Use of mixer torque rheometry to predict optimal L/S ratio for twin-screw granulation

S. Pohl[1,2], P. Kleinebudde[2]

[1] INVITE GmbH, 51373 Leverkusen, Germany

[2] Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, 40225 Duesseldorf, Germany

e-mail: pohl@invite-research.com; phone: +49 211-8113550

Introduction

Twin-screw granulation (TSG) is gaining interest as it enables flexibility regarding design, process and scale up as well as short residence times and continuous manufacturing [1]. A liquid attaches the particles to each other due to shear forces, capillary forces and surface tension [2]. Some previous studies already dealt with the mixer torque rheometer (MTR) as a tool to identify optimal liquid-to-solid (L/S) ratio for granulation processes in advance [3]. The L/S ratio at the inflection point (IP) on the torque curve displays an optimum to granulate materials using high shear granulation [3]. No thorough investigation on that has been done so far for TSG. Hence, the aim of this research was to examine different L/S ratios on the torque curve, inter alia IP and maximum (Max), to identify a L/S ratio, which produced granules with the desired properties. We focused on granule size distribution (GSD) for starters.

Materials and Methods

Mixer torque rheometer

Two formulations with water were investigated using the MTR and TSG: mannitol (P200) (Parteck M200, Merck, Germany) and dicalcium phosphate anhydrous (DA150) (Di-Cafos A150, Budenheim, Germany) with 3% (w/w) polyvinylpyrrolidone K30 (PVP) (Kollidon K30, BASF, Germany) each.

35 g of each blend were evaluated threefold at 100 rpm on a MTR (Brabender, Germany) with liquid addition every 60 s. Subsequently, the torque was related to the mass (normalised torque). With the aid of the moving average the graph fluctuations became smoothed. Finally, the determination of the L/S ratios at the IP and Max occurred by the 1st and 2nd derivatives.

Twin-screw granulation

The blends plus 0.2 % (w/w) fumed silica (Aerosil 200, Evonic, Germany) were blended for 20 min at 25 rpm (LM 40, L.B. Bohle, Germany) and granulated on a twin-screw granulator (barrel L/D 40:1, Pharma 16, Thermo Fisher Scientific, Germany) using a standard screw configuration (2 kneading blocks, no distributive element).

The granulation processes were performed at the defined L/S ratios obtained by the MTR analysis (Table 1). The moisture of the starting materials was measured in advance and taken into consideration for the liquid addition.

The GSD was determined using dynamic image analysis (Camsizer XT, Retsch, Germany, and CPA 2-1, Haver & Boecker, Germany). All experiments were performed at 25 °C.

Formulation	Process condition	L/S ratios							
		IP -2	IP -1	IP	IP +1	Max -1	Max	Max +1	Max +2
P200-PVP	3.3 kg/h, 350 rpm	0.159	0.171	0.184	0.197	0.209	0.222	0.235	0.247
DA150-PVP		0.198	0.222	0.246	0.270	0.294	0.318	0.342	0.366

Table 1. Investigated L/S ratios and process conditions.

Results and Discussion

Mixer torque rheometer

Figure 1 displays the recorded torque development of the single runs (a) and normalised torque (b) as well as the mathematical approach of the L/S ratio determination in (c) and (d) for DA150-PVP. The results of DA150-PVP showed good reproducibility regarding the analysed L/S ratios at the inflection point (0.246 ± 0.012) and maximum (0.318 ± 0.002). Similar good reproducibility was obtained for P200-PVP. Both, IP and Max, were regions of interest for in-depth investigations as deviations in liquid conditions might affect the granule formation to a different extent.

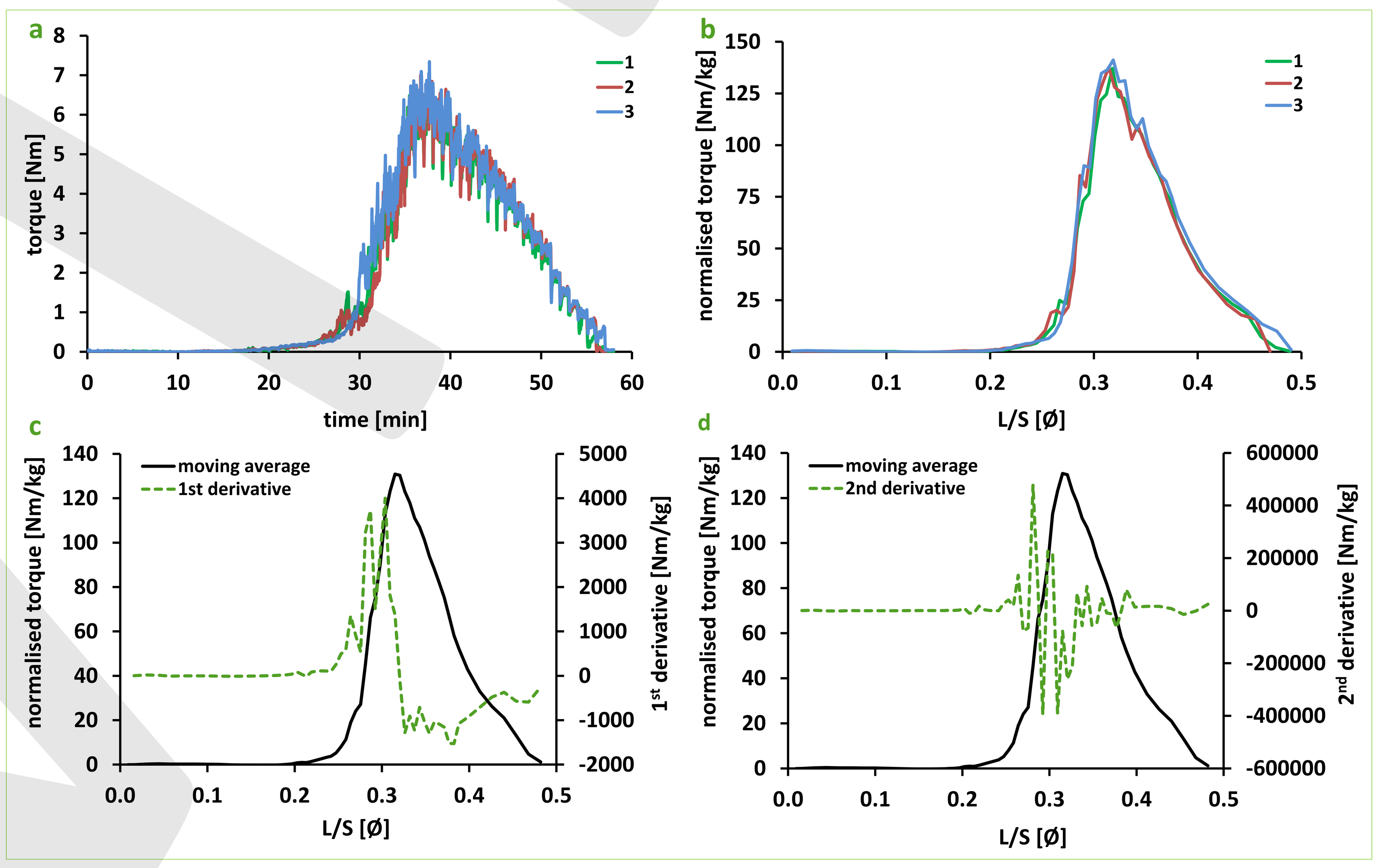

Figure 1. MTR results of DA150-PVP as an example: a) recorded torque and b) normalised torque, c) 1st and d) 2nd derivative of one run.

Twin-screw granulation

The GSD of P200-PVP (Figure 2) was already broad at low L/S ratios and became even broader with an increase in liquid content. The granules showed considerable growth at L/S ratio 0.184 (IP) and higher liquid levels.

On the contrary, for DA150-PVP (Figure 3) a monomodal size distribution was only revealed at L/S ratio 0.318 (Max) and higher. Similarly to P200-PVP, the GSD became broader at higher L/S ratios. The granules grew steadily up to L/S ratio 0.294, whereas a substantial growth could be observed at L/S ratio 0.318 (Max). It was expected that the lowest L/S ratios 0.198 and 0.222 would have shown smaller particle sizes due to lower liquid contents, but the process had to be stopped as deafening noises were demonstrating a lack of liquid and thus a lack of gliding effects between the screws and the barrel wall.

Further granule characterisation is still needed for a final conclusion as the results are inconclusive so far. The usage of a distributive element within the screw configuration would be attractive with regard to the change of the granule sizes, the breadth of the GSDs as well as other granule properties.

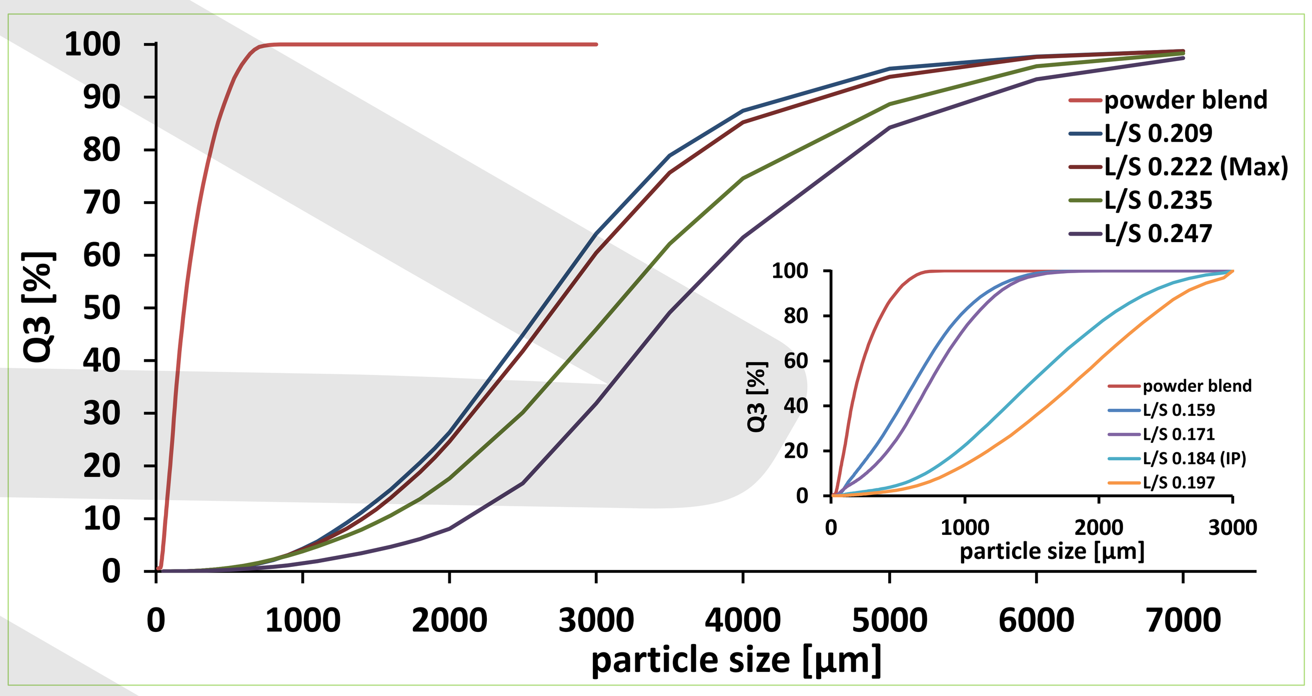

Figure 2. GSD of P200-PVP (n=3, mean; n=1 for the blend).

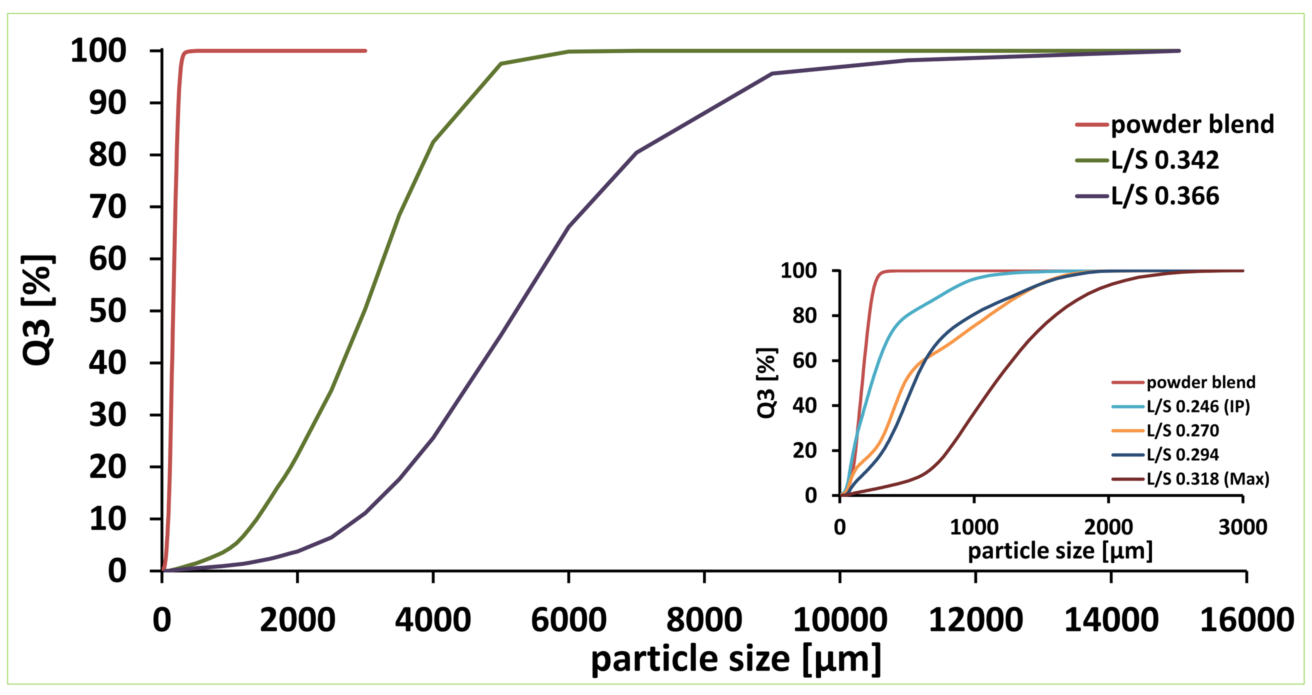

Figure 3. GSD of DA150-PVP (n=3, mean; n=1 for the blend).

CONCLUSION

The MTR appeared to be an appropriate tool to examine materials in advance and estimate suitable L/S ratios for TSG, but with the granule characterisation methods we used, a superiority of a specific L/S ratio on the torque curve could not be proven, neither at the inflection point nor at the maximum. It seems to be rather material-dependent, which L/S ratio might be optimal. Whereas the x_{50}-values for DA150-PVP were small at lower L/S ratios, the x_{50}-values for P200-PVP were essentially higher. Even the transitions from a bi- to a monomodal GSD as well as their breadths were completely different for the two formulations. Further investigations and characterisations are needed for a final conclusion. Based on the obtained GSDs and particle sizes, lower L/S ratios should be aimed for TSG, probably lower than the L/S ratio at the inflection point.

Acknowledgement

The authors gratefully acknowledge L.B. Bohle, Germany, for the opportunity of using the CPA 2-1. The authors also thank the Drug Delivery Innovation Center (DDIC) for financial support and providing the scientific network.

References: [1] Torrecillas, C. M.: A novel methodology to study polymodal particle size distributions produced during continuous wet granulation, Int. J. Pharm., 519, 230-239 (2017)
[2] Iveson, S. M.: Growth regime map for liquid-bound granules: further development and experimental validation, Pow. Tech., 117, 83-97 (2001)
[3] Santomaso, A. C.: Sugars with different thickening power in high shear granulation, Pow. Tech., 317, 391-399 (2017)

3rd European Conference on Pharmaceutics, Bologna, Italy, March 25-26, 2019