Scaling up a high shear granulation process to gain granules suitable to formulate orally disintegrating tablets

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INTRODUCTION

In regard to line extensions or improving administration convenience, orally disintegrating tablets (ODTs) have become a popular dosage form over the last years. Nowadays, the formulator has some ready-to-use aids on hand, allowing quick and simple drug formulation [1].

The application of these ready-to-use aids is limited, though. Certain formulation aspects such as high drug load or dedicated market demands (e.g. price sensitive markets) might call for customised ODT formulations. In order to match these special requirements, a formulation based on crospovidone and lactose (agglomerated with native maize starch) was developed. This formulation proved to result in orally disintegrating tablets offering superior features (e.g. quick disintegration, high crushing strength) [2–6]. Even upon stability, formulations based on these excipients showed an excellent performance [7].

The aim of this work was to scale-up the granulation process of lactose with starch paste, on which the whole ODT formulation is based. Investigating the crucial parameters impeller speed and granulation time on three different levels was supposed to deliver additional insights on the robustness of both formulation and process. The product gained was evaluated, formulated and compressed with a subsequent characterisation of the resulting tablets.

MATERIALS AND METHODS

Lactose (GranuLac® 230, Meggle Pharma) was agglomerated (wet granulation) with native maize starch (Cargill), applied as paste (10% solid matter content), resulting in 2% binder in the final product. The wet granulation process was conducted in a high shear mixer (Roto Cube 12 and Roto Cube 60, both IMA). Impeller speed and processing time were investigated at three different levels. The up-scaling was performed by maintaining the tip speed of the impeller, and processing time constant. The wetted agglomerates were passed through a conical screen mill (Imill, IMA) and dried in a fluid bed dryer (Ghibli Lab 003, Aria 120, both IMA).

After dry sieving (Imill, IMA) the agglomerates were mixed with 10% cross-linked poly(vinyl pyrrolidone) (crospovidone, Kollidon® CL-SF, BASF) and 0.5% magnesium stearate (Bärlocher) to gain the tabletting blend. The compression was done employing a lab scale rotary press (Pressima THC, IMA) assembled with four round, flat faced and bevelled edge punches of a diameter of 15 mm (Table 1).

The tablets were examined using a multi-tester (HT100, Sotax) allowing the calculation of tensile strength with respective standard deviation (n=20). The disintegration time (n=6) was determined (ERWEKA ZT 74) in demineralised water (37°C ±1 K).

Table 1. Equipment and process settings.

	Process setting	Lab scale	Pilot scale
Granulation	Equipment	Roto Cube 12	Roto Cube 60
	Equipment type	high shear mixer	high shear mixer
	Bowl size	12 l	60 l
	Batch volume	9 l	44 l
	Filling degree	72.6%	72.6%
	Batch size	4,000 g	20,000 g
	Processing time	**1, 3, 5 min**	**1, 3, 5 min**
	Impeller speed	**150, 200, 250 rpm**	**87, 116, 144 rpm**
	Tip speed	**2.45, 3.27, 4.08 m/s**	**2.45, 3.27, 4.08 m/s**
Wet sieving	Equipment	Imill	
	Equipment type	conical screen mill	
	Sieve type	square whole	
	Sieve size	6 mm	
	Impeller speed	1,000 rpm	
Drying	Equipment	Ghibli Lab 003	Aria 120
	Equipment type	fluid bed dryer	fluid bed dryer
	Inlet air quantity	200 m³/h	1,000 m³/h
	Inlet air temp.	50°C	50°C
Dry sieving	Equipment	Imill	
	Sieve type	conical screen mill	
	Sieve size	grinding wholes	
	Impeller speed	3 mm	
		500 rpm	
Tabletting	Equipment	Pressima THC	
	Equipment type	rotary press (lab scale)	
	Punch shape	round, flat faced, bevelled edge	
	Diameter	15 mm	
	Tablet mass	525 mg	
	Compression forces	15 – 35 kN	

RESULTS AND DISCUSSION

In the set of experiments merely alterations in the granulation process were considered (granulation time and impeller speed). The drying step in the fluid bed dryer was kept constant in regard to both essential parameters: fluidisation characteristics and processing temperature.

The scale up step of the high shear granulation process was calculated in such a way that circumferential speed (tip speed) of the impeller was similar in both scales. Additionally, processing time was the same in both granulators as well.

In lab scale, particle size of the agglomerates was affected by the process settings. A higher energy input led to a larger fraction of coarse particles and vice versa (Figure 1). This effect was less pronounced in pilot scale, where the resulting variations in particle size were narrower (Figure 2). Though, all granules showed excellent flow and tabletting characteristics, indicated by a low mass variation. Interestingly, mass variation was slightly lower for the agglomerates produced in pilot scale (Figure 3, Figure 4). Considering the different values of the centre point, crushing strength of the tablets can also be considered as being hardly affected by variations in particle size distribution (Figure 5, Figure 6).

As a result of its size and mass of the tablets (about 525 mg) the final product rather represented chewable tablets than ODTs. Due to the tablet's volume the 30 seconds disintegration time limit suggested for ODTs was not met (Figure 7, Figure 8). In order to accelerate disintegration, the tablets should be reduced in volume or altered in shape to enlarge the relative surface area. Alternatively, larger quantities of crospovidone could be added to the formulation.

CONCLUSION

The granulation process of lactose with native maize starch was very robust and reliable. Even though, variations in the settings of the high shear mixer did result in a certain variation of the granule's particle size distribution neither tabletting process nor tablet characteristics became affected. A generally low standard deviation of tablet mass indicated excellent flow characteristics of the tabletting formulation.

Up-scaling hardly presented any challenges. Both processes were robust and could be conducted without any problems. The formulation can be regarded as very robust. The granulation line (combination of Roto Cube 60 and Aria 120) allowed fast and economical processing.

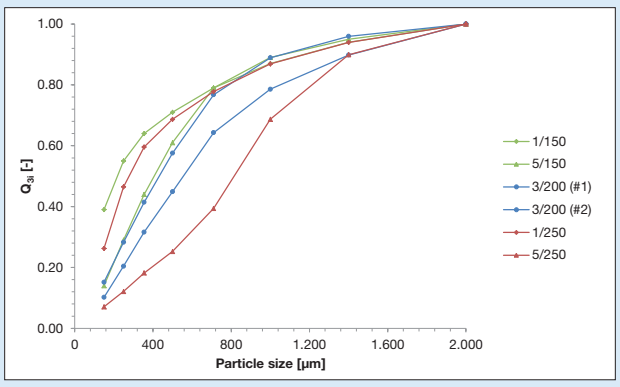

Figure 1. Lab scale, cumulative particle size distribution (Q_{3i}) as function of process settings.

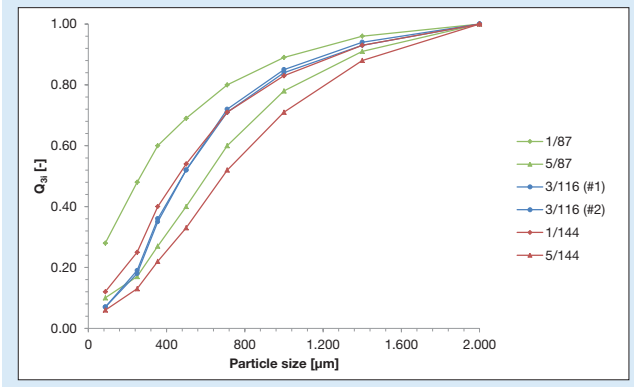

Figure 2. Pilot scale, cumulative particle size distribution (Q_{3i}) as function of process settings.

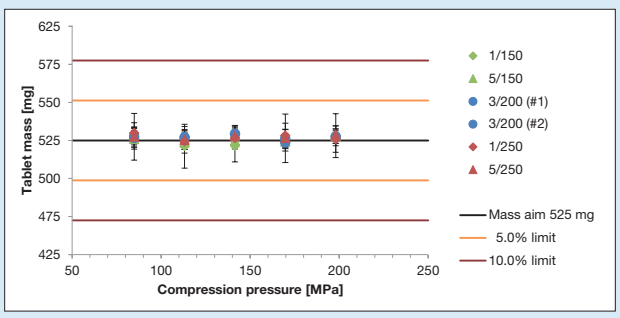

Figure 3. Lab scale, tablet mass as function of compression pressure (mean (n=20), ±SD).

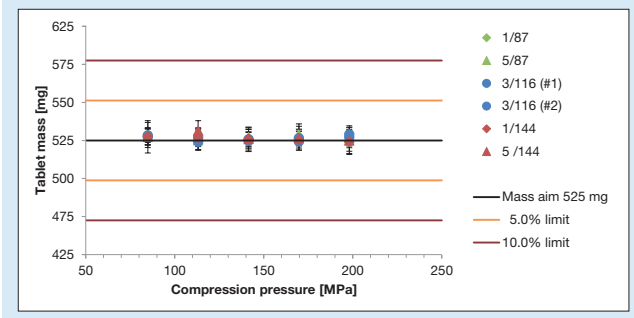

Figure 4. Pilot scale, tablet mass as function of compression pressure (mean (n=20), ±SD).

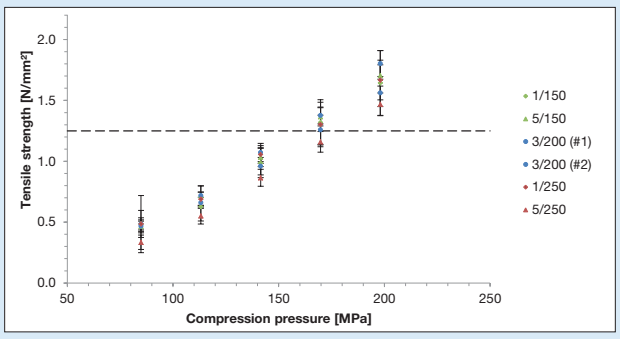

Figure 5. Lab scale, tensile strength as function of compression pressure (mean (n=20), ±SD).

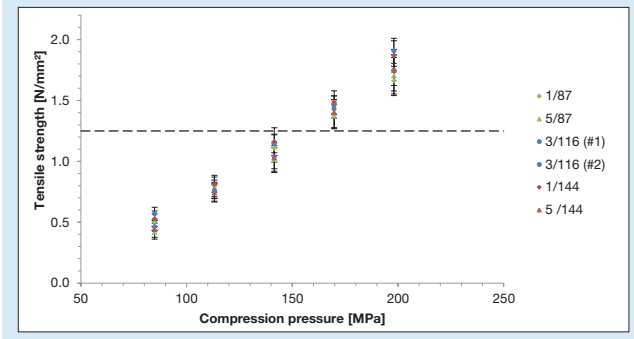

Figure 6. Pilot scale, tensile strength as function of compression pressure (mean (n=20), ±SD).

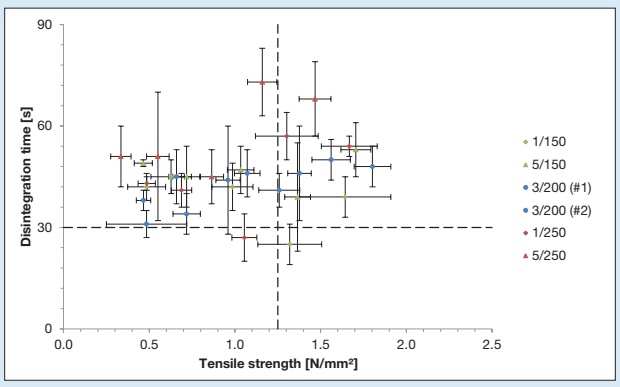

Figure 7. Lab scale, disintegration time as function of tensile strength (mean (n=6), ±SD).

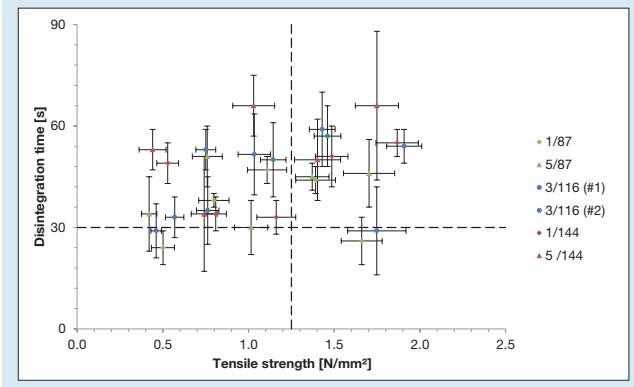

Figure 8. Pilot scale, disintegration time as function of tensile strength (mean (n=6), ±SD).

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