4 ± 0.7	27.2 ± 3.9	49.4 ± 2.8	69.2 ± 5.6	84.8 ± 11.3
Average deviation in bed surface vs. theoretical (%)	0.9	3.6	2.9	5.7	6.62
Granules (% APAP)	9.5 ± 0.6	29.1 ± 2.0	48.6 ± 3.0	64.4 ± 3.2	80.8 ± 8.2
Average deviation in granules vs. theoretical (%)	0.8	2.2	3.3	6.8	8.9
Normalized API (%)	1.01 ± 0.09	1.07 ± 0.17	0.98 ± 0.08	0.93 ± 0.09	0.95 ± 0.16

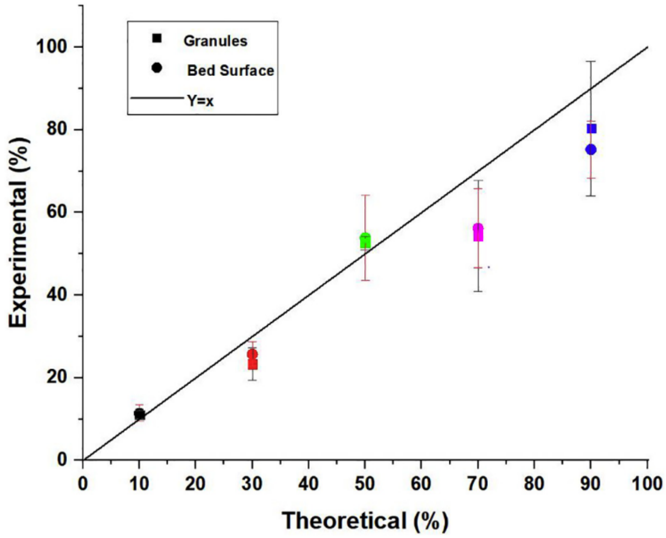


Fig. 9. Composition of granules and powder bed surface containing different proportions of APAP with MCC from Fine-MCC/Fine-APAP mixtures.

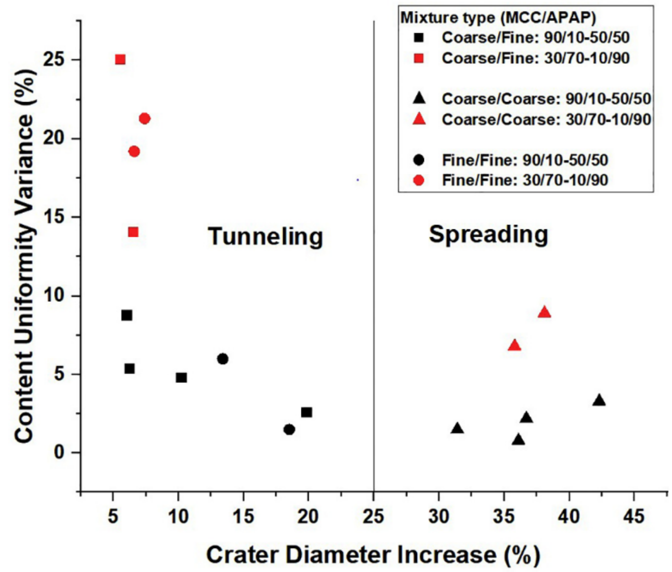


Fig. 10. Relationship between granule formation mechanisms and content uniformity.

(coarse/fine and coarse/coarse) increase, especially for the proportions of 30/70 and 10/90. Similar to the mixtures of Coarse-MCC/Fine-APAP, a non-uniform distribution of the binary components also exists in the powder bed before granulation, causing heterogenous mixing of the APAP with the MCC during granule formation. However, the preferential wetting effect was almost negligible for coarse/coarse and fine/fine mixtures, as demonstrated by the normalized API percentages that are close to 1 (see Tables 3 and 4).

For Fine-MCC/Fine-APAP mixture types, since both components are fine in size, the overall particle sizes of the powder beds are fine for all APAP amounts. Reducing the overall particle size of the powder bed introduces a higher content uniformity discrepancy that can reach twice or even triple the average deviation in some proportions than those from mixtures containing at least one coarse component.

From the results of three different mixture types (Coarse-MCC/Fine-APAP, Coarse-MCC/Coarse-APAP and Fine-APAP/Fine-APAP), the following preliminary findings are concluded.

Both the mixture particle size distribution and the hydrophobicity have an impact on the content uniformity. For a small amount of APAP (10%), the APAP content in both the granules and the bed surface are very uniform in all three mixture types, i.e., close to the theoretical values. In this proportion, since MCC dominates the mixture amount (90%), changing the particle size of MCC (hydrophilic component) will not have a significant effect on content uniformity. When the APAP amount increases above 30%, for the two mixtures with Fine-APAP, the content uniformity starts to become compromised, and the content discrepancies reach the highest around 70% and 80% APAP. On the other hand, for coarse/coarse mixtures, the content uniformity is much less compromised for the same APAP proportions compared with the other two mixture types. The overall

Table 5
The internal porosity of the powder bed packing.

Material	Dimensions	Total Volume (μm^3)	Porosity (%)
30% APAP dry powder bed - sample 1	900×1600×900	3.08E+10	81.08
	1375×1150×1100	4.13E+10	81.06
30% APAP dry powder bed - sample 2	900×1600×900	3.08E+10	83.24
	1100×1150×100	3.30E+10	83.25

content of APAP is much more uniformly distributed in coarse powder mixtures than in fine powder mixtures. However, in fine powder mixtures, higher APAP amounts in the mixtures (higher mixture hydrophobicity) also cause a greater content discrepancy than lower APAP amounts (lower mixture hydrophobicity).

The content uniformity results can also be associated with the granule formation mechanisms. Generally, the formation mechanisms are affected directly by the overall bed particle size, while hydrophobicity has a minimal effect. Spreading occurred for coarse particle sizes, while Tunneling occurred for fine particle sizes. The relationship between formation mechanisms and content uniformity is shown in Fig. 10. Generally, single drop granulation with the Spreading mechanism resulted in a less compromised content uniformity compared with granulation with the Tunneling mechanism. For batches with lower APAP amounts (10% to 50%, black data points), the content variances from Tunneling are slightly larger than those from Spreading. However, for larger APAP amounts (70% to 90%, red data points), this difference is much larger.

Table 4
Measured APAP weight percentage for each proportion in powder bed surface and granules from Fine-MCC/Fine-APAP mixtures (averages with standard deviations for two replicates for each mixture).

Fine-MCC/Fine-APAP	10% (APAP)	30%	50%	70%	90%
Theoretical (% APAP)	10	30	50	70	90
Bed surface (% APAP)	11.5 ± 2.0	25.7 ± 3.0	53.9 ± 10.3	56.2 ± 9.6	75.3 ± 6.9
Average deviation in bed surface vs. theoretical (%)	2.6	5.6	8.7	17.5	16.1
Granules (% APAP)	11.1 ± 0.9	23.3 ± 3.9	52.6 ± 1.6	54.3 ± 13.5	80.3 ± 16.3
Average deviation in granules vs. theoretical (%)	1.5	6.0	3.0	21.3	19.2
Normalized API	0.97 ± 0.19	0.91 ± 0.18	0.98 ± 0.19	0.97 ± 0.29	1.07 ± 0.24

Fig. 11. Photo of powder packing column sample of a 30% APAP mixture.

The interaction of a liquid droplet with a porous material surface is related to capillary penetration [24], where liquid is more likely to flow in a narrow space. With the Tunneling mechanism, since the capillary force is greater than the adhesive force between the dry aggregates, some aggregates are sucked into the droplets [9,10]. This migration of aggregates causes the collapse of the powder bed, allowing the particles and aggregates to be picked up by the droplet during Tunneling, introducing a heterogenous powder mixture and forming granules with non-uniformly distributed fine APAP.

3.4. Structure of powder bed packing

The internal porosities of two powder bed packing columns taken from different areas in a single Coarse-MCC/Fine-APAP mixture are shown in Table 5. The porosities of two different regions within each sample is consistent (~81.1% for one sample and ~83.2% for a second sample), and fairly consistent at ~81–83% within the same powder bed. By comparing the porosities of the granules made from the same proportion of APAP in previous work [1], which are only around 60%, the wet granulation densifies the internal structure during the formation of granules by decreasing the porosity by around 20%.

A photo of the column filled with the powder mixture is shown in Fig. 11 for a better illustration of the powder sample. The micro-CT results, with a 2D cross-section of granules made from 30% APAP, 2D cross-section of the powder column made from 30% APAP, and a 3D reconstruction of the whole powder column, are shown in Fig. 12a, b and c, respectively. As revealed by the internal structure of the powder bed, there are dense regions existing in the mixture (indicated by blue arrows in Fig. 12b). Dense regions of difference sizes are randomly distributed in the mixture (see Fig. 12c). Most of the dense regions are located in the upper half of the column, where the granules are typically formed when the droplet impacts the surface of the powder bed. There are also several denser regions observed in granules made from the same proportion in our previous study [1] (shown in Fig. 12a). This indicates that during the preparation of the powder mixture, an inhomogeneous powder packing is already created before the wet granulation. Thus, the dense regions in the granules are likely generated directly from the same regions in the dry powder bed.

In this study, the internal structure of the powder bed was only characterized for one mixture from one mixture type (Coarse-MCC/Fine-APAP), and the granules formed directly from this powder bed were not characterized. For a more complete understanding of how the powder packing influences the formation mechanism and subsequently formed granule, powder bed internal structure from both coarse mixtures (exhibiting Spreading) and fine mixtures (exhibiting Tunneling) should be investigated. Also, the internal structures of the granules should be analyzed from the same powder bed to directly compare the powder bed packing and granule porosity.

4. Conclusions

From this work, single drop granulation on MCC/APAP mixtures with three different particle size combinations were performed. The formation mechanisms, granule morphology, and the content uniformity of the surface of the powder bed and the granules were investigated. The structure of powder bed packing was studied for the Coarse-MCC/Fine-APAP mixture as well to compare with the internal structure of granules.

Tunneling and Spreading formation mechanisms occur in similar conditions as in previous work [1]. Specifically, in Coarse-MCC/Coarse-APAP mixtures, the formation mechanism is Spreading for all APAP amounts, while in Fine-MCC/Fine-APAP mixtures, the formation

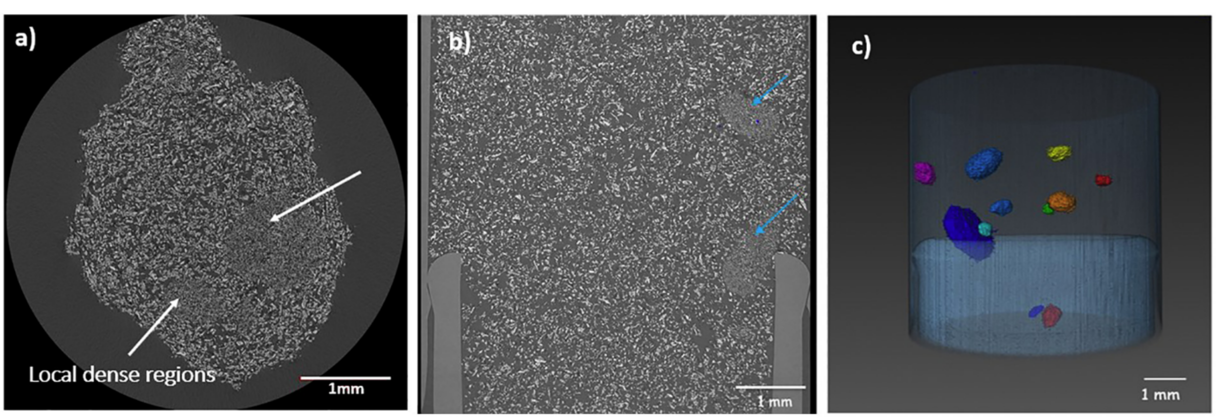


Fig. 12. a) 2D cross-section of a granule, b) 2D cross-section of the powder packing, and c) 3D reconstruction of the whole powder packing column (with dense regions highlighted in different colours).

mechanism is Tunneling. This is a strong indication that the bed particle size dominates over hydrophobicity in affecting the formation mechanism of the mixture. The same effect is also observed for granule morphology. The granules resulting from the Spreading mechanism are disk-shaped with high V.A.R.'s, and are relatively larger in size, while the granules from Tunneling are rounder with low V.A.R.'s and are smaller.

For content uniformity, both the overall particle size and the hydrophobicity of the powder bed have an effect. When the APAP proportion is low (less than 30%) in the bed, the component contents are close to the theoretical values in all mixture types. The effect of particle size on these APAP proportions are negligible. When using the Fine-APAP in mixtures, with the increase of APAP, the overall content uniformity of both the surface of the powder bed and the granules are compromised, especially for granules. Specifically, when the APAP proportion increases above 50%, the APAP content in the granules become much more non-uniform. However, for mixtures with Coarse-APAP, the content uniformity is also compromised for high APAP amounts (70% and 90%) but is much less compared with mixtures with Fine-APAP. This reveals a dominating effect of bed particle size over hydrophobicity on content uniformity for high APAP amounts in mixtures. By comparing the content uniformity of granules to the surface of the powder bed, a larger APAP proportion can cause higher content differences as well, explaining the preferential wetting of MCC compared to APAP.

The internal structure of the powder packing of Coarse-MCC/Fine-APAP at 30% APAP appears to have several dense regions within the mixture. The overall porosity of the powder bed is approximately 20% lower than that of the granules made from the same mixture.

We believe that the granule formation mechanism (affected mainly by the primary particle size of the powder bed) is the dominating factor that influences the content uniformity. When the mechanism transitions from Spreading to Tunneling, the granule content becomes less uniform. This has important implications for designing granules, where coarser powder bed mixtures will result in the Spreading mechanism with disk-shaped and uniform granules, and finer powder bed mixtures will result in the Tunneling mechanism with round and less uniform granules.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to acknowledge Science Foundation Arizona for the Bisgrove Scholar Award and the National Science Foundation CAREER Award number 1846858 for supporting this work.

References

[1] T. Gao, A.S.S. Singaravelu, S. Oka, R. Ramachandran, F. Štepánek, N. Chawla, H.N. Emady, Granule formation and structure from single drop impact on heterogeneous powder beds, Int. J. Pharm. 552 (2018) 56–66, https://doi.org/10.1016/j.ijpharm.2018.09.036.

[2] T.H. Nguyen, W. Shen, K. Hapgood, Effect of formulation hydrophobicity on drug distribution in wet granulation, Chem. Eng. J. 164 (2010) 330–339, https://doi.org/10.1016/j.cej.2010.05.008.

[3] S.M. Iveson, J.D. Litster, K. Hapgood, B.J. Ennis, Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review, Powder Technol. 117 (2001) 3–39, https://doi.org/10.1016/S0032-5910(01)00313-8.

[4] H.N. Emady, D. Kayrak-Talay, W.C. Schwerin, J.D. Litster, Granule formation mechanisms and morphology from single drop impact on powder beds, Powder Technol. 212 (2011) 69–79, https://doi.org/10.1016/j.powtec.2011.04.030.

[5] K.P. Hapgood, J.D. Litster, R. Smith, Nucleation regime map for liquid bound granules, AICHE J. 49 (2003) 350–361, https://doi.org/10.1002/aic.690490207.

[6] K.P. Hapgood, B. Khanmohammadi, Granulation of hydrophobic powders, Powder Technol. 189 (2009) 253–262, https://doi.org/10.1016/j.powtec.2008.04.033.

[7] K.P. Hapgood, J.D. Litster, S.R. Biggs, T. Howes, Drop penetration into porous powder beds, J. Colloid Interface Sci. 253 (2002) 353–366, https://doi.org/10.1006/jcis.2002.8527.

[8] T. Nguyen, W. Shen, K. Hapgood, Drop penetration time in heterogeneous powder beds, Chem. Eng. Sci. 64 (2009) 5210–5221, https://doi.org/10.1016/j.ces.2009.08.038.

[9] H.N. Emady, D. Kayrak-Talay, J.D. Litster, A regime map for granule formation by drop impact on powder beds, AICHE. 7 (2013) 405–410, https://doi.org/10.1002/aic.

[10] H.N. Emady, D. Kayrak-Talay, J.D. Litster, Modeling the granule formation mechanism from single drop impact on a powder bed, J. Colloid Interface Sci. 393 (2013) 369–376, https://doi.org/10.1016/j.jcis.2012.10.038.

[11] L. Farber, G. Tardos, J.N. Michaels, Use of X-ray tomography to study the porosity and morphology of granules, Powder Technol. 132 (2003) 57–63, https://doi.org/10.1016/S0032-5910(03)00043-3.

[12] S. Dale, C. Wassgren, J. Litster, Measuring granule phase volume distributions using X-ray microtomography, Powder Technol. 264 (2014) 550–560, https://doi.org/10.1016/j.powtec.2014.06.009.

[13] N.B. Davis, K. Waibel, K. Wang, J.D. Litster, Microstructure of single-droplet granules formed from ultra-fine powders, Powder Technol. 305 (2017) 19–26, https://doi.org/10.1016/j.powtec.2016.09.033.

[14] O. Kašpar, V. Tokárová, S. Oka, K. Sowrirajan, R. Ramachandran, F. Štěpánek, Combined UV/Vis and micro-tomography investigation of acetaminophen dissolution from granules, Int. J. Pharm. 458 (2013) 272–281, https://doi.org/10.1016/j.ijpharm.2013.10.032.

[15] M.X.L. Tan, T.H. Nguyen, K.P. Hapgood, Drug distribution in wet granulation: foam versus spray, Drug Dev. Ind. Pharm. 39 (2013) 1389–1400, https://doi.org/10.3109/03639045.2012.719233.

[16] S. Oka, D. Smrčka, A. Kataria, H. Emady, F. Muzzio, F. Štepánek, R. Ramachandran, Analysis of the origins of content non-uniformity in high-shear wet granulation, Int. J. Pharm. 528 (2017) 578–585, https://doi.org/10.1016/j.ijpharm.2017.06.034.

[17] S. Oka, H. Emady, O. Kašpar, V. Tokárová, F. Muzzio, F. Štěpánek, R. Ramachandran, The effects of improper mixing and preferential wetting of active and excipient ingredients on content uniformity in high shear wet granulation, Powder Technol. 278 (2015) 266–277, https://doi.org/10.1016/j.powtec.2015.03.018.

[18] H. Li, M.R. Thompson, K.P. O'Donnell, Examining drug hydrophobicity in continuous wet granulation within a twin screw extruder, Int. J. Pharm. 496 (2015) 3–11, https://doi.org/10.1016/j.ijpharm.2015.07.070.

[19] G.M. Mahours, D.E.Z. Shaaban, G.A. Shazly, S.H. Auda, The effect of binder concentration and dry mixing time on granules, tablet characteristics and content uniformity of low dose drug in high shear wet granulation, J. Drug Deliv. Sci. Technol. 39 (2017) 192–199, https://doi.org/10.1016/j.jddst.2017.03.014.

[20] S. Oka, O. Kašpar, V. Tokárová, K. Sowrirajan, H. Wu, M. Khan, F. Muzzio, F. Štěpánek, R. Ramachandran, A quantitative study of the effect of process parameters on key granule characteristics in a high shear wet granulation process involving a two component pharmaceutical blend, Adv. Powder Technol. 26 (2015) 315–322, https://doi.org/10.1016/j.apt.2014.10.012.

[21] A.A.P. Kumar, V.P. Sandireddy, T. Banerjee, D. Bandyopadhyay, Dynamics of a liquid droplet on a granular bed of microstructured particles: from lens formation to marble effect, Ind. Eng. Chem. Res. 54 (2015) 1131–1141, https://doi.org/10.1021/ie5024904.

[22] C.P. Whitby, X. Bian, R. Sedev, Spontaneous liquid marble formation on packed porous beds, Soft Matter 44 (2012) 11336–11342, https://doi.org/10.1039/c2sm26529j.

[23] K.P. Hapgood, L. Farber, J.N. Michaels, Agglomeration of hydrophobic powders via solid spreading nucleation, Powder Technol. 188 (2009) 248–254, https://doi.org/10.1016/j.powtec.2008.05.004.

[24] M. Denesuk, G.L. Smith, B.J.J. Zelinski, N.J. Kreidl, D.R. Uhlmann, Capillary penetration of liquid droplets into porous materials, J. Colloid Interface Sci. 158 (1993) 114–120, https://doi.org/10.1006/jcis.1993.1235.