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Effect of formulation hydrophobicity on drug distribution in wet granulation

Thanh H. Nguyen[a,b], Wei Shen[b], Karen Hapgood[a,*]

[a] Monash Advanced Particle Engineering Laboratory, Department of Chemical Engineering, Monash University, Melbourne, Victoria 3800, Australia
[b] Australian Pulp and Paper Institute, Department of Chemical Engineering, Monash University, Melbourne, Victoria 3800, Australia

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ABSTRACT

Wet granulation is a process of enhancing the powder properties by producing larger particles from the agglomeration of agitated fine particles with liquid. The production of enlarged "granules" is often carried out in high-shear granulators, an equipment item prevalent in the pharmaceutical and food industries. In the pharmaceutical industry, good wettability between the liquid binder and the powder components in the formulation are relied upon to produce strong granules with a narrow size distribution. The wettability of hydrophobic drugs in the formulation is often improved by the use of surfactants; but this may not always be possible. Previous work on heterogeneous-wetting granulation [1–3] has found that as the formulation hydrophobicity increases, the average granule size decreases. The decreasing proportion of hydrophilic component available for granulation may influence the decreasing average granule size, however an explanation for this has not been clearly proposed. The observation and reasoning behind the granulation behaviour for heterogeneous-wetting powders forms the basis of this paper.

Granulation experiments were carried out on varying degrees of formulation hydrophobicity and the granulation batch is sieved into different size fractions for sieve fraction assay analysis to determine the average granule composition and the drug distribution throughout the granulation batch. The sieve fraction assay analysis revealed that the drug distribution in the granular batch is strongly dependent upon the formulation wettability. This was seen for batches with water as the granulating fluid where the drug distribution was uneven and resulted in some sieve fractions being enriched or deficient of drug content. When the wettability of the formulation was improved a more uniform distribution of drug was achieved across all sieve fractions and formulation hydrophobicity. The average granule size decreased as the formulation hydrophobicity increased, supporting previous works, and this is due to the decreasing liquid bridge strength between the particles.

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1. Introduction

The process of wet granulation improves the powder properties by the coalescence of agitated primary particles with a liquid binder, to enlarge the particle size. In the pharmaceutical industry, the homogeneity of granules is critical for good quality control and fulfilling the strict content uniformity criteria from the Food and Drug Administration (FDA) for tablets and granulated material [4].

The inclusion of hydrophobic drugs in the formulation lowers the extent of wetting between the binder and the powder, which consequently may lead to non-uniform distribution of the drug in the granulation mixture. This problem is increasing in the pharmaceutical industry, where almost half of the approximately 150,000 new chemical drug compounds produced and screened annually show poor water solubility or hydrophobicity properties [5,6]. The common industrial practise of overcoming the poor wettability of hydrophobic drug is to use surfactants but surfactants cannot always be used due to economic infeasibility or incompatibility with the excipients [7]. Hence understanding the effects of the incorporation of hydrophobic drugs in wet granulation is becoming increasingly important for good granulation and particle design.

The inhomogeneity in drug distribution may partly be attributed to the effect of particle size differences between the drug and excipients in the granulation batch. The Stokes number theory [8], for a given pseudo-powder viscosity, states that the Stokes number is proportional to the particle radius. This suggests that a smaller particle radius is more likely to fulfil the condition of the Stokes number being smaller than the threshold Stokes number, and successful collisions are more likely to occur. This is evident in the studies where the drug particles were smaller than the excipient particle size. The content of the coarse granules is composed mainly of drugs, while smaller fractions consisted of fine granules and un-granulated excipients [4,9–12]. This is due to the preferential granulation of small sized drug components where binder is taken up more by the drug particles than the coarse excipient particles. The coalescence of small drug-enriched granules forms

* Corresponding author.
E-mail address: Karen.hapgood@eng.monash.edu.au (K. Hapgood).

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the coarse drug-enriched granules. Consequently, the granules produced at this condition will always be enriched with drug due to the preferential granulation of the small drug particles. However the distribution of drug is uneven in the granulation batch, unless the extent of granulation can be increased to granulate all the powder [4,10,11].

Heterogeneous-wetting granulation can also result in the composition of granules in each size fraction being different. Hence studies of granule composition, also known as *sieve fraction assays*, are carried out to investigate granule homogeneity as a function of granule size [10,11]. In one industrial study, two types of fine drugs (drug A and B), microcrystalline cellulose (Avicel) and lactose were granulated together [10,11]. The granulation process switched from producing granules that were enriched with drug and lactose to granules that were enriched with drug and Avicel at the point where 40% of the granulated mixture was greater than 125 μm. This was due to the ability of the Avicel component being able to absorb the binder water into its porous configuration before becoming saturated, thus delaying its capacity to form liquid bridges. As the percentage of coarse granule fraction increases (>125 μm), the drug and excipient concentration approaches the target amount across all granule size fractions, suggesting that coarser granule size may be desirable for achieving drug content specifications (100% target claim in cuts > 125 μm) [10,11].

The reverse trend is seen in cases where the drug particle size is coarser than the excipient particle size. The smaller granule fractions consisted of high drug content [4]. The distribution of active component can be improved by milling the drug and excipient powders, giving a homogeneous distribution of drug as demonstrated by Vromans et al. [4]. However, the reduction of particle size may not always result in homogeneity of granules due to the increasing tendency for particles to agglomerate [4,12].

Fundamental work on heterogeneous-wetting granulation was carried out by Lerk et al. [13] and Aulton and Banks [1], who investigated the effects of the powder wettability on the average granule size. The wettability of the powder mixture has a direct effect on the resulting average granule size and the ease of granulation process control [1,2,13]. A few studies that have looked into this area of granulation have found that as the proportion of hydrophobic component increases, the resulting granule size decreases [1–3]. This was attributed to the increase in hydrophobicity of the powder mixture, which increases the contact angle of the mixture and may slow down the granule growth and produce a smaller average granule size. However no mechanistic explanation for the decrease in average granule size has been given and forms a potential area of research to investigate.

The inclusion of hydrophobic drugs in the formulation would be expected to affect the nucleation of the powder and drug. An assessment of the interaction between the powder and liquid can be made through the drop penetration time, t_p. The drop penetration time is the time taken for a single droplet of liquid to penetrate into a powder surface [16]. A fundamental study investigated the effect of the binder and hydrophilic powder beds on the drop penetration time and found that the contact angle was a key factor. This work was later expanded to look at the effect of formulation wettability on the drop penetration time [17] and found that low concentrations of hydrophobic component can significantly affect the drop penetration time. A rapid increase in the drop penetration time indicated a transition from hydrophilic behaviour to hydrophobic wetting behaviour. This point of transition was defined as the *critical or threshold concentration ratio* p_c [17].

Studies into granulation of heterogeneous powder mixtures have shown that there is conflicting behaviour in heterogeneous-wetting granulation. Most of the studies done on granule homogeneity have concentrated on hydrophobic components that make up less than 10% of the formulation. The objective of this paper is to granulate a simple lactose–salicylic acid formulation over a wide range of drug loads, similar to the Aulton and Banks study [1], and to analyse the composition of each different granule size fraction to determine the reason behind the decrease in granule size as the hydrophobic component proportion increases [1–3]. The Aulton and Banks paper [1] is frequently cited, but the original paper is a short conference abstract with few experimental details. This paper significantly extends their work [1] to include in depth analysis of the granules size, structure and composition as a function of formulation hydrophobicity.

2. Experimental

2.1. Materials characterisation

Salicylic acid (Merck Pty. Ltd.) and lactose monohydrate 200 mesh (Wyndale, New Zealand) were chosen as the hydrophobic and hydrophilic components respectively. Salicylic acid (denoted by SA) particles are needle-like in shape and were chosen to compare the work of Aulton and Banks [1] and to represent the hydrophobic drug component in the formulation. Lactose 200 mesh (denoted by L2M) consists of tomahawk-shaped particles and is used extensively as a filler in tablet manufacture. Lactose and salicylic acid were used "as received". Powder formulations of salicylic acid and lactose in varying ratios (described in Table 1) were prepared for the granulation experiments. As this project is investigating the distribution of drug during wet granulation to further understand the granulation process and not looking into the application in an industrial setting [14], the composition variation due to weighing variations is estimated to be ±1% of the desired powder composition. Additional variation due to local segregation at the powder surface or beneath the small droplet contact area may also occur but this is very difficult to quantify.

A summary of the powder properties for the salicylic acid and lactose 200 mesh powder formulations are given in Table 1. The average particle density was calculated from the component fraction x and the true densities of the two components [7,17]:

$$\rho_{\text{average}} = x\rho_{\text{L2M}} + (1-x)\rho_{\text{SA}} \quad (1)$$

Two types of granulating fluid were used as binders to investigate the hydrophobicity effect of the formulation on the drug distribution. Water and an aqueous solution of 5% (w/v) PolyVinylPyrrolidone (PVP) (Sigma–Aldrich, K90 grade) were used. Orange and green dyes were added to the binders respectively to assist with visual observations of the granules. Water is completely hydrophobic to salicylic acid (contact angle is $\theta \approx 103^\circ$ [1]) while aqueous PVP undergoes a complexation reaction with salicylic acid to form water-soluble chemical complexes [15] and would display a contact angle of approximately 90°. Therefore PVP transitionally wets the salicylic acid (from $\theta \approx 103^\circ$ to $\theta < 90^\circ$) and this borderline wetting will be termed "transitional wetting" throughout this paper.

2.2. Experimental set-up and procedure

All granulation and sieve fraction assay experiments were carried out in duplicate. The granulation experiments involved preparing 750 g of various ratios of salicylic acid and lactose powder. The powders were granulated in a 5 L high-shear granulator (KG-5 model, Key International Inc.). The impeller speed was set at 285 rpm, which was beyond the minimum roping mixing speed to minimise any transitional fluctuations between the transitional mixing regime from 'bumping' to 'roping' mixing stages. The powders were dry-mixed for 1 min prior to granulation. The 5% PVP binder fluid was sprayed into the granulator for 1 min and 20 s through a flat spray nozzle (spray tip SS650017) connected to a

Table 1
Powder properties for salicylic acid and lactose 200 mesh formulations.

wt% salicylic acid in mixture	wt% lactose 200 mesh in mixture	True particle density (g/cm^3)	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
0	100	1.540[a]	5.0	37	173
20	80	1.518	5.8	33	147
40	60	1.496	6.6	30	120
50	50	1.485	7.0	28	107
60	40	1.474	7.4	26	94
80	20	1.452	8.2	23	67
100	0	1.430[b]	9.0	19	41

[a] Data taken from [17].
[b] Data taken from [7].

5 L spray pot (Spray systems) at a flow rate of 90 mL/min. Following the addition of 120 mL of binder, the batch underwent 2 min of wet massing.

After granulation, each batch was dried overnight in an oven at 60 °C and a representative sample of the granular batch was collected by using a chute splitter. Sieve fraction assay analysis was then performed to determine the composition of the granules in each sieve fraction. The granular material was sieved through 6 sieves using a mechanical dry sieve shaker (Retsch, A200), at an amplitude of 0.5, to measure the granule size distribution and to collect at least 5 g of granules in the following sieve fractions: pan, 125 μm, 250 μm, 425 μm, 710 μm and 1 mm. For each size fraction, a 5 g sample was dissolved in 100 mL of methanol to dissolve the salicylic acid but leave the lactose powder undissolved. The solution containing methanol, lactose powder and dissolved salicylic acid underwent vacuum filtration (Whatman filter grade number 2, 8 μm pore size) to filter out the lactose powder. The measurement of the lactose filtrate mass enabled the calculation of the average granule composition in each sieve fraction. Calibration of the vacuum filtration method showed that the method was accurate to within ±5% of the theoretical powder composition.

To further understand the granulation mechanism of the heterogeneous-wetting powder system and in particular the nucleation of powder mixtures with binder, single drop nucleation experiments were carried out on the powder mixtures to measure the drop penetration time. The drop penetration time t_p is the time taken for a droplet to completely penetrate into a powder bed [16]. The loosely packed powder conditions in the granulator were imitated by sieving powder through a 1.7 mm sieve into a Petri dish with the top of the powder bed scraped smooth with a spatula. A single droplet with an average volume of 12.3 μL was gently deposited onto the powder bed using a 1 cm^3/mL syringe and a 21 gauge needle tip. The syringe was clamped onto a rig such that the impact height stayed constant for all experimental runs at 0.5 cm. Once the droplet impacted onto the powder bed, the penetration time was measured using a stopwatch and complete penetration was signalled by the transition from dark green to pale green footprint. The drop penetration kinetics was compared to the water drop penetration kinetics taken from another study [17]. A total of 18 replicates were performed. Once the drop penetration was completed, the nucleated powder beds were dried overnight at room temperature (22 °C) and excavated to observe the granule morphology. Selected experiments were captured at different time intervals using a digital microscope camera (Motic).

3. Results

3.1. Effect of formulation hydrophobicity on the average granule size

The hydrophobicity of the formulation has a significant effect on the extent of wetting between the powder particles and the binder, which consequently affects the average granule size. Evidence that the average granule size decreases as the proportion of hydrophobic drug increases can be seen in granule size distributions (Figs. 1 and 2). The primary particle sizes for salicylic acid and lactose are approximately 20 μm and 37 μm respectively (see Table 1), and in this study, any material below 90 μm is considered to be un-granulated powder.

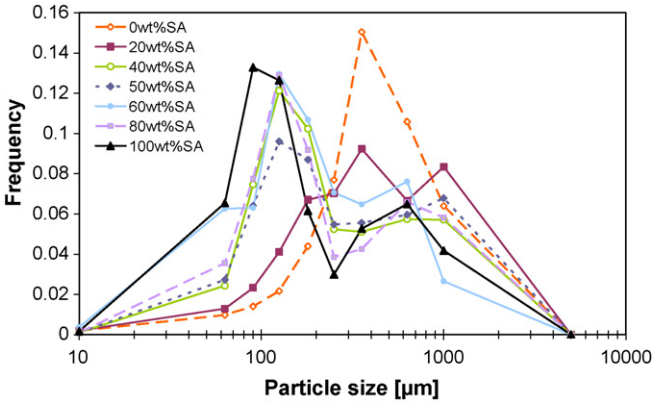

Fig. 1. Logarithmic granule size distribution of powder mixtures of increasing powder hydrophobicity with aqueous PVP as the granulating fluid.

Figs. 1 and 2 show the different trends in logarithmic granule size distribution as a function of proportion of hydrophobic salicylic acid (SA) in the powder mixture for PVP and water binders respectively. For PVP granules, the amount of fine granules or un-granulated powder in the granular product increases as the proportion of salicylic acid in the powder mixture increases. However the granule size distribution curves appear to show a weak trend with increasing proportion of salicylic acid in the mixture, as the median granule size is centered around the 100 μm size fraction for most formulation mixtures (see Fig. 1).

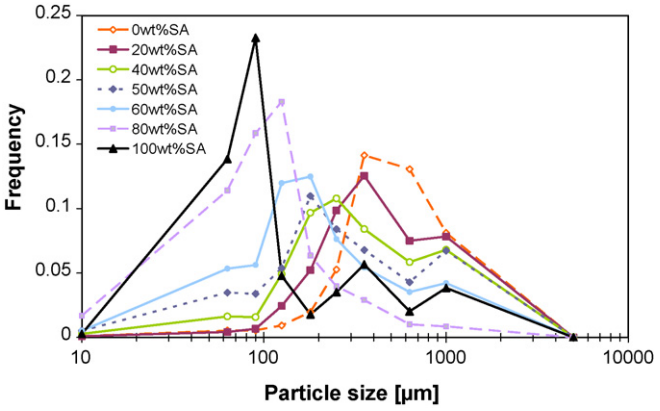

Fig. 2. Logarithmic granule size distribution of powder mixtures of increasing powder hydrophobicity with water as the granulating fluid.

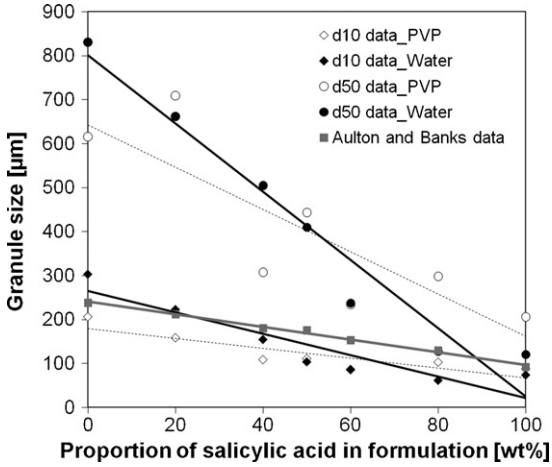

Fig. 3. Comparison of the d_{10} and d_{90} granule sizes for PVP (open symbols) and water (closed symbols) with Aulton and Banks [1] "average" granule size (grey squares).

A strong trend of decreasing average granule size as the concentration of salicylic acid increases can also be seen for water granulated granules (see Fig. 2). The peaks of the granule size distribution curves progress to the left towards 90 μm as the proportion of salicylic acid increases. The progression in average granule size towards 90 μm may suggest that there is weak granulation of salicylic acid particles, consequently leading to the fine size fractions consisting of predominantly un-granulated salicylic acid, particularly for high concentrations of salicylic acid in the formulation. The weak granulation of salicylic acid is also evident in the narrow granule size distribution curves produced by granulating with water, compared to the broader distribution curves produced by granulating with aqueous PVP fluid.

The decrease in granule size as a function of the formulation hydrophobicity can also be seen in Fig. 3, which shows the d_{10} and d_{50} granule sizes as a function of the formulation hydrophobicity for both PVP and water binder. To further understand the mechanisms behind Aulton and Banks' [1] work, a comparison between the experimental data and the Aulton and Banks data was carried out to see the similarity of the two studies. In Aulton and Banks' work, the "average" granule size was given [1] although the definition of "average" was not provided. The comparison in Fig. 3 shows that there is steady decrease in the d_{10} and d_{50} granule sizes, for both PVP and water data, which supports Aulton and Banks' work. However the water-bound granule size decreases at a steeper rate compared to PVP which may suggests that different granulation mechanisms (immersion vs. solid spreading nucleation, discussed in more detail in Section 3.4) are occurring at the extreme ends of the hydrophobicity spectrum. The d_{10} granule size for PVP appears to be most consistent with Aulton and Banks' data, possibly suggesting that a finer grade of primary powder was used in their work. However it should be noted that Aulton and Banks' study was carried out in a fluidised-bed granulator [1], which means that the granulation process is undertaken in different conditions compared to the high-shear mixer granulator used in this study (for example different binder flow rate, simultaneous drying and different powder agitation method). Despite the different granulating conditions, the high-shear mixer data agrees with the fluidised-bed data, showing that the decrease in the granule size with increasing hydrophobicity of the formulation is a consistent and important trend.

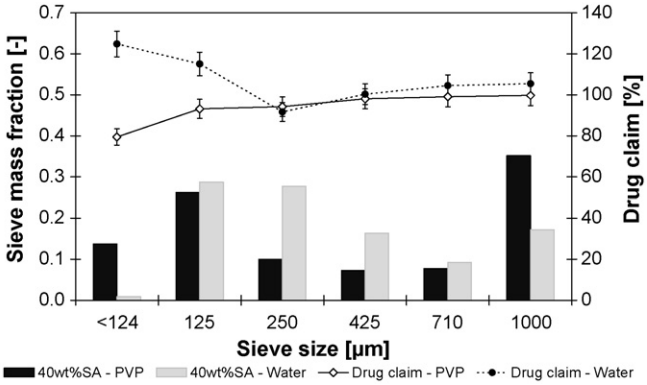

Fig. 5. Granule size distribution and drug claim represented by mass sieve fractions for 40 wt% salicylic acid and 60 wt% lactose 200 mesh.

3.2. Effect of formulation hydrophobicity on drug distribution

The drug distributions and the sieve mass fraction distributions as a function of the sieve fraction are shown in Figs. 4–8. The bars show the size distribution as the weight fraction retained in each sieve, while the line shows the % drug claim of each size fraction, which indicates the composition of each granule fraction. "100% drug claim" means that the composition of that sieve fraction was exactly equal to the theoretical drug claim (which is either 20%, 50%, 60% or 80% depending on the batch). A drug claim of "200%" would mean that the size fraction contained twice as much drug as was expected theoretically. The drug claim error bars reflect the ±5% maximum error in the vacuum filtration method used to measure the salicylic acid content. Theoretical drug mass balances are within 10% of the theoretical composition for each batch, except for the 80 wt% salicylic acid batch, where the discrepancy was found

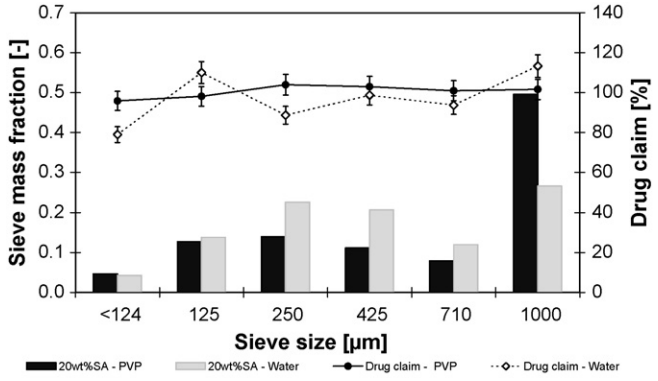

Fig. 4. Granule size distribution and drug claim represented by mass sieve fractions for 20 wt% salicylic acid and 80 wt% lactose 200 mesh.

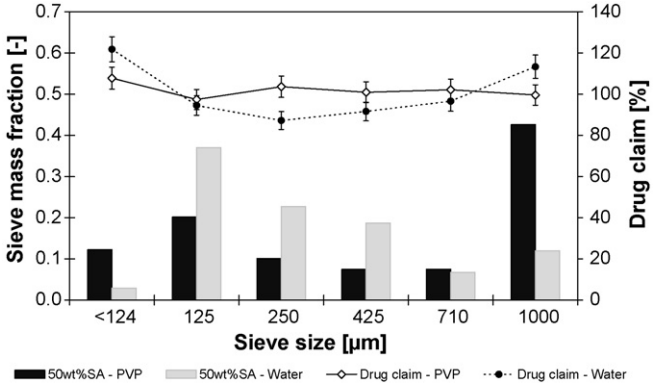

Fig. 6. Granule size distribution and drug claim represented by mass sieve fractions for 50 wt% salicylic acid and 50 wt% lactose 200 mesh.

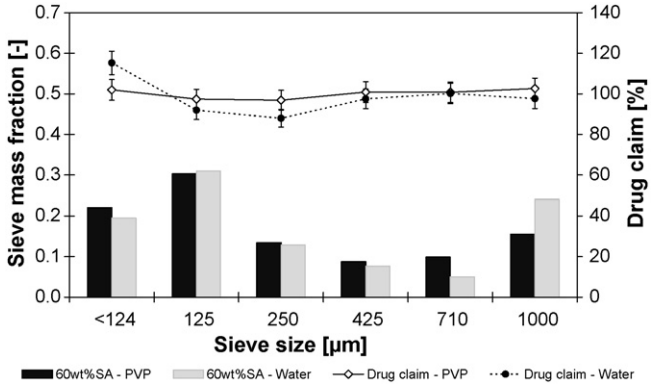

Fig. 7. Granule size distribution and drug claim represented by mass sieve fractions for 60 wt% salicylic acid and 40 wt% lactose 200 mesh.

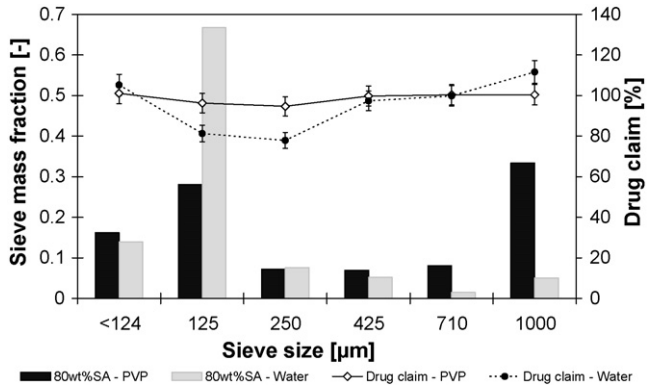

Fig. 8. Granule size distribution and drug claim represented by mass sieve fractions for 80 wt% salicylic acid and 20 wt% lactose 200 mesh.

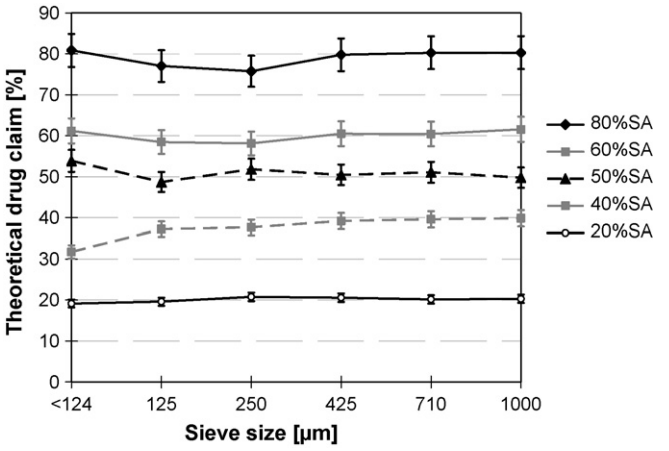

Fig. 9. Drug claim for various heterogeneous-wetting powder mixtures, granulated with 5% (w/v) aqueous PVP.

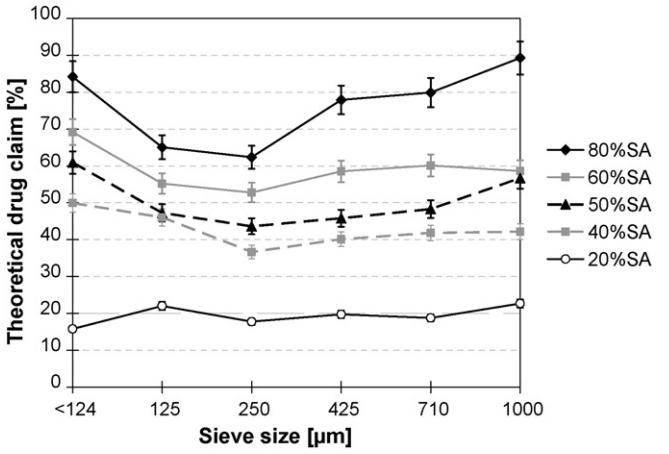

Fig. 10. Drug claim for various heterogeneous-wetting powder mixtures, granulated with water.

to the 12.4% between the actual and theoretical drug content. The discrepancy can be attributed to the highly static charge of the hydrophobic powder, which may have led to some drug loss during the sieve fraction assay analysis. The drug distribution for each granulation batch, shown in Figs. 4–8, can be more clearly compared using Figs. 9 and 10 for aqueous PVP and water respectively.

Figs. 4–10 show that the uniformity of the drug distribution is strongly dependent on the wettability of the formulation. Where the interaction between the binder and the powder formulation is not strongly hydrophobic, as is the case with the PVP binder, a homogeneous distribution of drug can be achieved across all granule size fractions in the granulation batches. The composition of the granules is relatively consistent across all size fractions, except for the 40 wt% salicylic acid batch which has a slight deviation away from the theoretical amount. Therefore, when the formulation wettability is mostly hydrophilic, the drug is uniformly distributed throughout the granular batch and closely approach 100% drug claim in all granule size fractions, regardless of the proportion of hydrophobic component in the powder mixture.

In contrast, hydrophobic formulations granulated with a water binder show a poor ability to achieve a uniform granule composition. From Fig. 10, it can be seen that the highest drug claims are found in mainly the finest and coarsest size fractions. Therefore it appears that the finest fractions compose of un-granulated salicylic acid powder, while the coarse fractions are enriched with salicylic acid that is granulated with lactose powder. The magnitude in deviations away from the theoretical drug content becomes progressively worse as the formulation batch becomes more hydrophobic. Consequently this leaves the intermediate granule size fractions being deficient of salicylic acid. Hence gran-

Table 2
Drop penetration time summary for heterogeneous powder systems with varying magnitudes of hydrophobicity.

wt% SA	wt% L2M	ε	5% (w/v) PVP				Water, data taken from [17]			
			t_p (s)	σ_μ (s)	Max. t_p (s)	Min. t_p (s)	t_p (s)	σ_μ (s)	Max. t_p (s)	Min. t_p (s)
0	100	0.75	7.9	0.51	12	4	0.02	0.0	0.02	0.02
20	95	0.75	13.8	0.90	24	9	0.3	0.1	1.8	0.03
40	90	0.77	13.9	0.60	19	11	17.8	2.5	34.9	0.7
50	85	0.77	16.7	0.79	25	11	57.7	1.8	67.4	48.5
60	75	0.78	17.9	0.42	22	16	57.4	3.8	87.4	33.9
80	50	0.80	20.7	0.64	28	17	88.8	2.6	104.4	74.0
100	0	0.85	18.4	0.66	23	13	91.8	1.8	102.3	75.7

Note: n, number of experiments; ε, bed porosity; V_0, drop volume; t_p, average penetration time.

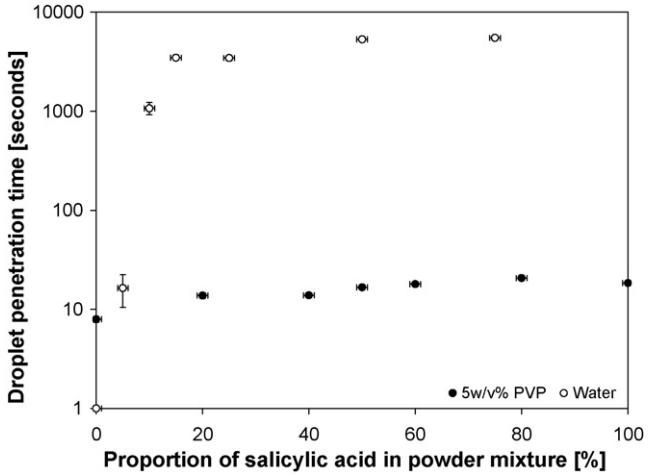

Fig. 11. Drop penetration time as a function of hydrophobicity of a powder bed consisting of varying ratios of salicylic acid and lactose 200 mesh.

ulation of hydrophobic formulations compromises the granulation performance. Designing a formulation that exhibits hydrophilic interactions between the powder and binder would facilitate in achieving the uniformity criterion for granular products set by the FDA and other regulatory agencies.

3.3. *Effect of drop penetration time*

Previous studies have shown that the drop penetration of a liquid binder into a powder bed is strongly dependent on the formulation properties [16,17]. Table 2 supports these conclusions as the drop penetration time is strongly influenced by the hydrophobicity of the formulation.

The drop penetration times t_p for a 5% PVP and water droplet penetrating into powder beds of varying degrees of hydrophobicity are summarised in Fig. 11. The bed voidage ε increases steadily across all degrees of powder formulation hydrophobicity from 0.75 to 0.85 due to subtle packing differences between the two powders and the inherent static of the salicylic acid which leads to poor packing of particles in the powder bed.

From Fig. 11, the drop penetration time increases as the proportion of salicylic acid in the formulation increases, in agreement with a previous study [17]. Because aqueous PVP transitionally wets the salicylic acid in the formulation, the penetration rate is faster than that compared to the powder formulation nucleated with water, which is completely hydrophobic to salicylic acid. In general for all degrees of formulation hydrophobicity, a narrow drop penetration time range is seen for formulations nucleated with aqueous PVP droplets (time ranges from 4 to 28 s) compared to water droplets (time ranges from 1 to 626 s).

The difference in the drop penetration time range can be more clearly seen in Fig. 11, which shows the relationship between drop penetration time and the amount of hydrophobic salicylic acid in the powder mixture. The data in Fig. 11 includes a constant estimated x-axis error of $\pm 1\%$ in the composition of the powder bed and the y-axis error bars represent the standard error of the mean. Although the penetration time is expected to increase with an increase in hydrophobic drug proportion, Fig. 11 shows that the sensitivity of the penetration time depends upon the formulation hydrophobicity. For instance for water-bound nuclei, the penetration time is very sensitive to the proportion of salicylic acid in the powder mixture and a critical region at approximately 20 wt% salicylic acid can be found where the penetration time increases significantly. This point indicates a transition from dominant hydrophilic penetration to the slower dominant hydrophobic penetration of binder droplets [17]. For formulations nucleated with aqueous PVP droplets there is no change in penetration kinet-

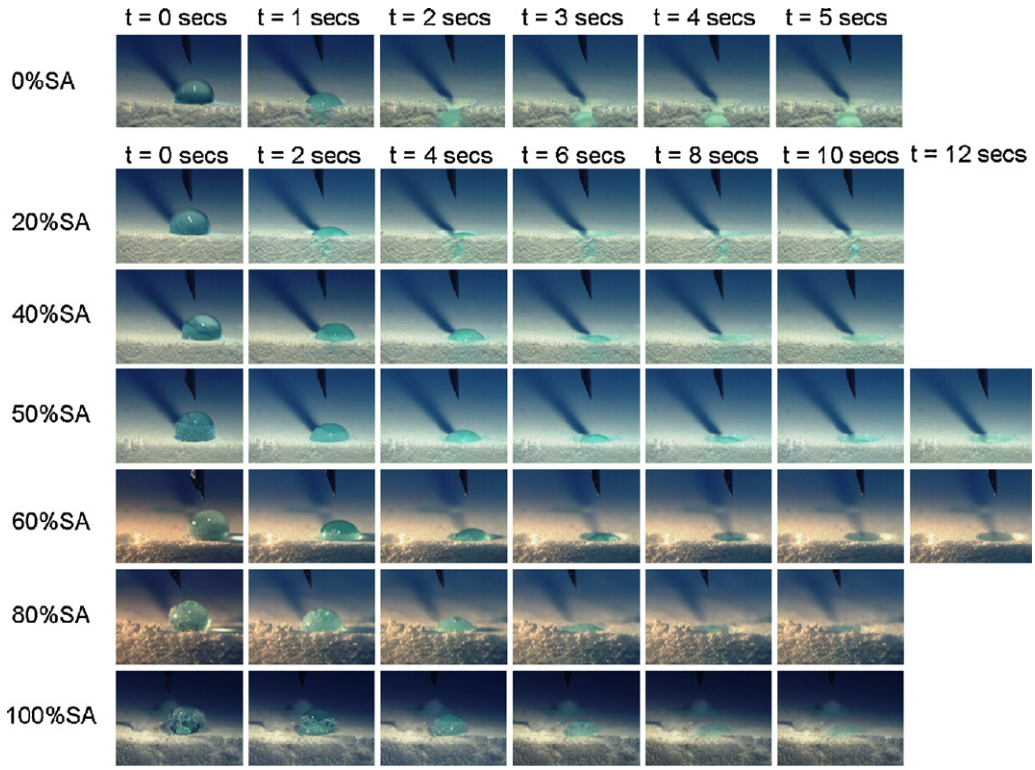

Fig. 12. Matrix of the drop penetration of a PVP droplet into heterogeneous-wetting powder bed composing of various ratios of salicylic acid (SA) and lactose 200 mesh (L2M) powders. Actual drop penetration times are longer than shown due to the difficulty of capturing the complete liquid penetration in the crater.

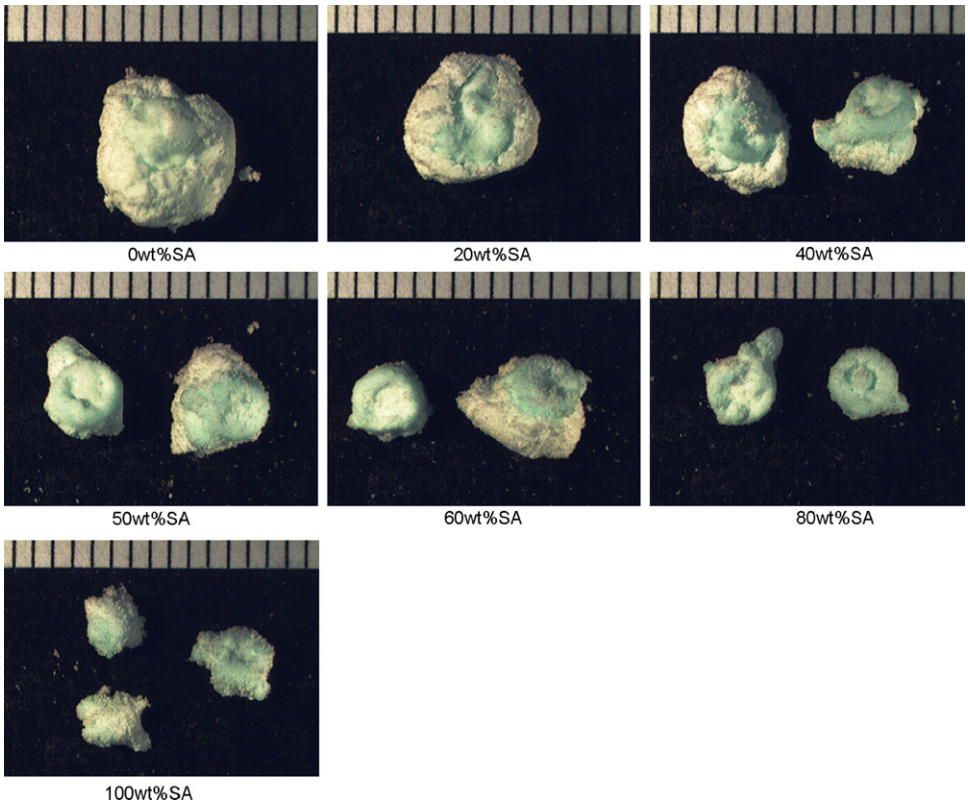

Fig. 13. The granule morphology as a function of the powder bed hydrophobicity. Drop size constant at ~12.3 μL. The scale markings indicate millimetres.

ics over the entire range of formulation hydrophobicity, which illustrates the transitional wetting that PVP undergoes with salicylic acid. The penetration kinetics are relatively insensitive to the formulation hydrophobicity for PVP binder.

3.4. Drop penetration behaviour and granule morphology

Fig. 12 shows that the penetration of a droplet into a heterogeneous-wetting powder bed can be complex with a transition from hydrophilic nucleation to hydrophobic nucleation.

For low proportions of hydrophobic component in the powder mixture, the droplet immediately penetrates down into the powder bed, indicating that the powder bed exhibits dominant hydrophilic penetration behaviour or "*immersion wetting*". When a significant amount of salicylic acid is in the formulation (40 wt% salicylic acid), there are signs that the powder bed is showing hydrophobic wettability with some degree of "*solid spreading nucleation*" [18] or spreading of hydrophobic particles over the droplet surface, while the droplet is still penetrating into the powder bed. This is shown more prominently in Fig. 12 for the 80% salicylic acid powder mixture.

After impact of the droplet onto 100% salicylic acid powder (see bottom row in Fig. 12), a liquid marble is initially formed, but after approximately 2 s, transitional wetting between the PVP and salicylic acid occurs [15], consequently leading to immersion wetting and the PVP droplet eventually penetrates into the powder bed to form a core-saturated granule. The fact that the 5% (w/v) PVP droplet does penetrate into the 100% salicylic acid powder indicates that the contact angle between the hydrophobic powder and binder fluid is high but still less than 90°, showing that drop penetration is still possible. Overall the drop penetration times for aqueous PVP are much faster than the penetration times for pure water for the same powder system [17] which suggests that the increased viscosity of the PVP binder solution is a minor effect compared to the decreased contact angle achieved by using a 5% (w/v) PVP solution instead of pure water.

Fig. 13 shows the transition in granule morphology from a core-saturated granule to the formation of a collapsed liquid marble to form a saturated nucleus. The granule morphology and strength is dependent upon the formulation hydrophobicity.

Granules produced from low proportions of salicylic acid exhibit a morphology that consists of a large granule with a highly saturated nucleus, surrounded by an outer layer of semi-saturated powder shell, similar to structures noted elsewhere [16,19–21]. The core-saturated granule demonstrates high granule strength as the granule is able to resist any deformation forces exerted on it during the excavation process.

However the granule structure begins to weaken as the proportion of salicylic acid increases. This is the case for 40 wt% salicylic acid, where the outer semi-saturated powder layer is broken away from the saturated core. Hence there is a formation of heterogeneous granule morphologies in the granulation batch from 40 to 60 wt% salicylic acid, although the mechanical or deformation forces in granulator would be expected to break away most of the semi-saturated powder layer making the granule morphology more consistent. The 80 wt% salicylic acid granular material morphology is more uniform where the batch is solely composed of saturated-core granules, which is also seen for the nucleation of pure salicylic acid powder. However, the saturated cores are irregular shaped, due to the weak adherence of salicylic acid particles to each other and the weak resistance of the core to deformation forces. The lack of a semi-saturated powder shell in granules produced from a higher loading of salicylic acid would assist in the explanation of the decrease in granule size with increasing proportion of hydrophobic component in the formulation. A similar trend was found for granules nucleated with water, however the granules looked less irregular and nucleation of pure salicylic acid composed of fragmented lens-shaped hollow granules [17].

4. Discussion

4.1. Effect of hydrophobicity on granule size

Fig. 3 shows that the incorporation of hydrophobic powder components into the formulation decreases the average granule size, supporting the original work of Aulton and Banks [1]. We attribute the observed decreases in average granule size to two complementary effects: smaller nuclei are formed from each drop (as seen in Fig. 13) and these granules are structurally weaker due to fewer and weaker liquid bridges between the hydrophobic particles.

The key finding that the nucleus size is smaller as the hydrophobicity increases is supported by Fig. 13 and a previous study [17] which shows that smaller granules are formed as the proportion of salicylic acid in the formulation increases, even when the drop size remains constant. This is due to a transition in nucleation mechanism and granule structure. For hydrophilic formulations, containing mostly lactose powder, the droplets of binder fluid form a core-saturated granule. Granules produced from formulations containing larger proportions of salicylic acid consist of only a saturated core, and lack a semi-saturated outer powder layer. Some hybrid nucleation [17], involving simultaneous solid spreading nucleation [18] and drop penetration [16,17] may also occur.

The weak adherence of salicylic acid to lactose or other salicylic acid powder particles during granulation exacerbates the reduction in granule size. During the nucleation stage, the wettability of granulating fluid determines the strength of the liquid bridges that binds the primary particles together. Where the granulation of salicylic acid and water occur, the hydrophobic interaction between salicylic acid and water leads to a high contact angle between the binder and the particle, which would form an unduloid liquid bridge [22]. This type of liquid bridge reduces the contact area of the solid–liquid interface, which subsequently leads to the binder being weakly adhered onto the particle. Weak nucleation is even seen for the granulation of a formulation containing a high loading of salicylic acid granulated with PVP. Although immersion wetting occurs with the PVP binder, the penetration of the binder through the powder bed is limited [17]. The binder does not diffuse extensively into the powder bed to form a strong semi-saturated powder shell surrounding the saturated core as seen in Fig. 13.

For formulations with water as the granulating fluid, the water is able to form strong nodoidal liquid bridges between the lactose particles [22], which would facilitate the formation of the semi-saturated powder layer around the nucleus. This would be the primary reason why the size of the granule made from a predominately hydrophilic powder mixture is coarser, even in the nucleation of the powder mixture with aqueous PVP fluid. This reasoning is supported by Fig. 13, where granules produced from a predominantly hydrophilic powder system consist of a thick semi-saturated powder layer, which reduces as the formulation hydrophobicity increases. The decrease in the average granule size could then be attributed to the increased breakage rate producing fragmented granules and/or liquid marbles. Therefore it would be the combination of weak liquid bridges and limited binder diffusion that account for the decrease in granule size as a function of increasing formulation hydrophobicity.

4.2. Drug distribution in wet granulation

To achieve a uniform distribution of drug within a granulation batch, good wettability between the granulating fluid and the powder is favourable. Figs. 4–10 demonstrate this where using aqueous PVP as the granulating fluid results in a fairly uniform distribution of salicylic acid. The granules of each PVP batch contained granules that approached the theoretical composition of 100% drug claim. The insensitivity of the distribution of drug in the granulation batch to the proportion of hydrophobic component in the mixture may be partially attributed to the primary particle sizes of the drug and excipients used in the granulation process. Previous works have demonstrated that granulation of a coarse drug with fine excipient and vice versa leads to preferential granulation of the finer particles or coarser particles due to the viscous Stokes law theory favouring the granulation of fine particles [8]. In this work, the size preferential granulation effect has been minimised with the use of a similar primary particle size for salicylic acid and lactose (see Table 1). Hence the powder components are able to mix and granulate more evenly and this is supported by the work of Vromans et al. [4] who found that granulation of similar-sized drugs and excipients leads to an even distribution of drug throughout the granulation batch. The uniform drug distribution is also attributed to the hydrophilic wettability of aqueous PVP to salicylic acid. Therefore, during nucleation of these formulations with PVP binder, immersion wetting is occurring and the nucleated salicylic acid and lactose powder are then dispersed by mechanical impeller forces ("destructive nucleation" [20]) which facilitate the even distribution of salicylic acid throughout the granulation batch.

In granulation batches using water as the granulating fluid, the drug distribution is severely compromised with a high drug claim for granules less than 124 μm and greater than 1000 μm for all cases except for 20 wt% salicylic acid concentration. This confirms that salicylic acid is completely hydrophobic to water which leads to poor nucleation and/or granulation, leaving the fine and coarse granular material being enriched with salicylic acid and the intermediate size fractions deficient in drug content. The uneven drug distribution can be explained by the preferential granulation of components due to preferential wetting of the hydrophilic lactose powder. This would account for the lower drug content in the granules between 125 and 710 μm. The high drug claim in granules greater than 1000 μm suggests that the agglomeration of lactose encases salicylic acid within the coarse lumps. While water granulates lactose particles very efficiently, the hydrophobic salicylic acid forms very weak unduloid liquid bridges [22] between the particles. These liquid bridges are easily broken through handling of the granular material or by impeller forces. In contrast to the PVP granulation process, the mechanical impeller forces does not facilitate material transfer between granules to distribute the drug, rather the mechanical forces tend to break the salicylic acid component from the granules. The resulting salicylic acid remains un-granulated or undergoes a weak adherence and breakage cycle. This phenomenon would account for the steep decrease in granule size with increasing salicylic acid content as seen in Fig. 3. Granulation with a hydrophobic formulation makes achieving the uniformity criterion difficult as the drug distribution is non-uniform and there is granulation competition between the hydrophilic and hydrophobic components in the formulation.

4.3. Drop penetration behaviour

The drop penetration time is strongly influenced by the powder formulation hydrophobicity (see Table 2). When predominantly hydrophilic powder is nucleated with a binder droplet, the penetration time is relatively short, as seen in the penetration times of less than 15 s for formulations up to 20 wt% salicylic acid. For the PVP binder solution, which shows a transition between initially hydrophobic behaviour and then hydrophilic wetting, the drop penetration time increases slightly to 20 s for penetration into 80 wt% salicylic acid powder mixture. The gradual increase in drop penetration time indicates the progression to limiting percolation [17] of the binder through the binary powder bed. However the limiting percolation is not a significant factor in the penetration

kinetics compared to water systems. In contrast, the hydrophobic interaction between the water and the salicylic acid is shown by a sharp increase in the drop penetration time (Fig. 11) which also corresponds to a dramatic transition in nucleation phenomena (Fig. 13). For low degrees of formulation hydrophobicity, there is a strong hydrophilic nucleation behaviour of immersion wetting, while for high degrees of hydrophobicity, the penetration time slows down significantly or may not penetrate into the powder bed at all, but instead undergoes solid spreading nucleation [17].

As seen with the drop penetration time profile of water [17], the point of transition between the hydrophilic and hydrophobic behaviour is defined by the rapid increase in penetration time. In the system studied, the rapid increase in penetration time occurred at approximately 20 wt% salicylic acid. This point of transition is defined as the *critical or threshold concentration ratio* p_c [17] and can be explained by the site percolation theory [23,24]. For the binary system of heterogeneous-wetting powder components, the threshold concentration ratio p_c defines the boundary at which the percolation reaches its lowest limit for successful liquid penetration through the powder capillaries. For a binary system that contains a large proportion of hydrophobic powder, successful penetration can only occur if there is a hydrophilic pathway present in the system and/or if the binder must overcome the high contact angle of the hydrophobic capillary walls. Nucleation with PVP initially exhibits hydrophobic behaviour, but transitional wetting gradually turned the hydrophobic formulation into a hydrophilic system, allowing for the droplet to eventually penetrate into the powder bed. The hydrophobic effect became more significant once the salicylic acid concentration was more than 40 wt%, where solid spreading nucleation and simultaneous immersion wetting was observed (Fig. 12). For concentrations below 40 wt% salicylic acid, the nucleation process undergoes immersion wetting producing core-saturated granules (Fig. 12). The drop penetration time corresponds to the wettability of the formulation and gives an excellent indication of the nucleation mechanisms involved during the granulation of heterogeneous powders.

The drop penetration time can also be correlated to the uniformity of drug distribution in the granulation batch. As seen in Figs. 9 and 10 for PVP and water binders respectively, the drug claim is relatively consistent at the theoretical drug claim for 20 wt% salicylic acid in both the PVP and water-nucleated formulations. When the proportion of salicylic acid is at least 40 wt%, larger deviations away from the target drug claim can be seen. This suggests that for formulations with a drop penetration time below the threshold concentration ratio p_c, the wetting of the powder is hydrophilic with minimum hydrophobic effects and hence the drug distribution is even throughout the batch. When the threshold concentration ratio is exceeded, the hydrophobicity effects of the salicylic acid become more dominant in the penetration kinetics and nuclei structure. This compromises the uniformity of the drug distribution in the granulation process. Therefore the drop penetration time and the threshold concentration ratio may be able to predict the extent of drug distribution for a granulation batch. This is the subject of further investigation.

4.4. Granule morphology

The granule morphology in Fig. 13 gives an insight into the complex nucleation mechanisms occurring during granulation of heterogeneous-wetting systems. Granulation of a hydrophilic formulation yields granules that are uniform in morphology and strong enough to resist forces in the granulator or subsequent handling. The formation of core-saturated granules from formulations with a high proportion of lactose allows for the dissolution of lactose into water or aqueous PVP. During the drying process, the lactose helps cement the lactose particles together [17]. The addition of even small amounts of salicylic acid causes the granule strength to be compromised, even at low magnitudes of hydrophobicity, which also compromises the uniformity of the granule structure for the granular product.

However, even for core-saturated granules formed from pure lactose, the liquid bridges formed in the semi-saturated crust are weaker than that formed in the saturated-core region and so the semi-saturated powder layer can break away. This is known as “destructive nucleation” [20] and will be a particularly important mechanism when a high proportion of salicylic acid is found in the formulation for both water and aqueous PVP nucleated systems. The higher proportion of salicylic acid in the granule would decrease the probability of the lactose particles cementing together. The weakening adhesion strength of the liquid bridge would make the granules more susceptible to attrition and breakage under turbulent granulator conditions, and the resulting granular product would compose of core-saturated nuclei without their original shell.

The limited percolation theory also supports the finding whereby the presence of salicylic acid in the system reduces the pathways available for the liquid to penetrate efficiently through the powder bed which hinders liquid bridge formation and reduces granule strength. This would explain why PVP nucleated granules in this paper are more irregular in shape compared to water-nucleated granules in a previous study [17]. Under typical granulator conditions, the strength of the granules produced at high drug loadings would not be able to resist the mechanical impeller forces, compared to granules produced from low drug loadings. Therefore the inclusion of complex hydrophobic drugs in granulation and tablet manufacture compromises the uniformity of the granulation batch in terms of granule morphology and strength. The wettability of the formulation can be improved through the inclusion of polymers in the binder, as seen in the case of nucleating and granulating with aqueous PVP.

This investigation demonstrates that formulation wettability is a critical factor in controlling the distribution of drug during the granulation. Formulations with a short penetration time are relatively hydrophilic and mechanical impeller forces would be important for distributing the drug evenly in the granulation batch to produce a final product with a narrow granule size distribution and close to 100% drug claim/content. However the granule morphology consistency may not be achieved due to the potential hydrophobic behaviour effect between the powder and binder (particularly at high drug loadings) which would lead to breakage and attrition of granules during the granulation process.

For more hydrophobic formulations with long drop penetration times, the nuclei formed will be smaller and the impeller forces would have a detrimental effect on the drug distribution as there is weak adherence between the powder and binder. To improve the drug distribution, physical operation procedures could be adopted such as a longer wet-massing period but this could broaden the granule size distribution. Coarse granules could also be selected (such as in this case 710 μm granules) with the desired drug content and recycle the undesired granules. However this approach may be economically infeasible or time, energy and material consuming. Using a surface chemistry approach and adding a polymer or surfactant to the binder will improve the wettability of the formulation, although this is not always feasible. Very low levels of hydrophobic powders (approximately up to 20% in proportion for this formulation) can be used in a granulation formulation without having a detrimental effect on the wetting between the binder and powder. However this may not meet the requirements of the final dosage design and so both surfactant and/or mechanical forces are expected to play an important role in breaking up caked saturated powder masses and evenly distribute the drug in the granulation batch.

5. Conclusions

Investigations into the granulation and nucleation of heterogeneous-wetting formulations have found that the nucleation and granulation of heterogeneous-wetting components are influenced by a complex combination of powder wettability and nucleation mechanism for a formulation with a matched particle size between the hydrophilic and hydrophobic components.

This study is a significant extension on the influential work of Aulton and Banks [1] which validates their original conclusions but provided a much more detailed analysis of the granules size, structure and composition. The study confirmed that the average granule size decreases as the proportion of hydrophobic powder increases. This is attributed to the weaker and less effective liquid bridges as well as due to smaller size of the nuclei formed due to the absence of the semi-saturated outer layer. These smaller and weaker granules would also be more susceptible to deformation and breakage. Granulation with a hydrophilic formulation produced a batch with uniform drug content, granule morphology and size. In contrast, granulation of hydrophobic formulations compromised the granule morphology and size uniformity and made achieving a consistent drug content that approached the ideal drug claim difficult for all size fractions. To improve the wettability of a hydrophobic formulation, the inclusion of a polymer or a surfactant into the binder can be employed. The drop penetration time increased as the proportion of salicylic acid in the powder mixture increased, where there was a weak threshold concentration of approximately 40 wt% salicylic acid for aqueous PVP nucleated cases and a strong threshold concentration of approximately 20 wt% for water cases. The threshold signalled the transition of hydrophilic to hydrophobic nucleation behaviour as evident by hybrid solid nucleation-immersion wetting penetration of the droplet into the powder bed. The threshold concentration may also give an indication to the magnitude of the hydrophobic effects and hence the uniformity of drug distribution in the granulation batch.

The granulation of heterogeneous-wetting formulation is not deemed to pose significant problems in achieving a uniform granular product as long as the primary particle sizes of the drug and excipients are relatively similar and there is a hydrophilic wettability between the powder and binder to produce strong liquid bridges, essential for granule growth and strength. An even distribution of drug during the granulation process relies on efficient material transfer between granules and this is dependent on the hydrophilic wettability of the formulation and mechanical impeller forces to induce granule material transfer.

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