HEAT ACTIVATED DRY GRANULATION WITHIN THE TWIN SCREW GRANULATOR

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Abstract

This paper highlights preliminary results related to a new dry granulation process that is run in a twin-screw extruder. This heat-activated dry granulation method can produce suitable dry granules representing an exciting new area for continuous granulation. However, the current method makes starting granulation difficult. It is believed that high compaction produces sufficient friction at the barrel wall to cause the binder to soften. Once a plug of dense granular matter is built up in the kneading section of the screws, it appears that any flow condition will produce granules but establishing this plug initially represents a major challenge and is where further studies are needed to simplify the approach.

Introduction

Methods of particle enlargement are crucial to the pharmaceutical industry in the preparation of many solid oral dosage forms. The preparation of granules from a mixture of excipients (ex. diluents, disintegrants, glidants, lubricants) and active ingredients ensures compositional uniformity, excellent solids flow, and yields fewer problems during tableting operations as well as stronger, more aesthetically acceptable finished tablets. The preparation of these granules has been traditionally accomplished by batch operations such as in a high shear mixer or fluidized bed, and by the methods of wet, melt, foam, or dry granulation. Wet granulation is considered the most robust method, capable of binding difficult particle formulations with good particle size control and strong bridges. However, the method is marred by the necessity for long drying times (on occasions greater than 24 h) adding considerable time and expense to the process. Some of the issues with wet granulation have diminished recently due to the rise of continuous processing techniques such as the use of a twin-screw granulator (i.e. a co-rotating intermeshing twin screw extruder with a modified exit and no die) where less liquid is necessary to achieve equivalent particle sizes [1]. Use of a foamed liquid for binder addition has been shown to further reduce the quantity of water necessary to granulate [2]. However, since this extruder is unable to address the drying step due to its short residence time, a dryer often remains a necessity of the process. Due to the costs to validate a manufacturing process for a drug, pharmaceutical companies are less likely to switch their existing products to continuous wet granulation despite its economic benefits and so it seems more likely a twin-screw granulator will gain a stronger foothold with alternative granulation methods and with new products.

Melt granulation holds the most promise for twin-screw granulation since the method eliminates the drying step and takes advantage of the machine's strength in handling viscous media at elevated temperatures. The method has already shown great promise for producing high dosage granulates [3]. The method is more often considered for moisture-sensitive drugs to avoid losses in efficacy but the high temperatures employed to melt a polymer binder like polyvinyl-pyrrolidone, modified hydroxypropyl methyl-cellulose, copovidones, or lipids like glycidyl behenate, are also concerning to formulators, in general, for the potential of drug damage. The short residence time of the extruder seems to diminish this concern [4] but with so little knowledge available pertaining to heat/shear interactions for most drug components, there remains considerable trepidation surrounding the approach. Dry granulation is more ideal since it requires neither significant amounts of liquid or heat but it is admittedly difficult to deploy in batch processing and there exists no known continuous process.

Dry granulation is most commonly performed in a roller compactor, forming dense sheets from the dry ingredients by high mechanical force and then milling to a suitable granule size. The technique only works with specific drug ingredients and is commonly employed only with moisture-sensitive drugs; in light of the comments above, it is an alternative to melt granulation and certainly should be considered when there are heat sensitivity concerns as well. The particles are described in the literature as being bound by mechanical interlocking and available interfacial associations like London forces and hydrogen bonding [5]. It seems likely that plastic energy dissipation is a participant in particle bridging, producing local melting/softening of a polymer binder in the presence of high compression. Since these compressive forces are extremely high (hundreds or thousands of times greater than the capacity of a normal twin-screw extruder), this method does not translate to shear granulation processes, as in a high shear batch mixer or even a twin-screw granulator. In fact, direct tableting

studies by Keleb et al [6] have effectively proven that the compacted powders from a twin-screw extruder are too porous and friable to be considered useful. However, at least in the case of the high shear batch mixer for ingredients tolerant of moisture, an alternative method has been proposed known as moisture-activated dry granulation (MADG). The technique stresses that the important fact of dry granulation is only that the finished granules are dry without the use of a dryer and this approach is unsuitable for moisture-sensitive ingredients. MADG causes granulation to occur with only small amounts of moisture (1-4%) yet can still produce acceptable granules [7]. By MADG, the polymeric binder is moistened to the point of becoming sticky to the majority of ingredients and once no further agglomeration will occur, excipients with high water sorption capacity are added to 'dry out' the granules.

The purpose of this paper is to present a dry granulation alternative for the twin-screw granulator, which will be referred to as heat activated dry granulation (HADG). Like MADG, the method limits exposure to the potential harmful factors, i.e. moisture and heat in this case, to produce granules that are dry at the exit of the process and require no downstream drying step. In fact, HADG done optimally should release a company from the necessities of doing either drying or milling after the granulation process. The process is believed to be uniquely limited to twin-screw granulators as there is a dependency upon the confined flow space and intense, controlled shear to produce the necessary particle bridging. This paper is intended to introduce the method, highlight its capacity and also shows its challenges.

Experimental

Materials

The fillers were spray-dried α-lactose monohydrate (Flowlac 100; Meggle Pharma; Germany) and microcrystalline cellulose (MCC) (Avicel PH101, FMC Biopolymer; Newark, NJ). The binders were hydroxypropyl methylcellulose (AFFINISOL™ HPMC HME, The Dow Chemical Company; Midland, MI) and vinylpyrrolidone-vinylactetate copolymer (Kollidon® VA64, BASF; Florham Park, NJ). METHOCEL™ F4 Prem. (The Dow Chemical Company; Midland, MI) was used as a control for the selection of binders since it was not anticipated to adequately soften and flow in these experiments. Acetaminophen (USP grade) was purchased from Spectrum Chemicals (Gardena, CA). Magnesium stearate (Sigma Aldrich; Mississauga, ON) at 0.5 wt% was included in all formulations.

Twin-Screw Granulation

HADG was performed in a ZSE-HP 27mm 40 L/D co-rotating intermeshing twin-screw extruder (American Leistritz Extrusion Corp.; Somerville, NJ). The screw design consisted of conveying elements along the entire screw with the exception of a 30 mm long 5-disc 60° offset kneading block in zone Z8 of the nine zone barrel and a 30 mm long comb mixing element immediately after the kneading block to help 'slow down' the flow of powders. All barrel zones were set to 35 °C except zone Z8 which was varied from 80-120 °C. Premixed formulations were added at the feed zone, zone Z(0), by a T-20 gravimetric feeder (Brabender Technologie Ltd.; Mississauga, ON) at a flow rate varying from 5-25 kg/h. The formulations consisted of 74.5% lactose, 5% MCC, 15% binder, 5% acetaminophen and 0.5% magnesium stearate.

Analysis of the samples in this paper was limited to particle sizing using a Ro-Tap sieve shaker with 5 min of mechanical agitation. The sieves selected had openings of 3350, 2360, 1180, 850, 500, 300, and 150 μm. The feed powders possessed no sizes larger than 250 μm. In addition, the process was studied visually based on observations at the barrel exit and by abruptly halting the extruder and pulling out the screws while still filled with powder (i.e. a screw pull-out experiment [8]).

Results and Discussion

To begin this discussion it is important to highlight that initially when all barrel zones were set to 35 °C it was possible to run each powder formulation through the extruder at flow rates from 5-40 kg/h without blockage or change in particle size, at screw speeds from 100-300 RPM. There was no factor in the process to initiate particle bridging under these conditions in a clean screw.

Identifying the HADG process

The HADG process was initially uncovered while looking at a formulation with AFFINISOL HPMC HME, for wet granulation and the binder's metering pump failed. Despite the absence of water entering the extruder, granulation continued and the particles appeared more spherical, smaller but nonetheless acceptable. One notable change was that the exiting granules now showed a significant increase in temperature, close to 90 °C, despite a flat barrel temperature profile of 35 °C. Removing the screws, cleaning them, and then attempting to restart to granulate the powders failed to reproduce this result. As mentioned above, the powders passed through the clean screws without change in particle size. It was realized that by cleaning the screws, the filled zone of powders around the kneading block was no longer present and as a result, there was nothing to decrease the velocity of these particles across the non-conveying section of the screws. The previously added water had caused the particles to slow, agglomerate and ultimately compact across the kneader and when the water had stopped being

added, the plug of material remained for a sufficient period of time to cause newly entering powder to the zone to increase in temperature by frictional forces in the absence of any lubricating liquid, to the point that the binder softened/melted. The binder, AFFINISOL HPMC HME, which is a new extrudable form of hydroxypropyl methylcellulose (HPMC) has a glass transition temperature (T_g) of 115 ^oC. It was believed then that Kollidon VA64, which has a similarly low T_g (101 ^oC), would therefore be equally suitable to initiate granulation in this type of system but that a regular HPMC, like METHOCEL F4 should not, as its T_g is much higher.

A set of trials were conceived to test the principals of HADG by looking at three formulations (based on varying the binder ingredient). It appeared that the addition of water, even momentarily, could initiate the process but if the restriction in the kneading section was not sufficient to let the powder temperature rise granulation did not continue. Considering the design of an extruder and its capacity for locally controlled high temperatures, it was estimated that elevating the barrel zone temperature just around the kneading section should be sufficient to produce a similar fill to that achieved when adding water. By having only one zone heated and considering the residence time in the extruder was 18-25s, too short for high temperatures to build in the powders, it was felt that this process should be differentiated from melt granulation. The first trials set barrel zone Z8 to 100 ^oC with all other zones set to 35 ^oC. It was hoped the continual heating of this one zone would offer more long-term stability to the process. Certainly it was found by turning off the zone heater instead that the temperature rose uncontrollably to as high as 118 ^oC now that granulation had started. Conversely, by now attempting to cool the zone, motor load rose to the point that the machine stopped. The trial data is listed in **Table 1**.

Table 1. Process conditions

Sample	Binder	Screw speed	Sample Temp* (^oC)
V1	VA64	150	83
V2	VA64	200	74
V3	VA64	250	53
V4	VA64	300	44
F1	F4	150	37
F2	F4	300	36
A1	Affin	150	58
A2	Affin	300	41

* flow rate 10 kg/h Kollidon VA64, 20kg/h AFFINISOL

To start the granulation process by this method, the flow rate had to be progressively increased while operating at a fixed screw speed (150 RPM) until the channel fill was high enough that the kneading section became densely filled and frictional/viscous heat was generated. The softening of the binder was enough to decrease the velocity of particles around it and initiate compaction which likely further facilitated more of the binder to melt by the increased lateral stresses. For the lower T_g binder, Kollidon VA64, granulation began at 10 kg/h. Comparatively, a flow rate of 20 kg/h was required when using AFFINISOL HPMC HME. Once granulation began, it was possible to change the screw speed (as shown in the table) or flow rate. The exiting particle temperatures, determined by a hand-held infrared pyrometer, are included in **Table 1**. These values highlight the fact that the bulk temperature never rose to the T_g of either binder, implying a localized heat phenomenon – which is reasonably related to friction due to the reliance upon densification in the kneading section. The fact that the very high Tg METHOCEL F4 did not produce granules at any flow rate was seen as further evidence that what initiated the phenomenon of granulation was related to heat and not chemical interactions.

The particle size distributions of samples that successfully granulated listed in Table 1 are presented in **Figure 1**. It can be seen that for both binders, the screw speed of 150 RPM where granulation began, produced very large chunks. In both cases, the majority of particles were above 3.35 mm in size. By increasing screw speed, the fraction of particles categorized as chunks (i.e. above 2mm) decreased and the desired size range of 0.5-2mm became prevalent. The particles had a typical aspect ratio of 1.2-1.7 (long axis/short axis) for the twin-screw granulator and an off-white appearance.

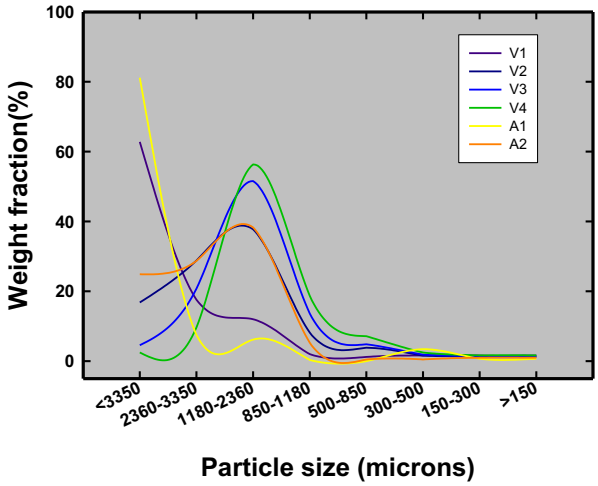


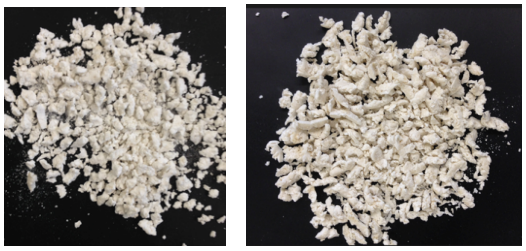
Figure 1. Particle size distributions for successfully granulated samples listed in Table 1.

Revisiting HADG

Despite the challenges associated with initiating HADG, the outcome is quite positive in terms of the ability to granulate a dry powder with minimal exposure to high temperatures that might harm the drug. It was therefore interesting to comment upon more detailed runs, which followed.

The second trial was designed to determine the effect of temperature in zone Z8 by varying it from 80-120 °C and to begin to examine material attributes of the resulting granules. A 20 MPa pressure transducer had also been added atop the kneading section to confirm the hypothesis of compaction. Unfortunately, the trial also demonstrated the effects of moisture, as the new set of runs were done in a higher humidity environment (62% RH compared to 35% RH) due to the time of year. The moisture content in the room had increased and, correspondingly, the water in the feed formulations rose from 2% to 6% as a result. It was evident from the results that the water made it more difficult to start HADG.

The first runs of this new trial were done with 10% MCC and no active. For both formulations, with either Kollidon VA64 or AFFINISOL HPMC HME, granulation could not be produced at any tested temperature except 120 °C for zone Z8. For the formulation with Kollidon VA64, a slower screw speed of 100 RPM and higher flow rate of 20 kg/h was required for pressure to buildup in the kneading block of a clean screw, indicating the initiation of granulation. In this case the extruder needed to be quickly ramped to 300 RPM in order to prevent a motor overload – this urgency to change conditions had not been seen in the first trial. Once granulation was started by this procedure, any flow rate could be selected, with some of the samples collected being listed in **Table 2**. The temperatures of the granules were surprisingly high at 110 °C and did not vary with flow rate; temperatures of the exiting powders which never granulated were lower around 42 °C to 54 °C for flow rates of 23 kg/h to 5 kg/h, respectively, when attempting to start HADG at higher screw speeds (150-300 RPM) in a clean screw. The collected granules under HADG were dry (as evident by the measured moisture content) but appeared as very coarse particles now, shown by photo in **Figure 2** and particle size distribution in **Figure 3**.



Sample A Sample D

Figure 2. Photos of samples A & D from Table 2 showing coarse granules being prepared with Kollidon VA64.

For the formulation with AFFINISOL HPMC HME yet no active, the high humidity had the same impact as seen with Kollidon VA64 relative to the first trial, making it much harder to initiate granulation. In this case, the screw speed had to be reduced to 70 RPM to initiate HADG at 20 kg/h; the lower moisture uptake of HPMC may be the reason these conditions were closer to the first trail than with vinylpyrrolidone-vinylactetate copolymer. A sample was collected at this condition which was observed to exhibit similar size, shape and appearance to the granulated samples with Kollidon VA64. The sample is described in **Table 3** and its particle size distribution is included in **Figure 3**. The system with AFFINISOL HPMC HME was verified to once again granulate at any flow rate or screw speed once HADG had been initiated but no further samples were collected as they showed no differences from any other conditions in the second trials. The formulation with F4 HPMC was tested but once again, no condition would produce granulation and so it was not reported below.

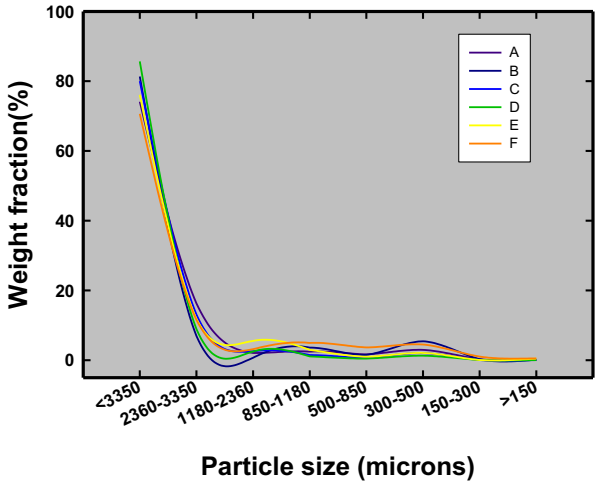


Figure 3. Particle size distributions for successfully granulated samples listed in Table 2-3.

Having access to different grades of AFFINISOL HPMC from Dow Chemical, it was possible to gain some insights into the rheological contributions of the binder to HADG. The original HPMC discussed earlier was developmental and had a viscosity of 20 cP (2% aqueous solution, vendor quoted) whereas the newly provided binder is a commercial grade with a viscosity of 15 cP. These tests were done under the same high humidity environment mentioned in the previous section but now similar to the first trial, acetaminophen was included. In the tests, screw speed was now held constant at 150 RPM, similar to the first trial and the flow rate was increased until HADG began. The zone Z8 temperature could be lowered to 100 °C by the inclusion of the active, although granulation was not possible at 80 °C. Exiting mean particle size was consequently lower but higher than seen in the first trial. The samples with the original AFFINISOL HPMC HME, A3-20, A4-20 and A5-20 listed in **Table 4** were collected once HADG began at 23 kg/h, and speed had to be immediately increased to 200 RPM to prevent the motor from overloading. At 200

RPM and 250 RPM the granules were very coarse and showed a curved shape. However, reducing the flow rate to 5 kg/h while still at 250 RPM, a broad size range of coarse and fines were collected. Images of the granules are shown in **Figure 4** and particle sizes are given in **Figure 5**. Working with the lower molecular weight AFFINISOL HPMC HME, samples A6-15, A7-15, A8-15 and A9-15 were collected after HADG began at a flow rate of 20 kg/h. The speed did not need to be immediately increased so the table shows results for 150, 200, and 250 RPM with this new binder. Like with the original binder, the granules were very coarse and curved at 20 kg/h but decreasing to 5 kg/h produced much more acceptable granules.

Figure 4. Photos of granules exiting with different molecular weight HPMC binders (see Table 4)

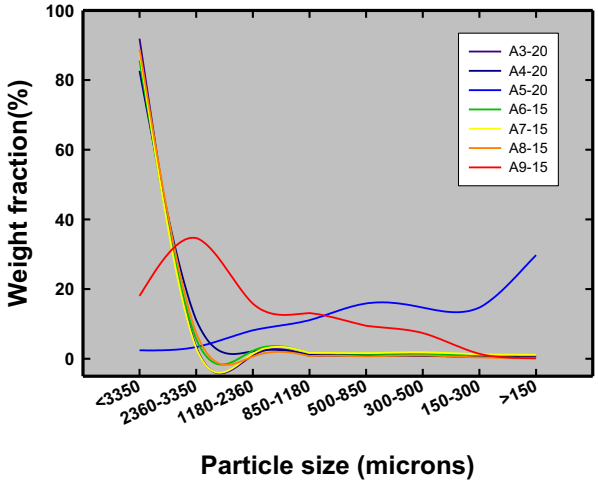


Figure 5. Particle size distributions for successfully granulated samples listed in Table 4.

Conclusions

A newly reported dry granulation process is discussed in this paper for the twin-screw granulator. The process is capable of producing dry granules of appropriate size for tabletting but requires additional study for complete mechanistic understanding. The process is reliant upon forming a dense granular bed in the restrictive kneading section of the screw, causing all subsequent particles to slow. Once the plug is established the current study indicates that any flow rate or screw speed will produce granules and, similar to wet granulation, these particles may be too fine or coarse in size unless operating conditions are optimized. The method is hypothesized to rely upon frictional heating to cause the polymeric binder to soften and sinter with adjacent particles. To minimize the duration of high temperature exposure, the method limits heat addition to one zone of the extruder, differentiating the method from melt granulation. Residence time and compaction are necessary for adequate frictional heat to develop and is aided by having the temperature of the barrel in the area of the compact mass close to the softening temperature of the binder. A binder with lower Tg and lower molecular weight improves the ability of the process to produce appropriate granules under less extreme conditions. Moisture, which lubricates the ingredients, appeared to interfere with the state of compaction, needing operating conditions that more intensely filled the screws before comparable friction could be generated.

Acknowledgements

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Table 2 Results of KOLLIDON V64 formulation without drug under certain strategy

ID	T at Z8 (°C)	RPM	Flow rate (kg/h)	Extruder load (A)	Average Press at Z8 (psi)	T of exiting particle	Moisture content
A	120	100 first then increased to 300 rapidly	17	20	40	110	2.66%
C	120		12	15	33	110	2.33%
C	120		10	10	40	110	2.53%
D	120		8	9	28	110	2.17%
E	120		5	5	24	110	3.33%

Table 3 Results of AFFINISOL formulation without drug under certain strategy

ID	T at Z8 (°C)	RPM	Flow rate (kg/h)	Extruder load	Average P at Z8	T of exiting particle	Moisture content
F	120	70 first then increased to 300 rapidly	20	20-30	/	100	2.92%

Table 4. Comparison of two AFFINISOL grades under HADG

Samples	T at Z8 (°C)	RPM	Flow rate (kg/h)	Extruder load (A)	Average P at Z8 (psi)	T (°C) exiting particle	Moisture content
A3-20	100	200	23	26	33	81	4.15%
A4-20	100	250	23	22	25	69	4.11%
A5-20	100	250	5	20	20	65	5.68%
A6-15	100	150	20	28	56	86	4.72%
A7-15	100	200	20	23	48	95	4.47%
A8-15	100	250	20	18	50	73	4.13%
A9-15	100	150	5	16	50	60	5.86%